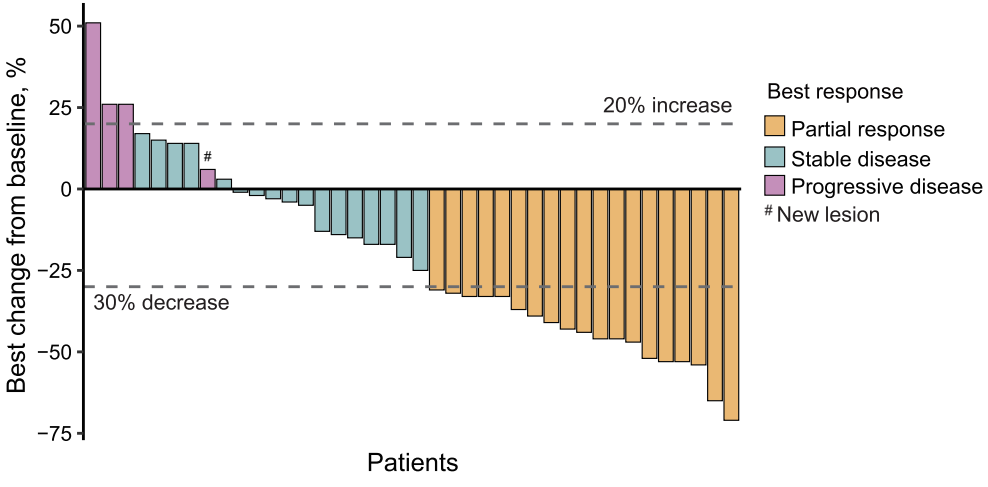
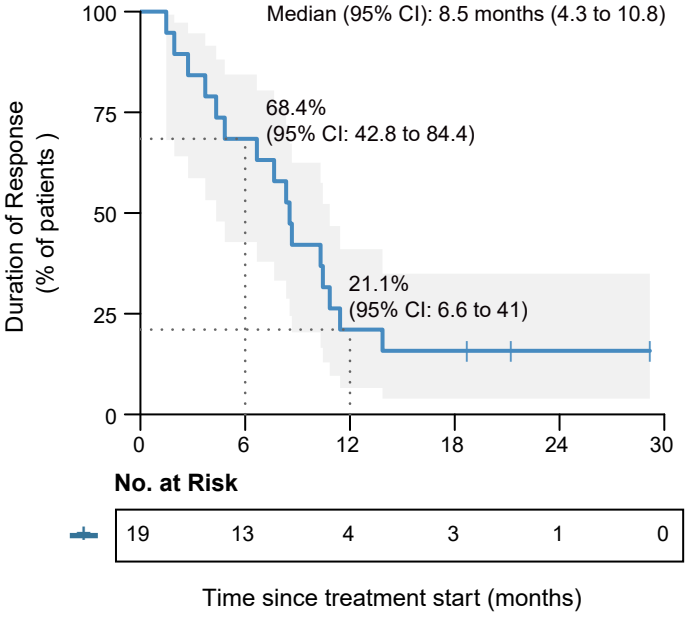
Contents for Supplementary Information

Supplementary figure 1



Supplementary figure 1. Best overall response for each patient.
Waterfall plot illustrating the best percentage change in tumor size relative to baseline, grouped by patient's best overall response (BOR) to treatment (n = 40). Each bar represents an individual patient, with colors indicating their BOR category: orange for partial response (PR), blue for stable disease (SD), and purple for progressive disease (PD). Hash sign (#) indicates the patient who experienced disease progression due to developing new lesions. The upper dotted line at 20% (labeled 20% increase), labelled as 20% increase, represents the threshold for assessing progressive disease per RECIST v1.1 criteria. The lower dotted line at -30%, labelled as 30% decrease, represents the threshold for assessing partial response. Source data are provided as a Source Data file.

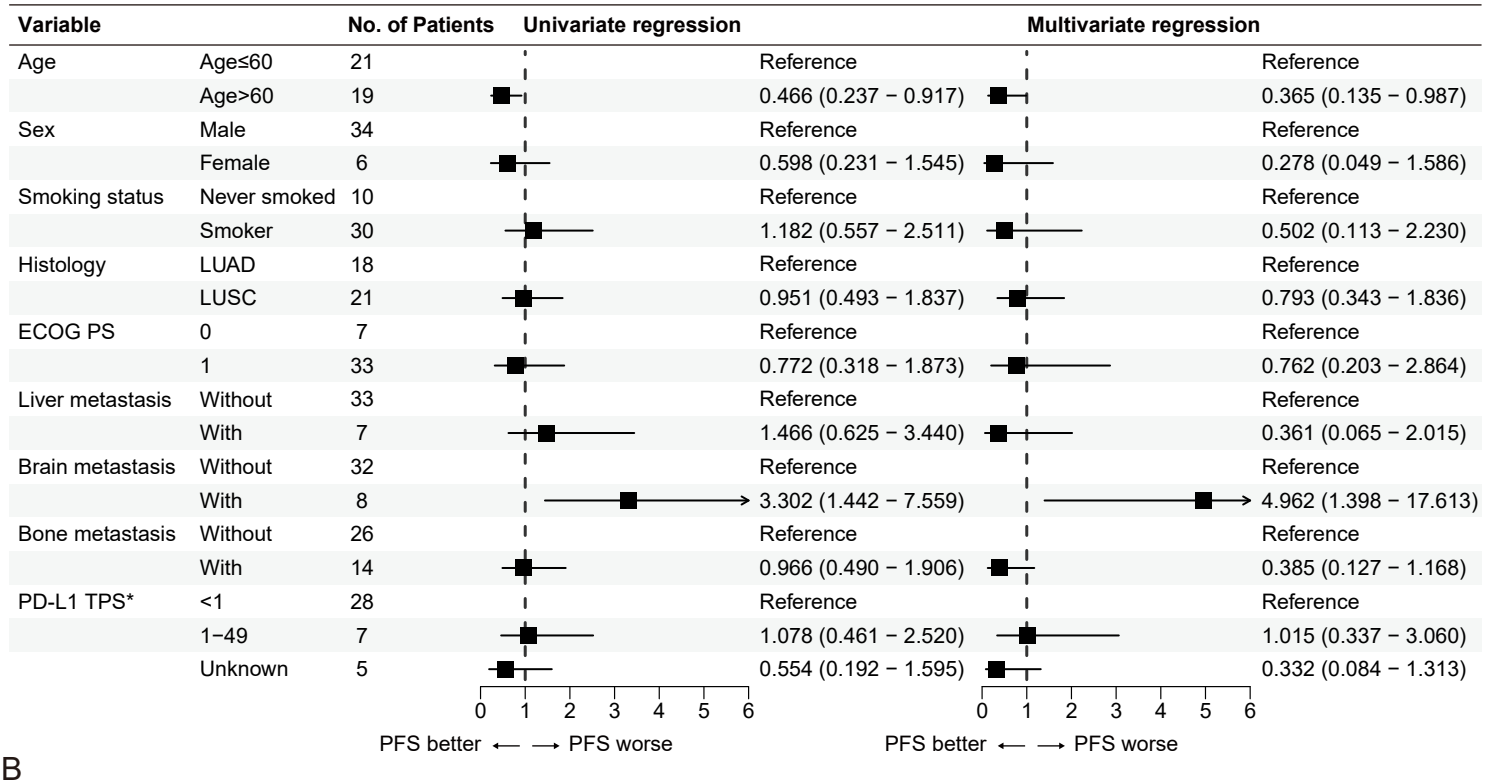
Supplementary figure 2



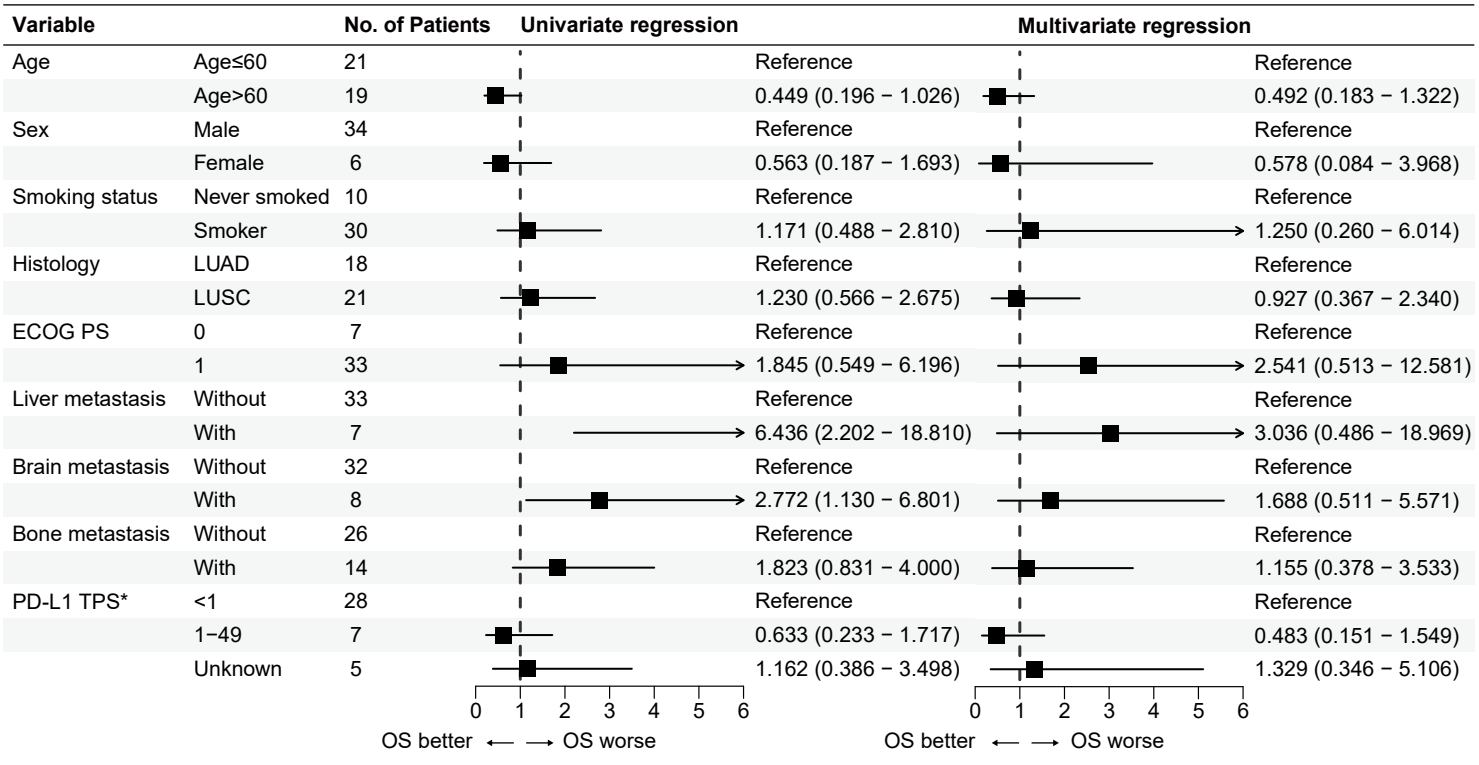
Supplementary figure 2. Duration of response in patients achieving partial response.
Kaplan-Meier curve illustrating the duration of response in patients who achieved partial response (PR) after receiving IBI318 plus lenvatinib (n = 19). Gray area along the survival curve indicates the confidence intervals (CI). Dotted lines mark the 6-month and 12-month survival milestones. Cross marks indicate censored data. Risk table below indicates the number of patients included in the analysis per time point. DOR, duration of response; This analysis demonstrates the durability of treatment response in this subset of patients. Source data are provided as a Source Data file.

Supplementary figure 3

A

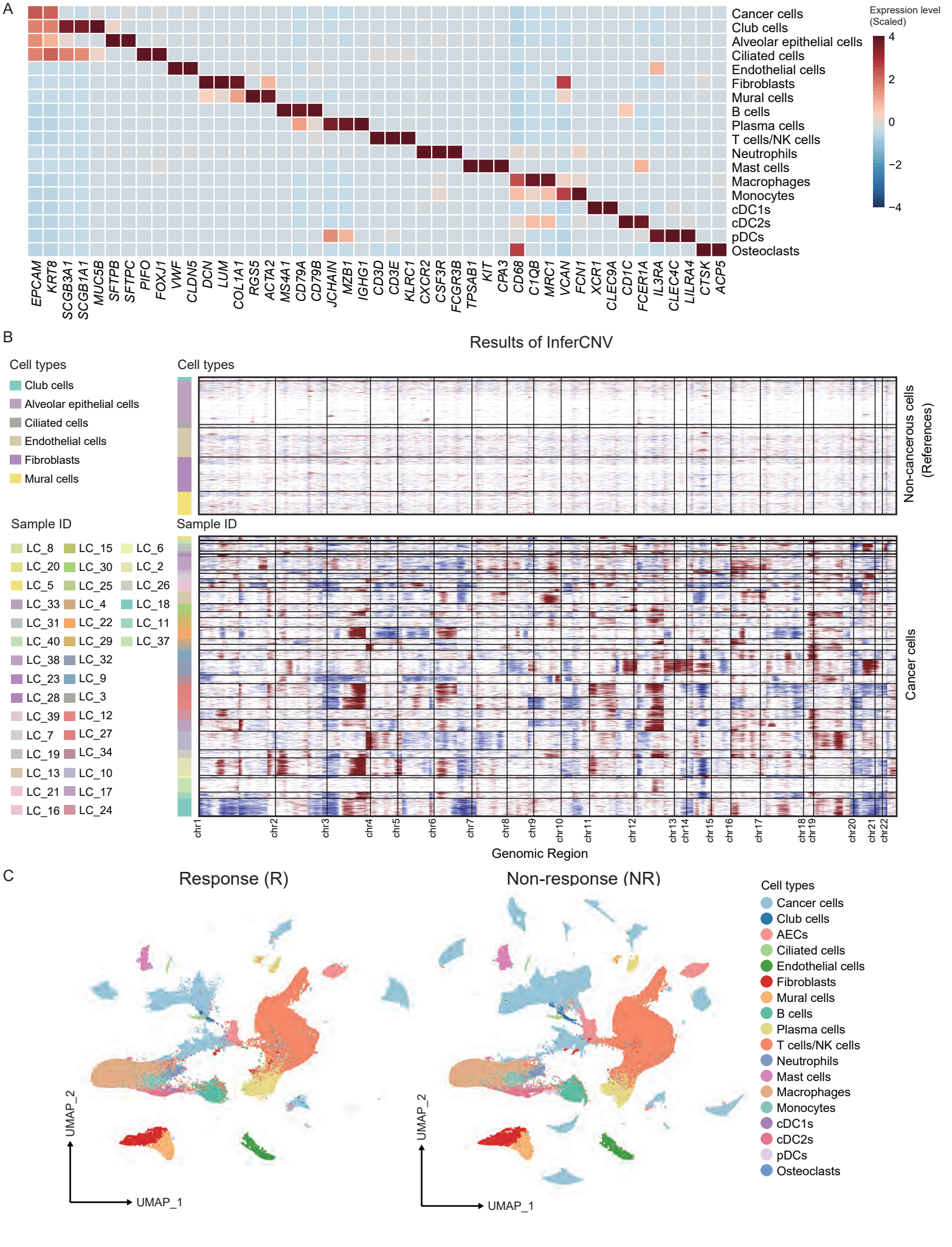


B



Supplementary Figure 3. Univariate and multivariate Cox regression analyses of patient characteristics (n = 40). Forest plots showing the results of univariate and multivariate Cox regression analyses for progression-free survival (PFS) (A) and overall survival (OS) (B). Each row represents a specific patient characteristic, with squares indicating the point estimate of the HR and horizontal lines representing the 95% confidence interval (CI). HRs greater than 1 (right side of the vertical reference line at HR = 1.0) indicate increased risk of progression or death, while HRs less than 1 (left side) indicate decreased risk. The 'Other type of NSCLC' subgroup, which included only one patient, is not shown in the figure. CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LUSC, lung squamous cell carcinoma; LUAD, lung adenocarcinoma. * PD-L1 TPS (tumor proportion score) refers to the PD-L1 tumor proportion score assessed from rebiopsy samples obtained after developing disease progression following first-line ICI therapy, i.e., prior to IBI318 plus lenvatinib treatment. These analyses identify potential prognostic factors associated with treatment outcomes. Source data are provided as a Source Data file.

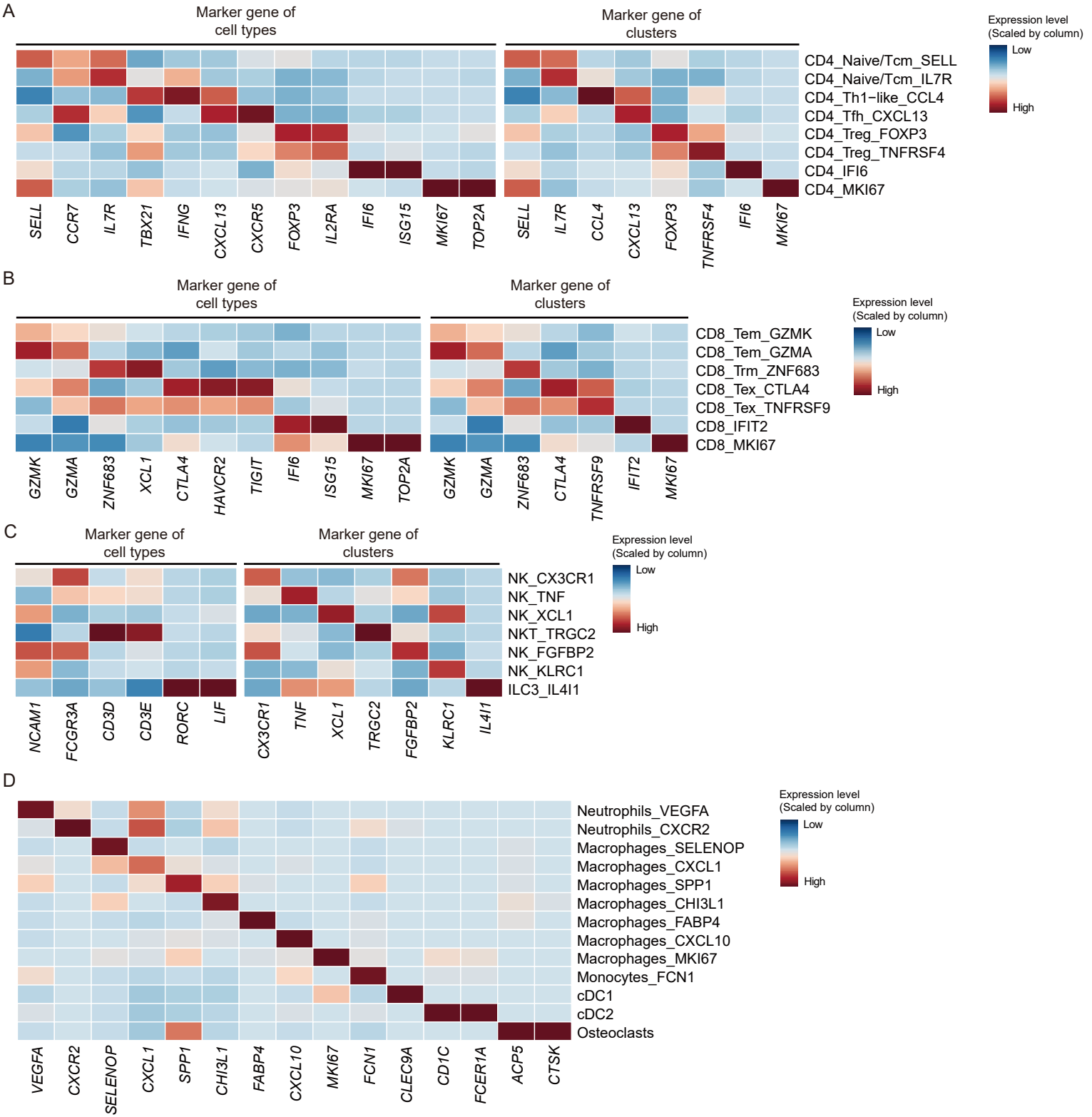
Supplementary figure 4



Supplementary figure 4. Single cell landscapes in pre-treatment tumor microenvironment (TME) of responders and non-responders (n = 40).

(A) Heatmap displaying the normalized mean expression levels of marker genes (rows) across different cell types (columns). The colors represent the scaled expression levels ranging from low (blue) to high (red). (B) Heatmap illustrating the large-scale copy number variations (CNVs) in identified malignant cells and reference cells (rows). Red indicates copy number gains/amplifications, while blue indicates copy number losses/deletion. Chromosomal positions are shown along the x-axis. (C) Uniform manifold approximation and projection (UMAP) plots showing the abundance of single cells from 18 distinct cell types within the TME of responders (right) and non-responders (left). Each dot represents an individual cell, and colors represent the different cell types. CNV, copy number variations. This comprehensive single-cell characterization reveals the cellular composition and genomic features of the pre-treatment TME in relation to treatment response.

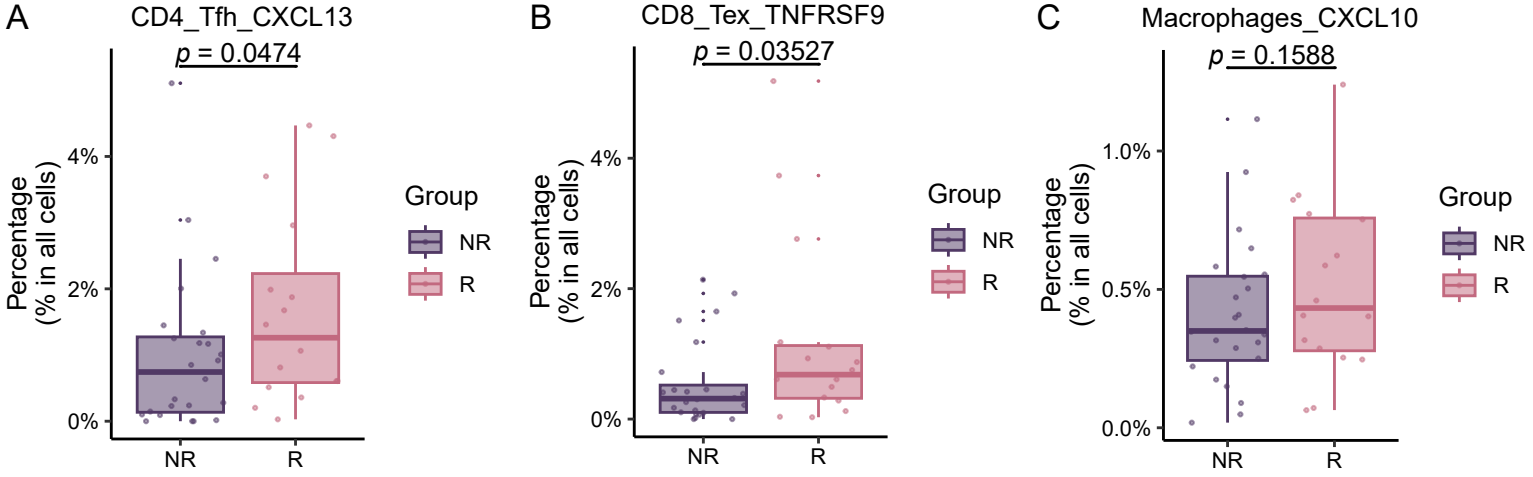
Supplementary figure 5



Supplementary figure 5. Cell subsets of T cells/NK cells and myeloid cells (n = 40).

Heatmaps showing the normalized mean expression of marker genes (rows) for each cell subsets (columns) in T cells/NK cells (A-C) and myeloid cells (D). Each heatmap shows marker genes (rows) across different T cell/NK cell subpopulations (columns), revealing the molecular signatures that distinguish each subset. In all heatmaps, colors represent scaled expression levels ranging from low (blue) to high (red), with intermediate expression shown in white or yellow.

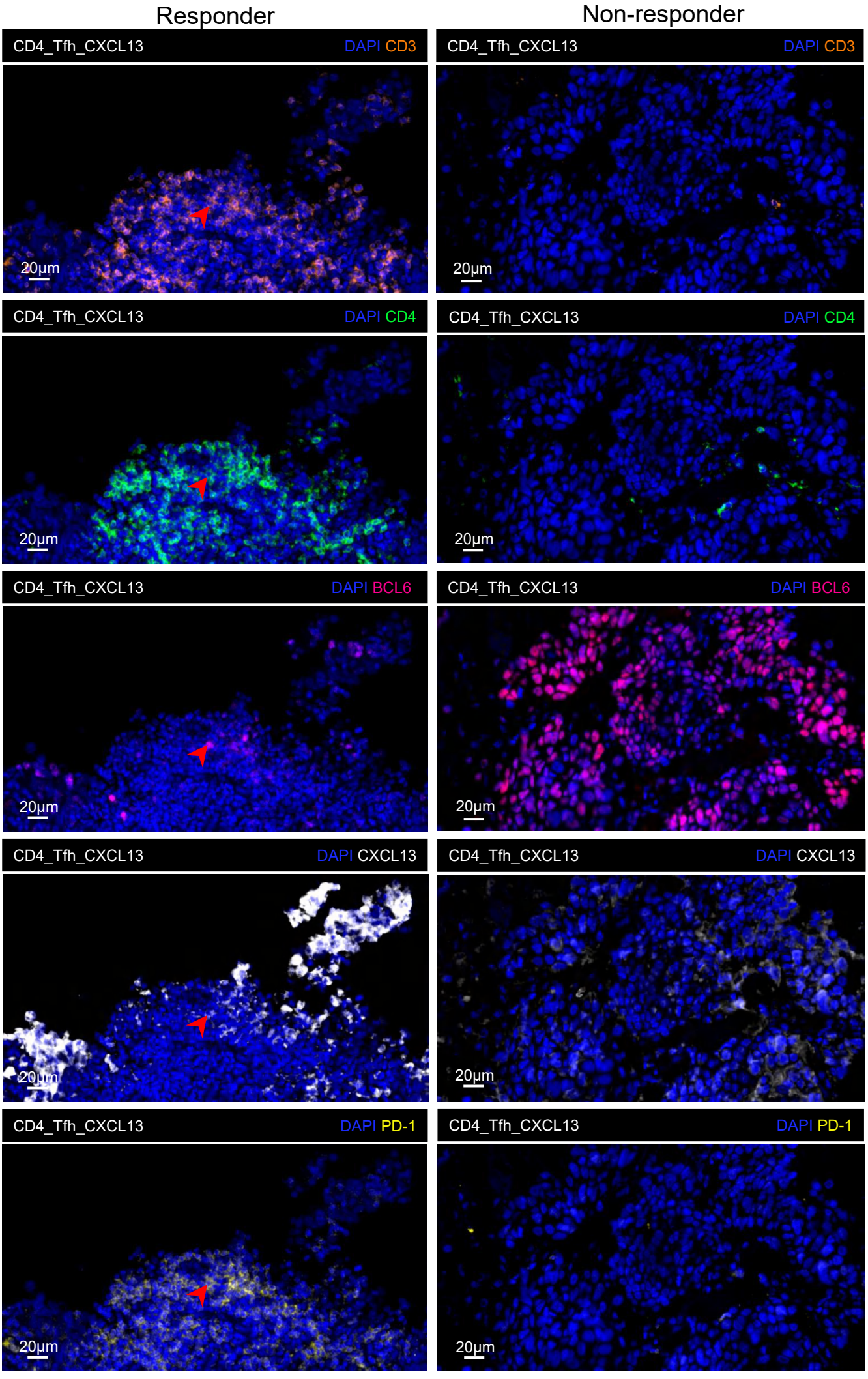
Supplementary figure 6



Supplementary figure 6. Difference in proportion of pre-treatment tumor microenvironment cell subsets of responders and non-responders.

Boxplots showing the proportions of cell subsets, including CD4_Tfh_CXCL13 (A), CD8_Tex_CTLA4 (B) and Macrophages_CXCL10 (C) in pre-treatment tumor microenvironment of responders (R, n = 16) and non-responders (NR, n = 24). The "box" shows the interquartile range (IQR) between the 25th and 75th percentiles, the "center line" marks the median, the "whiskers" to the minimum and maximum values. A one-sided Wilcoxon rank-sum test was employed to compute P-values, with no correction applied. Statistical significance was set at $P < 0.05$.

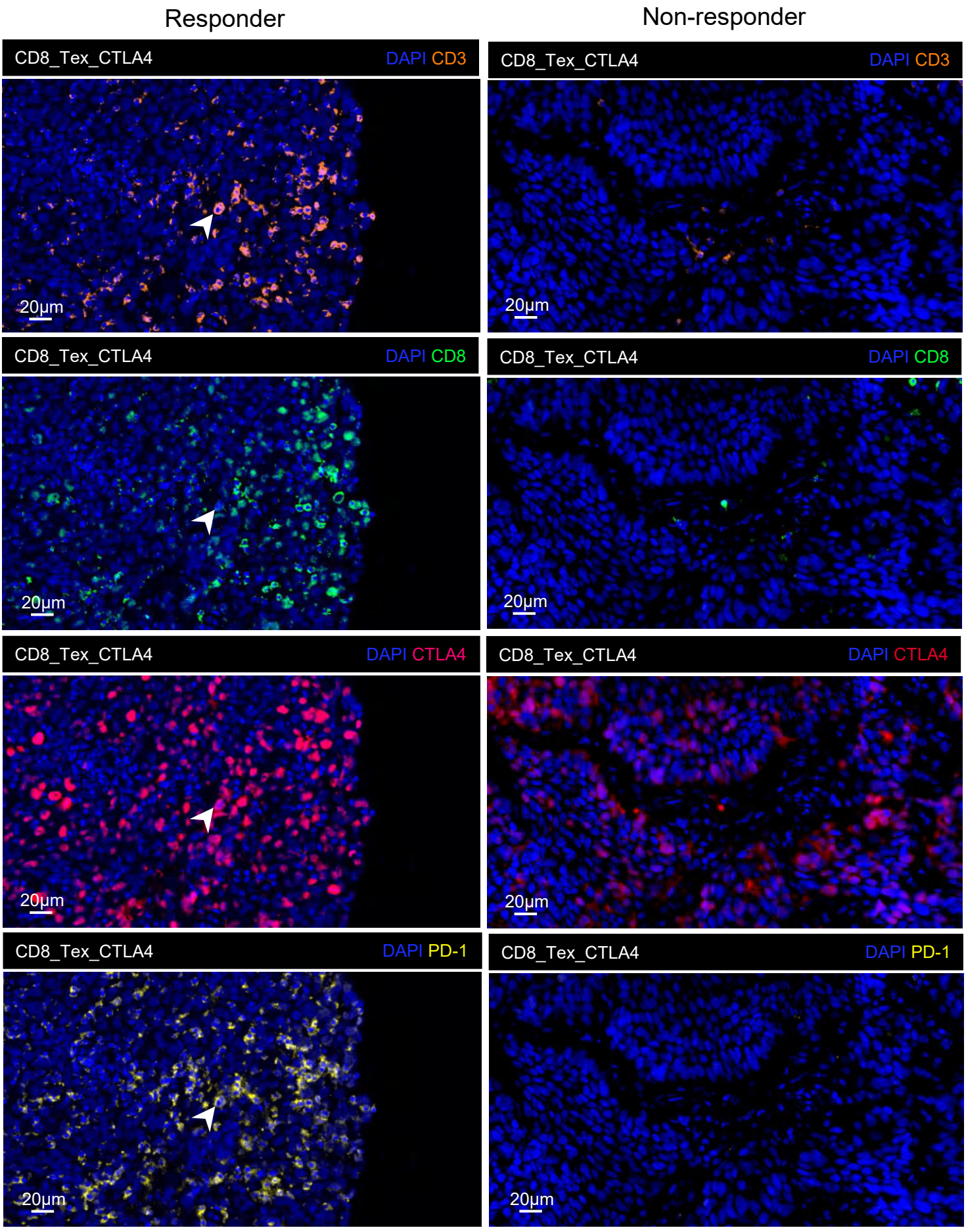
Supplementary figure 7



Supplementary figure 7. Representative multiplex immunofluorescence staining images for CD4_Tfh_CXCL13 for responder and non-responder to second-line IBI318 plus lenvatinib treatment.

Representative multiplex immunofluorescence images of $CD4^+$ T follicular helper cells expressing CXCL13 in pre-treatment tumors. Left panels representative images from responder patient. Right panels representative images from non-responder patients. Similar results were observed in samples from 5 responders and 4 non-responders. Tissue sections were stained with fluorescently-labeled antibodies targeting CD4, CXCL13, and nuclear counterstain, acquired using standardized confocal microscopy. Signal intensity and distribution reflect CD4_Tfh_CXCL13 abundance and localization. Visual comparison reveals qualitative differences in cell density and spatial organization between responders and non-responders, consistent with quantitative analysis in Supplementary Figure 6. mIF, multiplex immunofluorescence.

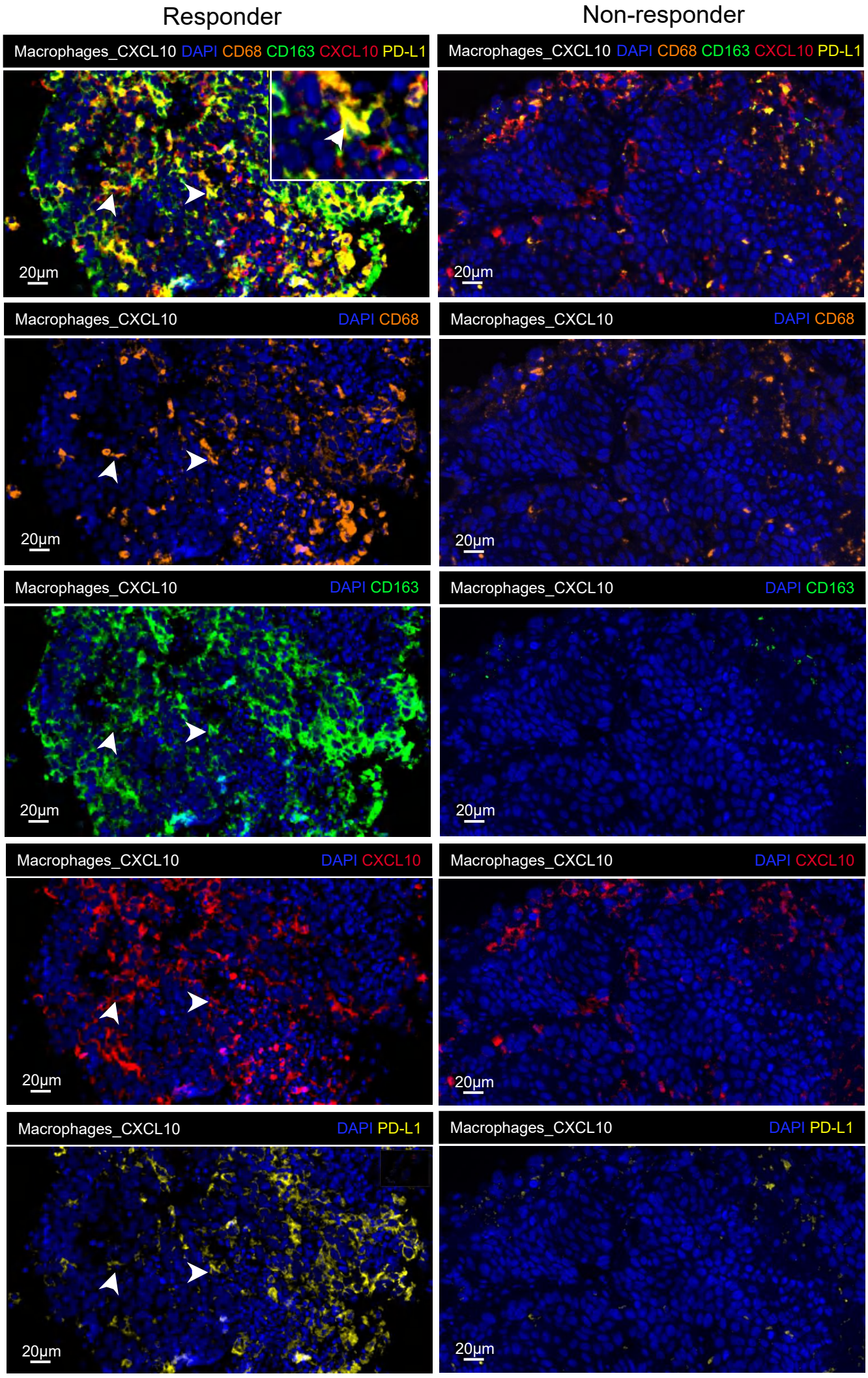
Supplementary figure 8



Supplementary figure 8. Representative multiplex immunofluorescence staining images for CD8_Tex_CTLA4 for responder and non-responder to second-line IBI318 plus lenvatinib treatment.

Representative multiplex immunofluorescence (mIF) images of $CD8^+$ exhausted T cells expressing CTLA-4 (CD8_Tex_CTLA4) in pre-treatment tumor tissues. Left panels representative images from a responder (R) patient. Right panels representative images from a non-responder (NR) patient. Similar results were observed in samples from 5 responders and 5 non-responders. Tumor tissue sections were stained with fluorescently-labeled antibodies against CD8, CTLA-4, and nuclear counterstain, acquired using standardized confocal microscopy. Signal intensity and distribution reflect CD8_Tex_CTLA4 abundance and localization within tumors. Visual comparison reveals qualitative differences in CD8_Tex_CTLA4 density and spatial organization between responders and non-responders, consistent with quantitative analysis in Supplementary Figure 6.

Supplementary figure 9



Supplementary figure 9. Representative multiplex immunofluorescence staining images for Macrophage_CXCL10 for responder and non-responder to second-line IBI318 plus lenvatinib treatment.
Representative multiplex immunofluorescence (mIF) images of macrophages expressing CXCL10 (Macrophage_CXCL10) in pre-treatment tumor tissues. Left panels representative images from a responder (R) patient. Right panels representative images from a non-responder (NR) patient. Similar results were observed in samples from 5 responders and 5 non-responders. Tumor tissue sections were stained with fluorescently-labeled antibodies against macrophage markers, CXCL10, and nuclear counterstain, acquired using standardized confocal microscopy. Signal intensity and distribution reflect Macrophage_CXCL10 abundance and localization within tumors.

ClinicalTrials.gov Identifier: NCT04777084

The Efficacy and Safety of the Bispecific Anti-PD-1/ PD-L1 Antibody IBI318 Combined with Lenvatinib in NSCLC

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VERSION HISTORY/AMENDMENT HISTORY

Document	Version Date	Rationale for Amendment and Summary of Changes
V2.0	August 9, 2021	

1 PROTOCOL SYNOPSIS

Study Title	The Efficacy and Safety of the Bispecific Anti-PD-1/PD-L1 Antibody IBI318 Combined with Lenvatinib in NSCLC
Study Leading Site	Hunan Cancer Hospital
Principal Investigator	Professor Yongchang Zhang
Participating Sites	Hunan Cancer Hospital
Study Objectives	**Primary objective:** ● **Cohort A:** Administer compassionate treatment to patients with advanced NSCLC that is negative for driver genes, who have failed previous PD-1/PD-L1 inhibitor therapies and currently have no viable treatment options. Evaluate the 12-week objective response rate (ORR) of IBI318 combined with lenvatinib in patients with advanced NSCLC, negative for driver genes, who have experienced failure with prior PD-1/PD-L1 inhibitor therapies. ● **Cohort B:** Provide compassionate treatment to patients with advanced NSCLC harboring EGFR-activating mutations or ALK fusions, who have developed resistance to EGFR-TKI or ALK-TKI. Evaluate the 12-week ORR of IBI318 combined with lenvatinib in patients with advanced NSCLC harboring EGFR-activating mutations or ALK fusions, following resistance to EGFR-TKI or ALK-TKI. ● **Cohort C:** Measure the ORR according to RECIST v1.1 criteria in patients with advanced NSCLC that is wild-type for EGFR, ALK, and ROS1, and negative for PD-L1 expression, treated with first-line therapy of the bispecific PD-1/PD-L1 antibody IBI318 in combination with lenvatinib.

	Secondary Objectives: ● Evaluate the best overall response (BOR) ● Evaluate progression-free survival (PFS) ● Evaluate overall survival (OS) ● Evaluate disease control rate (DCR) ● Measure the duration of response (DOR) ● Assess the safety and tolerability of the combination of IBI318 and lenvatinib, including the incidence of adverse events (AEs) and serious adverse events (SAEs), as well as the rate of treatment discontinuation due to AEs/SAEs.
	Exploratory objectives: Conduct single-cell sequencing and multiplex immunofluorescence to explore potential predictive biomarkers of therapeutic efficacy in tumor tissue.
Study Endpoints	**Primary study endpoints:** ● **Cohort A: 12-week ORR:** The 12-week ORR is defined as the proportion of subjects who achieve a complete response (CR) or partial response (PR) among all subjects evaluated around 12 weeks after administration of treatment regimen. ● **Cohort B: 12-week ORR:** The 12-week ORR is defined as the proportion of subjects who achieve a CR or PR among all subjects evaluated around 12 weeks after administration of treatment regimen. ● **Cohort C: ORR:** The ORR is defined as the proportion of subjects who achieve a confirmed CR or PR among all evaluated subjects.
	Secondary efficacy endpoints: ● **Best objective response (BOR):** Defined as the proportion of subjects achieving a best response of CR or PR among all evaluated subjects.

	• **Progression-free survival (PFS):** PFS is defined as the time from the start of treatment to the first occurrence of radiographic disease progression or death (whichever occurs first). Disease progression will be determined by the investigator based on the RECIST v1.1 criteria. Participants without documented disease progression or death at the time of analysis will be censored at the date of their last tumor assessment. • **Overall survival (OS):** OS is defined as the time from the start of treatment to death from any cause. Participants still alive at the end of the study will be censored at the date of their last known survival status. • **Disease control rate (DCR):** DCR is defined as the proportion of participants achieving CR, PR, or stable disease (SD). • **Duration of response (DOR):** DOR is defined as the time from the first documented response (CR or PR) to disease progression or death (whichever occurs first). • **Safety and tolerability:** AEs, SAEs, as well as the rate of treatment discontinuation due to AEs/SAEs.
	Exploratory endpoints: • Explore the mechanism and screen biomarker based on single-cell sequencing and multiplex immunofluorescence.
Study Design	This study is a prospective, multi-cohort clinical trial designed to evaluate the efficacy and safety of the combination therapy of IBI318 and lenvatinib across different subsets of patients with advanced NSCLC. Cohort A will focus on patients with advanced NSCLC who have experienced failure with first-line PD-1/PD-L1 inhibitors. Cohort B will include patients with advanced NSCLC harboring EGFR-activating mutations or ALK fusions, who have developed resistance to EGFR-TKI or ALK-TKI therapies. Cohort C will examine the efficacy and safety of this combination as a first-line

	treatment in patients with advanced NSCLC who are negative for PD-L1 expression and wild-type for *EGFR*, *ALK*, and *ROS1*. Eligible participants who meet the inclusion criteria will receive treatment with IBI318 and lenvatinib until disease progression, death, intolerable toxicity, withdrawal of consent, initiation of new anti-cancer therapy, or any other reason specified in the protocol necessitating discontinuation. Tumor imaging assessments will be conducted every 6 weeks during the treatment period, in accordance with RECIST v1.1 criteria. After 24 weeks of treatment, the imaging evaluations may be extended to every 8 weeks. For patients receiving IBI318 combined with lenvatinib who present with initial imaging evidence of progressive disease (PD) according to RECIST v1.1, continuation of treatment may be considered if the patient's clinical condition remains stable, there is no evidence of rapid radiologic progression, and the investigator believes that the patient may still benefit from the study therapy. In such cases, a follow-up imaging assessment should be performed to confirm PD at least 6 weeks (±7 days) after the initial evidence of PD. If PD is confirmed upon reassessment, the patient should discontinue the study treatment. If PD is not confirmed, the patient will continue with the study treatment, with ongoing imaging assessments at protocol-specified intervals until PD is definitively confirmed by imaging.
Study Drug	IBI318, Lenvatinib
Route of Administration	● IBI318 will be administered as an intravenous infusion at a dose of 300 mg on the first day of each cycle, with each cycle lasting 2 weeks (Q2W). ● Lenvatinib will be taken orally at a daily dose of 8 mg. ● Both treatments will be continued until one of the following occurs: disease progression, death, unacceptable toxicity, withdrawal of informed consent, initiation of a new anti-cancer therapy, or other reasons specified in the protocol, with a maximum treatment duration of

	2 years.
Inclusion Criteria	**Inclusion Criteria:** Eligible subjects selected for this study must meet all of the following criteria: 1. Signed informed consent before implementing any trial-related procedures; 2. Age ≥ 18 years old and ≤ 75 years old; 3. No limit on the gender; **Cohort A:** Histological or cytological confirmed locally advanced (stage IIIB-IIIC) or metastatic (stage IV) NSCLC (International Association for the Study of Lung Cancer and Joint Committee on the American Classification of Cancer, TNM Lung cancer stage 8) without EGFR gene activating mutations, ALK gene fusion or ROS1 gene fusion confirmed by histological specimens who experienced disease relapse after receiving first-line anti-PD-1 /PD-L1 antibody therapy, as follows: 1) Only one anti-PD-1/PD-L1 antibody monotherapy or combination therapy is accepted in the advanced stage of the disease, and other immunotherapy is not allowed; 2) Previous anti-PD-1/PD-L1 antibody monotherapy or combination therapy has the best curative effect (according to RECIST 1.1 criteria) as CR, PR, or SD for ≥6 months (defined as disease control within 6 months from receiving the first dose of the treatment regimen); 3) Disease progression confirmed by imaging studies occurred during or after the most recent treatment. **Cohort B:** Histological or cytological confirmed locally advanced (IIIB-IIIC) or metastatic (stage IV) NSCLC (International Association for the Study of Lung Cancer and Joint Committee on the American Classification of Cancer, TNM Lung cancer 8th edition) with histologically confirmed EGFR-activating mutations or ALK fusion who experience disease relapse after treatment failure with anti-EGFR-TKI or ALK-TKI therapy, as follows:

	In patients with EGFR-TKI sensitizing mutations, the specific history of previous EGFR-TKI treatment can be one of the following: 1) Absence of EGFR T790M mutation after treatment with first- or second-generation EGFR-TKI (including gefitinib, erlotinib, icotinib and afatinib); 2) EGFR T790M mutation detected after disease progression with first or second generation EGFR-TKI monotherapy (including gefitinib, erlotinib, icotinib, and afatinib, etc.), and experienced disease progression after treatment with osimertinib or other third-generation EGFR-TKI; 3) Disease progression after osimertinib or other third-generation EGFR-TKI therapy as the first-line therapy (regardless of EGFR T790M mutation status); 4) Those who are allowed to receive neoadjuvant/adjuvant targeted therapy in the early stage and develop drug resistance after subsequent adjuvant targeted therapy, and their drug resistance status meets one of the three requirements of appeal. 5) For patients with ALK-rearranged NSCLC, disease progression should occur after adequate ALK-TKI treatment, and there is no opportunity for subsequent targeted therapy. **Cohort C:** Locally advanced NSCLC that is not suitable for radical surgery or radiotherapy, or that has relapsed without systematic treatment, or that has metastasized without systematic treatment and is negative PD-L1 expression. Patients who have previously received neoadjuvant or adjuvant therapy can also receive neoadjuvant or adjuvant therapy (but neoadjuvant or adjuvant therapy is chemotherapy/radiotherapy, not immunotherapy), and the end of neoadjuvant/adjuvant therapy should be ≥ 6 months after tumor progression; If the pathological type is adenocarcinoma, the absence of EGFR-activating mutations or ALK fusion or ROS1 fusion should be confirmed. Negative expression of PD-L1 was defined as TPS < 1% using 22C3 test.

5. According to the evaluation criteria for the efficacy of solid tumors (RECIST v1.1 version), there is at least one measurable lesion. The lesions located in the radiation field of the previous radiotherapy can be regarded as measurable lesions if disease progression is confirmed;

6. Subjects with brain metastases who are either asymptomatic or has stable symptoms after local treatment can be included in the study, as long as the subjects meet the following conditions:

1) There are measurable lesions outside the central nervous system (CNS);
2) Absence of any CNS symptoms or no worsening of symptoms within at least 2 weeks;
3) Does not require glucocorticoid therapy, or stop glucocorticoid therapy within 7 days before the first administration, or the dosage of glucocorticoid is stable and reduced to less than 10mg/day prednisone (or equivalent dose) within 7 days before the first administration;

7. Subjects can receive palliative radiotherapy (including craniocerebral radiotherapy for symptomatic brain metastases), but the radiotherapy must be completed at least 1 week before enrollment, and the radiotherapy-related toxicity should be restored to less than or equal to 1 degree (CTCAE 5.0, except for hair loss).

8. Eastern Cooperative Oncology Group (ECOG) performance status of 0-1;

9. Expected survival time should be > 3 months;

10. Sufficient organ function, subjects need to meet the following laboratory indicators:

1) The absolute value of neutrophils (ANC) ≥ $1.5x10^9$/L when no granulocyte colony-stimulating factor is used in the past 14 days;
2) In the case of no blood transfusion in the past 14 days, platelets ≥

	100×10^9/L; 3) In the past 14 days without blood transfusion or erythropoietin, hemoglobin > 9g/dL; 4) Total bilirubin ≤ 1.5×upper limit of normal (ULN); 5) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) within ≤ 2.5×ULN (subjects with liver metastases are allowed to have ALT or AST ≤ 5×ULN); 6) Serum creatinine ≤ 1.5×ULN and creatinine clearance rate (calculated by Cockcroft-Gault formula) ≥ 50ml/min; 7) Good coagulation function, defined as international normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 times ULN; 8) Normal thyroid function is defined as thyroid-stimulating hormone (TSH) within the normal range. If the baseline TSH is out of the normal range, subjects whose total T3 (or FT3) and FT4 are within the normal range can also be included in the group; 9) Myocardial enzyme spectrum is within the normal range (for example, simple laboratory abnormalities that are judged by the investigator to be of no clinical significance are also allowed to be included in the study); 11. For female subjects of childbearing age, a urine or serum pregnancy test and the result should be negative within 3 days before receiving the first study drug (day 1 of cycle 1). If the urine pregnancy test result cannot be confirmed as negative, a blood pregnancy test is required. Women of non-bearing age are defined as at least 1 year after menopause, or have undergone surgical sterilization or hysterectomy; 12.. If there is a risk of conception, all subjects (whether male or female) need to adopt a low annual failure rate during the entire treatment period until 120 days after the last study drug administration (or 180 days after the last study drug administration) less than 1% of contraceptive measures;

	13. Blood pressure can be adequately controlled with or without anti-hypertensive medication, defined as blood pressure ≤ 150/ 90 mm Hg, and blood pressure was under stable control within 1 week before treatment initiation. 14. Patients must have recovered from toxicity or complications if they have previously received surgery or radiation > 30Gy.
Exclusion Criteria	**Exclusion Criteria:** Subjects who meet the following criteria cannot be selected for this study: 1. The pathology is small cell lung cancer (SCLC), including lung cancer mixed with SCLC and NSCLC; 2. Imaging results show evidence of tumor voids, tumor inclusion or invasion of large vessels. In addition, the proximity of the tumor to the large blood duct should be considered and the risk of severe bleeding associated with tumor shrinkage/necrosis after lenvatinib treatment should be excluded. (The large vessels in the chest include the main pulmonary artery, left pulmonary artery, right pulmonary artery, 4 pulmonary veins, superior vena cava, inferior vena cava and aorta); 3. For cohort A: subjects who have previously used anti-PD-1, PD-L1 or other immunotherapy agents and meet the following conditions: 1). The toxicity that caused permanent discontinuation occurred before the termination of immunotherapy; 2). Prior to the administration of the study drug, the toxicity of the previous immunotherapy has not recovered or has not recovered to level 0-1. Asymptomatic and stable control of endocrine toxicity level 2 with appropriate replacement therapy is allowed to enter the group; 3). Adverse events that require additional immunosuppressive agents in addition to corticosteroids, or adverse events that still recur in the use of corticosteroids during previous immunotherapy. For cohorts B and C: Prior treatment: anti-PD-1, anti-PD-L1, or anti-PD-L2

	drugs or drugs that target another stimulating or co-inhibiting T-cell receptor (including but not limited to CTLA-4, OX-40, CD137, etc.); Anti-PD-1, anti-PD-L1, or anti-PD-L2 drugs or drugs that target another stimulating or co-inhibiting T cell receptor (including but not limited to CTLA-4, OX-40, CD137, etc.); 4. Have received the following treatments: 1) Received systemic anti-tumor therapy within 2 weeks before treatment, such as chemotherapy, targeted therapy, immunotherapy (including Chinese herbal medicine with anti-tumor indications), etc.; 2) Previously received lenvatinib, bevacizumab, anlotinib monotherapy or in combination with anti-PD-1 / PD-L1 drugs 3) Have received any investigational drug treatment within 4 weeks before treatment; 4) Received large doses of immunosuppressive drugs within 4 weeks before treatment (systemic glucocorticoid exceeding 10 mg/day prednisone or its equivalent dose); 5) Received live attenuated vaccine within 4 weeks before treatment (or plan to receive live attenuated vaccine during the study period); 6) Have received major surgery (such as open cavity, thoracotomy), or unhealed surgical wounds, ulcers or fractures within 4 weeks before treatment. 5. Clinically significant cardiovascular damage occurred within 12 months of the first dose of study treatment. 6. Gastrointestinal diseases that may affect oral absorption of study drugs. 7. Prior gastrointestinal or grade ≥ 3 non-gastrointestinal fistula. 8. A known history of other malignancies, and unless the participant has undergone potentially curative treatment, there is no evidence of disease recurrence in the 3 years since the start of that treatment. 9. Severe allergy to IBI318 and lenvatinib.

	10. There is clinically uncontrollable pleural effusion/abdominal effusion (subjects who do not need to drain the effusion or stop drainage for 3 days without a significant increase in effusion can be included in the study); 11. Subjects who have received thoracic radiotherapy of greater than 30 Gy within 6 months before treatment or palliative radiotherapy of 30 Gy or less within 7 days before treatment (allowing palliative treatment of bone lesions or intracranial lesions, radiation therapy); 12. An active autoimmune disease that requires systemic treatment (such as the use of disease-relieving drugs, glucocorticoids, or immunosuppressive agents) occurred within 2 years before the first administration. Alternative therapies (such as thyroxine, insulin, or physiological glucocorticoids for adrenal or pituitary insufficiency, etc.) are not considered systemic treatments; 13. Known allogeneic organ transplantation (except corneal transplantation) or allogeneic hematopoietic stem cell transplantation; 14. Before starting treatment, have not fully recovered from toxicity and/or complications caused by any intervention (ie, ≤ grade 1 or reached baseline, excluding fatigue or hair loss); 15. Known history of human immunodeficiency virus (HIV) infection (ie HIV 1/2 antibody positive); 16. Untreated active hepatitis B (defined as HBsAg positive and the number of HBV-DNA copies detected at the same time is greater than the ULN value of the laboratory department of the research center); Note: Hepatitis B subjects who meet the following criteria can also be included in the group: 1) Before the first administration, the HBV viral load is less than 1000 copies/ml (200 IU/ml), and the subject should receive anti-HBV treatment during the entire study chemotherapy drug treatment to avoid viral reactivation;

2) For subjects with anti-HBc (+), HBsAg (-), anti-HBs (-) and HBV viral load (-), there is no need to receive preventive anti-HBV treatment, but close monitoring of virus reactivation is required.

17. Active hepatitic C virus (HCV)-infected subjects (HCV antibody-positive and HCV-RNA level is higher than the lower limit of detection);

18. Live vaccines have been administered within 30 days before the first dose of study regimen (cycle 1, day 1). Note: It is allowed to receive inactivated virus vaccine for seasonal influenza injection within 30 days before the first administration; however, it is not allowed to receive live attenuated influenza vaccine for intranasal administration.

19. Pregnant or lactating women;

20. There are any serious or uncontrollable systemic diseases, such as:

1) The resting electrocardiogram has major abnormalities in rhythm, conduction or morphology that are severe and difficult to control, such as complete left bundle branch block, heart block above degree II, ventricular arrhythmia or atrial fibrillation;
2) Left ventricular ejection fraction (LVEF) is lower than normal;
3) QTc interval is extended to more than 480 ms;
4) Unstable angina pectoris, congestive heart failure, chronic heart failure of New York Heart Association (NYHA) grade ≥ 2;
5) Myocardial infarction occurred within 6 months before enrollment;
6) A history of non-infectious pneumonia requiring glucocorticoid treatment within 1 year before the first administration, or current clinically active interstitial lung disease;
7) Active tuberculosis;
8) Active or uncontrolled infection that requires systemic treatment;
9) Clinically active diverticulitis, abdominal abscess, gastrointestinal obstruction;
10) Liver diseases such as liver cirrhosis, decompensated liver disease,

	acute or chronic active hepatitis; 11) Poorly controlled diabetes (fasting blood glucose [FBG] > 10mmol/L); 12) Urine routine tests suggest that urine protein is ≥ ++, and the 24-hour urine protein quantification is confirmed to be greater than 1.0 g; 13) Subjects who have mental disorders and cannot cooperate with treatment; 21. The medical history or disease evidence, abnormal treatment or laboratory test values that may interfere with the test results, prevent the subject from participating in the study, or the investigator believes that it is not suitable for study inclusion.
Study Withdrawal Criteria/ Termination of Study Treatment Criteria	A subject must be withdrawn from the study under the following circumstances: ● The subject or their legal representative withdraws informed consent for study participation. ● The subject is lost to follow-up. A subject must discontinue study treatment but continue follow-up in the following scenarios: ● The subject experiences intolerable adverse reactions related to the study drug. ● Imaging results or clinical symptoms indicate tumor progression, unless the subject meets the criteria to continue treatment after disease progression and agrees to do so. ● Any clinical AEs, laboratory abnormality, or other medical condition arises that, in the investigator's judgment, precludes the subject from benefiting from continued treatment. ● The subject's overall health status deteriorates to a point where continued participation in the study is not feasible. ● Pregnancy occurs in female subjects during the study.

	● The subject initiates other systemic anti-tumor therapy. ● The investigator determines that the subject cannot continue treatment due to other reasons, such as mental illness, social circumstances that may interfere with the subject's rights, safety, cooperation, or participation in the study, or poor compliance. ● The investigator deems it in the subject's best interest to discontinue study treatment.
Sample Size Calculation	This investigation was designed to be a study with a fixed sample size (n = 40 in cohort A). For cohort A: Historical data indicate that the ORR for chemotherapy as second-line therapy is approximately 12%.[1] This trial aims to detect an improvement of an additional 18%, targeting to achieve an ORR of 30%. Based on a power of 80%, an alpha of 0.05, and accounting for a 15% dropout rate, the required sample size is 40 patients. Sample size was calculated using PASS software (version 15.0, NCSS LLC, Kaysville, Utah, USA).
Data Analysis and Statistical Methods	**Analysis sets:** **Full analysis set (FAS):** The FAS will include all patients enrolled who received at least one cycle of the study treatment. The primary and secondary efficacy analysis will be conducted in the FAS. Additionally, demographic information and baseline characteristics will be summarized for this population. **Per-Protocol Set (PPS):** The PPS is a subset of the FAS. It will include patients who have any major protocol deviations that could impact efficacy evaluation, as well as those who were enrolled but did not receive treatment. **Safety Analysis Set:** The safety analysis set population will include all patients who have received at least one dose of the study medication. This set will be used for the analysis of safety endpoints.

General analysis:

Categorical variables will be described using frequencies and percentages, with overall percentages presented alongside 95% confidence intervals when relevant. Continuous variables will be summarized with descriptive statistics such as the mean, standard deviation, median, and range (minimum and maximum values). Time-to-event outcomes will be evaluated using the Kaplan-Meier method to estimate survival functions, produce survival curves, and calculate median survival times with corresponding 95% confidence intervals.

Efficacy analysis:

Primary endpoint:

12-week ORR: The 12-week ORR is defined as the proportion of subjects who achieve a CR or PR among all evaluated subjects after 12 weeks of receiving the study regimen. The 12-week ORR will be evaluated in the FAS.

Secondary endpoints

Secondary endpoints included BOR, PFS, OS, DCR, DOR and safety. The secondary endpoints will be evaluated in the FAS.

BOR: BOR is defined as the proportion of participants who achieve a CR or PR as part of their best treatment assessment. The DCR and its 95% confidence intervals (CI) will be estimated using a binomial distribution.

PFS: PFS curves will be estimated using the Kaplan-Meier method, with the median PFS determined separately for each cohort. Standard errors will be calculated via Greenwood's formula, and two-sided 95 CIs for the median PFS will be computed for each cohort using the log-transformed Brookmeyer-Crowley approach.

OS: OS curves will be estimated using the Kaplan-Meier method, and the median OS will be determined for each cohort. Greenwood's formula will be applied to compute standard errors, while two-sided 95% CIs for the median OS time will be derived using the log-

	transformed Brookmeyer-Crowley method. **DCR:** DCR is defined as the proportion of participants achieving CR, PR, or SD. DCR will be calculated as (number of CR + PR + SD participants) / total number of participants * 100%. The DCR and its 95% CI will be estimated using a binomial distribution. **DOR:** DOR is defined as the time from the first documented response (CR or PR) to disease progression or death (whichever occurs first). The median DOR will be estimated using the Kaplan-Meier method, and a survival curve will be plotted. **Safety and tolerability:** Number of patients with AEs, SAEs, as well as the rate of treatment discontinuation due to AEs/SAEs will be reported. **Exploratory endpoint:** Conduct single-cell sequencing and multiplex immunofluorescence to explore potential predictive biomarkers of therapeutic efficacy.

2 SCHEDULE OF ACTIVITIES

Period	Screening Period	Treatment Period (Q2W)				Safety Follow-up [18]	Survival Follow-up [19]
		C1/D1	C2/D1	C3/D1	Cn/D1		
Days	-28~-1	1	15	29（n-1）+1		30 days post last dose	Every 60 days
Time Window (Days)	NA	+3	±3	±3	±3 days	±7 days	±7 days
General Study Procedure							
Informed consent form [1]	X						
Inclusion/Exclusion Criteria	X						
Patient Demographics (Age/Gender/Medical History/Prior anti-tumor therapies) [2]	X						
Prior and Concurrent Medications	X	X	X	X	X	X	
Vital Signs [3]	X	X	X	X	X	X	
Body Weight/Height [4]	X	X	X	X	X	X	
Physical Examination	X	X	X	X	X	X	
ECOG PS Score	X	X	X	X	X	X	
12-lead Electrocardiogram [5]	X		X	X	X	X	
Laboratory Assessments							
Complete Blood Count (CBC) [6]	X		X	X	X	X	
Blood Chemistry (including blood glucose, amylase, electrolytes, etc.)[6]	X		X	X	X	X	
Urinalysis [6]	X		X	X	X	X	
Coagulation Function [7]	X		X	X	X	X	

Pregnancy Test [8]	X						
Thyroid Function [9]	X		X	X	X	X	
Cardiac Enzyme Profile [9]	X		X	X	X		
Virology Antibody Testing (HIV, HBV, and HCV) [10]	X						
If HCV antibody is positive, test for HCV-RNA[11]	X		X	X	X	X	
If HBsAg and/or HBcAb are positive, test for HBV-DNA [12]	X		X	X	X	X	
Safety Monitoring and Survival							
Adverse Event Assessment[13]	X	X	X	X	X	X	X
Subsequent Anti-tumor Treatments							X
Survival Status							X
Efficacy Evaluation							
Tumor Imaging Assessment [14]	X			X	X	X	
Investigational Drug Administration [15]							
IBI318		X	X	X	X		
Lenvatinib		q.d.					

Biomarker Exploration							
Archived/Fresh Tumor Tissue [16]	X						
Whole Blood [17]		X		X	X	X	

Note:

1. Informed consent must be signed before performing any procedures specified in the protocol.
2. A complete history of all prior treatments for the tumor, including chemotherapy, radiotherapy, and surgical interventions, must be documented.
3. Vital signs, including body temperature, pulse, respiratory rate, and blood pressure, should be recorded.
4. Height should be measured during the screening period only. Weight should be measured before each treatment session. If the patient's weight fluctuates by less than 10% from the baseline weight (at the time of the first dose of the study treatment), the baseline weight will be used for chemotherapy dosage calculations. If the weight fluctuates by 10% or more, the actual weight on the treatment day will be used to calculate the dosage.
5. A 12-lead electrocardiogram (ECG) should be performed during the screening period, before each treatment cycle starting from cycle 2, and during the safety follow-up visits.
6. Complete blood count (CBC) should include RBC count, hemoglobin (HGB), hematocrit (HCT), WBC count, platelet count (PLT), and differential counts (lymphocytes, neutrophils, monocytes, eosinophils, basophils). Biochemistry tests should include liver function tests (TBIL, DBIL, ALT, AST, γ-GT, ALP, ALB, TP, LDH, CK), renal function tests (UREA, Cr), electrolytes (Na, K, Cl, Mg, Ca, P), amylase, and glucose. Urinalysis should include pH, urinary white blood cells (UWBC), urinary protein (UPRO), urinary red blood cells (URBC), urinary glucose (UGLU), and specific gravity. If proteinuria ≥2+ is detected during the screening period, a 24-hour urine protein quantification test is required. These tests should be conducted within 7 days before the first dose of the study treatment, at the start of each treatment cycle from cycle 2, and during the safety follow-up.
7. Coagulation function tests, including prothrombin time (PT) and international normalized ratio (INR), should be performed within 7 days before the first dose during the screening period, at the start of each treatment cycle from cycle 2, and during the safety follow-up.

8. Women of childbearing potential should undergo a urine or serum pregnancy test within 3 days before the first dose during the screening period. If the urine pregnancy test result is not definitively negative, a serum pregnancy test should be conducted, with the serum test result being definitive.
9. Thyroid function and cardiac enzyme tests should be performed within 28 days before the first dose, at the start of each treatment cycle from cycle 2, and during the safety follow-up.
10. Tests for HIV and HCV antibodies, as well as the hepatitis B panel (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb), should be completed within 28 days before the first dose.
11. HCV antibody testing should be performed during the screening visit. For patients who test positive for HCV antibodies, HCV-RNA levels should be measured every 3 weeks (21±7 days) starting from the first treatment day or earlier if clinically indicated.
12. The hepatitis B panel should be tested during the screening visit. For patients who test positive for HBsAg and/or HBcAb, HBV-DNA levels should be measured every 3 weeks (21±7 days) starting from the first treatment day or earlier if clinically indicated.
13. Adverse events (AEs) and laboratory safety assessments should be evaluated according to the CTCAE v5.0 criteria. The definition, recording, assessment of causality and severity, reporting timelines, and management of AEs and serious adverse events (SAEs) should follow the guidelines outlined in section 8 of the protocol.
14. Tumor assessments should include RECIST 1.1 evaluations. Tumor imaging studies typically involve contrast-enhanced CT or MRI, covering the chest, abdomen, head, and pelvis. A full-body bone scan should be performed at baseline. If there is lymphadenopathy in the neck, a contrast-enhanced CT of the neck should be included. PET/CT is acceptable for baseline assessment. If any abnormalities are detected, corresponding CT/MRI scans should be performed to facilitate follow-up assessments. The same imaging technique should be used consistently throughout the study for each patient. Baseline imaging assessments should be completed within 28 days before randomization. Tumor imaging evaluations should be conducted every 6 weeks (±7 days) from the first dose of the study treatment, and every 9 weeks (±7 days) after 24 weeks. If the investigator observes radiologic progression during the first RECIST 1.1 assessment, patients with stable clinical disease and no evidence of rapid radiologic progression may continue with the current study treatment and undergo a confirmatory imaging assessment at least 4 weeks later. If the subsequent evaluation confirms progressive disease (PD), the patient should discontinue study treatment. If PD is not confirmed, the patient should continue the study treatment, with follow-up imaging assessments at protocol-specified intervals until radiologic confirmation of PD. If the patient discontinues study treatment for reasons other than objective disease progression, an imaging assessment should be performed at the time of treatment discontinuation, with follow-up imaging assessments conducted at protocol-specified intervals until one of the following occurs: initiation of new anti-

tumor therapy, objective disease progression, loss to follow-up, death, or withdrawal of informed consent, whichever occurs first. If the patient exhibits clinical instability during the study, an unscheduled imaging assessment may be performed at any time. If the patient shows clinical instability after the first imaging evidence of PD, confirmation of PD after 4-6 weeks is not required, and the patient should discontinue the study treatment.

15. IBI318 will be administered intravenously at a dose of 300 mg on the first day of each cycle, with each cycle lasting 2 weeks (Q2W). Lenvatinib will be administered orally at a daily dose of 8 mg. Both treatments will continue until disease progression, death, unacceptable toxicity, withdrawal of consent, initiation of new anti-tumor therapy, or other protocol-specified reasons for discontinuation, with a maximum treatment duration of 2 years.
16. At the investigator's discretion, patients should provide 5-15 archived or fresh tumor tissue samples during the screening period that meet testing requirements. If clinically feasible, a biopsy is required upon radiologic evidence of disease progression.
17. At the investigator's discretion, patients should provide a 10 ml blood sample at the following time points for tumor biomarker analysis: before the first dose, before each imaging assessment during the treatment period and before the next treatment cycle, and upon confirmation of disease progression.
18. Safety follow-up should occur 30±7 days after the last dose or before the initiation of new anti-tumor therapy, whichever occurs first. All AEs occurring before the safety follow-up visit should be recorded until they resolve to grade 0-1, return to baseline levels, or the investigator determines that further follow-up is not required due to the AE being either non-reversible or improved. SAEs occurring within 90 days after the last dose or before the initiation of new anti-cancer therapy (whichever occurs first) should be followed and documented.
19. Survival follow-up should be conducted every 60 days (±7 days) after the safety visit and may be performed via telephone.

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3 Introduction: study background

3.1 Current treatment for lung cancer after resistance to immune checkpoint inhibitors

Lung cancer is the most common malignancy in China. According to data from the National Cancer Registry in 2016, lung cancer ranks first in incidence among male participants and second only to breast cancer among females.[2] The main types of lung cancer include non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).

Based on the World Health Organization (WHO) classification, lung cancer is divided into two major categories: SCLC and NSCLC. NSCLC accounts for 80%-85% of cases and includes three main subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.[2] Approximately 70% of patients with NSCLC are diagnosed at a locally advanced or metastatic stage, making them unsuitable for surgical resection. Additionally, a significant portion of patients who undergo surgery for early-stage NSCLC experience recurrence or distant metastasis, leading to advanced disease progression. A subset of patients with advanced NSCLC and positive driver gene mutations can receive targeted therapy. However, for those without driver mutations, recent advances in research have focused on immune checkpoint inhibitors (ICIs), which activate the immune system to attack tumor cells. The use of ICIs, such as anti-PD-1/PD-L1 antibodies, haveemerged as a new treatment option for advanced NSCLC patients without actionable driver gene mutations.

Keynote189 and Keynote407 studies have demonstrated that pembrolizumab combined with chemotherapy significantly improves progression-free survival (PFS) and overall survival (OS) in patients with advanced NSCLC. Keynote024 and Keynote042 showed that pembrolizumab monotherapy can improve survival in patients with high or positive PD-L1 expression. The Impower150 study revealed that atezolizumab combined with bevacizumab and platinum-based chemotherapy improves survival compared to bevacizumab and chemotherapy alone. Based on these findings, the Chinese Society of Clinical Oncology (CSCO) and National Comprehensive Cancer Network (NCCN) guidelines recommend ICIs (including anti-PD-1 and anti-PD-L1 antibodies) as monotherapy or in combination with chemotherapy for the first-line treatment of advanced NSCLC without actionable driver gene mutations.

Moreover, studies such as CheckMate017, CheckMate057, CheckMate078, and KEYNOTE-

010 confirmed that ICIs as the second-line treatment for advanced NSCLC improve survival compared to docetaxel.[3-5] The CSCO and NCCN guidelines now recommend ICIs monotherapy for the second-line treatment of patients without actionable driver gene mutations.

Despite the clear benefits of ICIs, resistance remains a challenge. Whether to continue using ICIs after resistance is a critical clinical question, especially since there is no established standard of care for the second-line treatment of these patients. Although current guidelines suggest ICIs or chemotherapy (e.g., docetaxel) as the treatment option for the second-line setting, the clinical trials that informed these recommendations involved patients who progressed after platinum-based chemotherapy in the first-line setting, and are not those who had received ICIs. Similarly, the clinical trials that investigated the clinical utility of chemotherapy as second-line treatment focused on patients who received platinum-based chemotherapy as first-line treatment, instead of ICIs. Consequently, there is a lack of evidence on the optimal second-line treatment for patients who develop resistance to ICIs after first-line therapy. Currently, chemotherapy agents like docetaxel remain the main second-line options, but their efficacy is limited, with median overall survival of around six months. This represents a significant unmet medical need.

The possibility of re-challenging the immune system after failure of first-line immunochemotherapy is a pressing question for clinicians. Currently, patients with advanced or metastatic NSCLC that lack actionable driver mutations and have progressed on PD-1/PD-L1 inhibitors are ineligible for existing IBI318 clinical trials. Therefore, Cohort A of this study aims to evaluate the efficacy and safety of the bispecific PD-1/PD-L1 antibody IBI318 in combination with lenvatinib as the second-line therapy in patients with advanced or metastatic NSCLC who have developed resistance to PD-1/PD-L1 inhibitors. This exploratory study has the potential to offer a novel therapeutic option for these patients, improving outcomes and quality of life.

3.2 Current status of treatment for advanced lung cancer with targeted therapy resistance in patients with driver gene mutations

Historically, the 5-year survival rate for patients with advanced NSCLC has been below 5%. However, the development of targeted therapies against common oncogenic drivers such as

epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), vascular endothelial growth factor (VEGF), Kirsten rat sarcoma viral oncogene (KRAS), and c-ros oncogene 1 (ROS-1) has significantly improved outcomes. As a result, the 5-year survival rate for patients who harbor actionable driver mutations has risen to 31.1%-75%.[6,7] Despite these advances, tumor progression and the inevitable development of acquired resistance to targeted therapies remain major challenges.

Once resistance develops, subsequent treatment options are limited. Historically, platinum-based doublet chemotherapy without or with bevacizumab have been the primary treatment options, though their efficacy is limited. Immunotherapy, particularly ICIs, has become a standard treatment for advanced NSCLC, and indications for the first-line use are now included in clinical practice guidelines. In September 2019, the World Conference on Lung Cancer (WCLC) presented updated 5-year survival data from the global phase III CheckMate 017/057 trials, showing that nivolumab extended overall survival (OS) fivefold compared to chemotherapy (13.4% vs. 2.6%, HR = 0.68, 95% CI: 0.59-0.78).[1]

Following the success of immunotherapy monotherapy, combination strategies involving immunotherapy with radiotherapy, chemotherapy, or dual immunotherapy have further improved patient outcomes. The integration of multiple therapies is becoming the dominant treatment trend in lung cancer. However, treatment responses vary between patients, and there is a growing focus on identifying patients who will benefit from immunotherapy through precision medicine approaches. Subgroup analyses in early studies suggested that patients with EGFR or ALK mutations derive limited benefit from immunotherapy monotherapy.[8,9] However, some studies indicate that certain patients with EGFR or ALK mutations may benefit from combination immunotherapy, offering new hope for these patients.[10-12] In the IMpower150 trial, patients with EGFR-activating mutations who received atezolizumab, bevacizumab, carboplatin, and paclitaxel (ABCP) had a median OS of 29.4 months compared to 18.1 months in the bevacizumab, carboplatin, and paclitaxel (BCP) group, a difference of 11.3 months (HR = 0.6, 95% CI: 0.31-1.14). However, the small number of enrolled patients (26 in the ABCP group and 32 in the BCP group) may have affected statistical power. In addition, the IMpower150 trial included 34 patients with EML4-ALK mutations (13 in the experimental group), showing extended PFS and OS in the experimental group compared to the control group

(PFS: 8.3 months vs. 6.8 months; OS: 9.7 months vs. 6.1 months).

It is worth noting that 57% of patients in the atezolizumab combination group experienced grade 3-4 adverse events, highlighting the need for careful risk-benefit assessment when considering this treatment approach. Moreover, due to the small number of mutation-positive patients, especially those with ALK mutations, the lack of an ALK-specific analysis raises some controversy regarding the results.

For patients with EGFR-activating mutations or ALK fusions who have developed resistance to EGFR-TKIs or ALK-TKIs, whether immunotherapy represents an optimal treatment option remains a pressing clinical question. Previously, patients with advanced or metastatic NSCLC who had developed resistance to EGFR-TKI/ALK-TKI therapy were not eligible for existing IBI318 clinical trials. Thus, cohort B of this study aims to evaluate the efficacy and safety of IBI318 in combination with lenvatinib in patients with advanced NSCLC harboring EGFR-activating mutations or ALK fusions who have developed resistance to EGFR-TKI/ALK-TKI therapy. This study may offer a new potential treatment option for patients with driver gene-positive NSCLC who have developed resistance to targeted therapy, ultimately improving patient outcomes and quality of life.

3.3 Current status of first-line treatment for PD-L1 negative advanced NSCLC

In recent years, ICIs have demonstrated significant anti-tumor efficacy in NSCLC. Clinical trials involving combination immunotherapy in treatment-naive patients, regardless of biomarker status, have shown superior outcomes compared to previous standard therapies, improving overall prognosis. Subgroup analyses across trials suggest that combination immunotherapy offers better outcomes than chemotherapy in patients with PD-L1 expression levels below 1%.

In non-squamous NSCLC, the efficacy of immunotherapy combined with chemotherapy has been well established. In the KEYNOTE-189 trial, patients with metastatic non-squamous NSCLC without EGFR or ALK mutations showed a significant improvement in OS, PFS, and response rates when treated with pembrolizumab combined with pemetrexed and platinum-based chemotherapy. Pembrolizumab provided survival benefits across all PD-L1 expression subgroups. In patients with PD-L1 expression <1%, pembrolizumab plus chemotherapy

significantly improved median PFS (HR 0.64) and OS (HR 0.52) compared to chemotherapy alone.

The IMpower130 trial evaluated atezolizumab in combination with chemotherapy for first-line treatment of EGFR/ALK wild-type, non-squamous NSCLC. The results showed a notable survival benefit for the combination therapy group, with a median OS of 18.5 months compared to 13.9 months in the chemotherapy group (HR 0.79, p=0.033). Median PFS was 7.0 months in the combination group versus 5.5 months in the chemotherapy group (HR 0.64, p<0.0001). Subgroup analysis based on PD-L1 expression levels demonstrated that PFS and OS in the combination group were significantly superior to those in the chemotherapy group across all subgroups.

Additionally, immunotherapy research involving locally developed agents is underway in China. At the 2019 WCLC, the results of the phase III Camel study were presented, which compared camrelizumab plus chemotherapy with chemotherapy alone in non-squamous NSCLC. The combination therapy group achieved a median PFS of 11.3 months, significantly longer than the 8.3 months in the chemotherapy group (HR 0.61, 95% CI 0.46-0.80, p = 0.0002, one-sided). Subgroup analysis showed that in patients with PD-L1 expression <1%, camrelizumab plus chemotherapy improved median PFS compared to chemotherapy alone (HR 0.74).

The results of the ORIENT-11 trial were released. This study demonstrated that first-line treatment with sintilimab plus chemotherapy significantly improved outcomes in patients with advanced or recurrent non-squamous NSCLC without EGFR mutations or ALK rearrangements compared to chemotherapy alone. Median PFS was 8.9 months in the combination group versus 5.0 months in the chemotherapy group (HR 0.482, 95% CI 0.362-0.643, p < 0.00001). Subgroup analysis indicated that in patients with PD-L1 expression <1%, sintilimab plus chemotherapy improved median PFS compared to chemotherapy alone (HR 0.664).[13]

The RATIONALE 304 study, presented at the 2020 European Society for Medical Oncology (ESMO), demonstrated that combining tislelizumab with chemotherapy significantly improved PFS compared to chemotherapy alone in patients with advanced non-squamous NSCLC (IRC assessment: P = 0.0044; HR = 0.645 [95% CI: 0.462, 0.902]; median PFS: 9.7 months vs. 7.6 months). The study also showed higher ORR and longer DoR. Subgroup analysis revealed that,

in patients with PD-L1 <1%, tislelizumab combined with chemotherapy improved median PFS compared to chemotherapy alone (HR 0.758).[14]

In squamous NSCLC, combination immunotherapy has also shown efficacy. In the KEYNOTE-407 study, pembrolizumab combined with carboplatin and taxane-based chemotherapy for first-line treatment of metastatic squamous NSCLC significantly improved OS (17.1 months vs. 11.6 months, HR 0.71) and PFS (8.0 months vs. 5.1 months, HR 0.57).[15] The ORR was also notably higher (62.6% vs. 38.4%, p = 0.0001). These survival benefits were observed across all PD-L1 expression levels.[15]

Positive results have also been reported from China's own research on ICIs. The RATIONALE 307 study, presented at the 2020 American Society of Clinical Oncology (ASCO) meeting, showed that tislelizumab combined with chemotherapy demonstrated strong anti-tumor activity and durable efficacy in patients with squamous NSCLC, with good tolerability.[16] Median PFS for both the tislelizumab plus chemotherapy arms (Arms A and B) was 7.6 months, significantly longer than the 5.5 months in the chemotherapy-only group, with HRs of 0.52 (P = 0.0001) and 0.48 (P < 0.0001), respectively. Subgroup analysis indicated that PFS improvement was independent of PD-L1 expression, with similar benefits across all PD-L1 subgroups.[16]

In dual immunotherapy, the CheckMate227 study investigated nivolumab combined with ipilimumab or chemotherapy as first-line treatment for NSCLC patients.[17] In patients with PD-L1 <1%, the dual immunotherapy combination significantly improved median OS compared to chemotherapy alone (17.2 months vs. 12.2 months, HR 0.62). One-year OS rates were 60% vs. 51%, and two-year OS rates were 40% vs. 23%, respectively.[17]

Regarding immunotherapy combined with anti-angiogenesis treatment, based on results from the IMpower150 study, in December 2018, the US FDA approved the use of the PD-L1 inhibitor atezolizumab (Tecentriq) in combination with bevacizumab, paclitaxel, and carboplatin as first-line therapy for metastatic non-squamous NSCLC without EGFR or ALK mutations. At the 2019 WCLC meeting, interim results from a phase I trial showed that sintilimab combined with anlotinib was safe and well tolerated as first-line treatment for patients with advanced NSCLC without EGFR/ALK/ROS1 mutations. The trial reported an impressive ORR of 72.7% and a disease control rate (DCR) of 100%.

In summary, combinations of immunotherapy with platinum-based doublet chemotherapy or

anti-angiogenic therapy have shown strong anti-tumor activity, regardless of PD-L1 expression status. However, such combinations often increase toxicity, and some patients decline chemotherapy in clinical practice. In PD-L1-positive patients, studies such as KEYNOTE-024 and KEYNOTE-042 have shown that single-agent immunotherapy can provide significant benefits. For patients with PD-L1 <1%, guidelines from NCCN and CSCO recommend combinations of immunotherapy with chemotherapy, or immunotherapy combined with chemotherapy and anti-angiogenesis therapy. Currently, there are no established combinations of immunotherapy and anti-angiogenesis therapy specifically for patients with PD-L1 <1%, and further investigation into different treatment regimens is warranted. Cohort C of this study aims to explore the efficacy and safety of IBI318, a bispecific PD-1/PD-L1 antibody, in combination with lenvatinib as the first-line treatment for advanced NSCLC (EGFR, ALK, and ROS1 wild-type) with PD-L1-negative expression.

3.4 IBI318

3.4.1 Mechanism of action of IBI318

IBI318 blocks the PD-1 and PD-L1/PD-L2 pathways via its anti-PD-1 and anti-PD-L1 heavy chains, as well as the PD-L1 and CD80 signaling pathway. By inhibiting all three interactions within the PD signaling axis, IBI318 restores T-cell activation, thereby enhancing the anti-tumor response. In the tumor microenvironment, IBI318 also bridges PD-L1-expressing tumor cells and PD-1-expressing T cells, forming immune synapses. This direct interaction facilitates T-cell activation in the tumor microenvironment, leading to a more effective and specific anti-tumor response.

3.4.2 Clinical study results of IBI318

Efficacy data for IBI318 is primarily from the phase Ia CIBI318A101 study, which is currently in its 1200 mg expansion phase. The CIBI318A101 trial is an open-label, multicenter, phase Ia/Ib study designed to evaluate the safety, tolerability, and preliminary efficacy of IBI318 in patients with advanced malignancies. The phase Ia part focuses on tolerability, safety, and PK/PD analysis.

As of July 7, 2020, a total of 50 participants were enrolled in the phase Ia study, with 48 receiving at least one dose of IBI318 and included in the full analysis set (FAS). Efficacy data is based on 40 participants from the FAS who underwent at least one post-treatment tumor assessment. According

to RECIST v1.1 (for solid tumors) and Lugano 2014 (for lymphomas) criteria, the ORR for the IBI318 Q2W treatment groups at 10 mg and 300 mg were 100% (1/1 patient) and 40% (2/5 patients), respectively. The DCR for the FAS population was 47.5% (19/40 patients). In the 600 mg dose group, 57.8% (11/19 patients) achieved DCR, with a median tumor shrinkage rate of 24% (range 21%–46%). The 600 mg dose demonstrated greater tumor target lesion shrinkage, preliminarily indicating the anti-tumor activity of IBI318.

Safety analysis was based on the 48 participants in the FAS, with all participants (100%) experiencing at least one treatment-emergent adverse event (TEAE). Grade 3 or higher treatment-related adverse events (TRAE) occurred in 10.4% (5/48) of participants. TRAE incidence was 77.1% (37/48), and 17 participants (35.4%) experienced treatment-emergent serious adverse events (TESAE), with 22.9% (11/48) of patients having grade 3 or higher TESAE. Three participants (6.2%) died due to TEAE, and 10 participants (20.8%) discontinued treatment due to TEAE. Immune-related adverse events (irAE) occurred in 25% (12/48) of participants, with 8.3% (4/48) experiencing grade 3 or higher irAEs, including three cases of immune-related hepatitis and one case of immune-related myocarditis. As of now, three patients have recovered or are improving, and one patient continues treatment (immune-related hepatitis and myocarditis). Grade 1-2 irAEs were seen in 8 participants (16.6%), including one case of myocarditis, which resolved after two weeks of steroid treatment. Two dose-limiting toxicity (DLT) events (4.2%) occurred in the 1200 mg dose group.

3.5 Lenvatinib

3.5.1 Mechanism of action of lenvatinib

Angiogenesis, the formation of new blood vessels from the existing vascular network, is critical for tumor growth and metastasis. The VEGF receptor family (VEGFRs 1-3) plays a major role in tumor angiogenesis.[18,19] There is increasing evidence that the FGF receptor tyrosine kinase family (FGFR) also plays a significant role in tumor angiogenesis.[20-22]

Lenvatinib is a potent multi-receptor tyrosine kinase (RTK) inhibitor, selectively inhibiting VEGFR1 (FLT1), VEGFR2 (KDR), VEGFR3 (FLT4), FGFR1-4, PDGFRα, KIT, and RET. Among clinically used kinase inhibitors, lenvatinib is one of the few that targets both VEGFR and FGFR, both of which are thought to be critical for tumor angiogenesis.

Lenvatinib inhibits the cellular free kinase activities of VEGFR1-3 and FGFR1-3, with Ki values of approximately 1 nmol/L and 8-22 nmol/L, respectively. In cell-based assays, lenvatinib inhibits VEGF- and FGF-induced tube formation in HUVEC cells, with IC50 values of 2.1 nmol/L and 7.3 nmol/L, respectively. In vivo studies have demonstrated significant anti-tumor activity across various xenograft models, including thyroid, renal cell, hepatocellular, melanoma, gastric, NSCLC, ovarian, Ewing sarcoma, and osteosarcoma models.

In summary, lenvatinib inhibits VEGF-driven VEGFR2 phosphorylation and prevents proliferation and tube formation in HUVEC models. It has shown robust anti-tumor activity in vivo across several animal xenograft models, suggesting that lenvatinib represents a novel anti-tumor therapy through angiogenesis inhibition, both as a monotherapy and in combination with other anti-tumor agents.

4 Study objectives and study endpoints

4.1 Study Objectives

This study aims to evaluate the efficacy and safety of the dual anti-PD-1/PD-L1 antibody IBI318 combined with lenvatinib, a chemotherapy-free approach, in various populations with advanced non-small cell lung cancer (NSCLC).

4.1.1 Primary Objectives

- **Cohort A:**

Evaluate the 12-week objective response rate (ORR) of IBI318 combined with lenvatinib in patients with advanced, driver gene-negative NSCLC who have failed first-line PD-1/PD-L1 therapies and have no other effective treatment options.

- **Cohort B:**

Evaluate the 12-week ORR of IBI318 combined with lenvatinib in patients with advanced NSCLC with EGFR-activating mutations or ALK fusions who have developed resistance to EGFR-TKI or ALK-TKI therapies.

- **Cohort C:**

Evaluate the ORR according to RECIST 1.1 criteria for IBI318 combined with lenvatinib as a first-line treatment in patients with PD-L1-negative advanced NSCLC (wild-type for EGFR, ALK, and ROS1).

4.1.2 Secondary Objectives

- Evaluate the best overall response (BOR).
- Evaluate the median progression-free survival (PFS).
- Evaluate overall survival (OS).
- Measure the disease control rate (DCR) based on RECIST v1.1 criteria.
- Evaluate the duration of response (DOR) according to RECIST v1.1 criteria.
- Assess the safety and tolerability of the combination of IBI318 and lenvatinib, including the incidence of adverse events (AEs) and serious adverse events (SAEs), as well as the rate of treatment discontinuation due to AEs/SAEs.

4.1.3 Exploratory Objectives

- Explore underlying mechanisms and identify potential biomarkers through single-cell

sequencing and multiplex immunofluorescence.

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

- **Cohort A:** 12-week objective response rate (ORR).
- **Cohort B:** 12-week ORR.
- **Cohort C:** objective response rate (ORR)

4.2.2 Secondary Study Endpoints

- Best overall response (BOR)
- Progression-free survival (PFS)
- Overall survival (OS)
- Disease control rate (DCR)
- Duration of response (DOR)
- Safety and tolerability: incidence of adverse events (AEs), serious adverse events (SAEs), and the rate of treatment discontinuation due to AEs/SAEs

4.2.3 Exploratory Study Endpoints

Investigate underlying mechanisms and identify biomarkers using single-cell sequencing, and multiplex immunofluorescence.

5 Study design

5.1 Overall Design

This is a prospective, multi-cohort clinical study. Cohort A will evaluate the efficacy and safety of IBI318 combined with lenvatinib in patients with advanced NSCLC who have failed first-line PD-1/PD-L1 inhibitor therapy. Cohort B will assess the efficacy and safety in patients with advanced NSCLC harboring *EGFR*-activating mutations or *ALK* fusions who have developed resistance to EGFR-TKI or ALK-TKI therapies. Cohort C will investigate the efficacy and safety of first-line treatment in patients with advanced NSCLC who are PD-L1-negative and wild-type for *EGFR*, *ALK*, and *ROS1*.

Eligible patients, once screened and enrolled, will receive IBI318 in combination with lenvatinib until disease progression, death, intolerable toxicity, withdrawal of consent, initiation of new anti-tumor therapy, or discontinuation due to other reasons specified in the protocol. Tumor response will be evaluated using RECIST v1.1 criteria every 6 weeks. After 24 weeks of treatment, assessments may be performed every 8 weeks.

For patients showing radiographic evidence of disease progression (PD) per RECIST v1.1, if their clinical condition is stable, without rapid radiographic progression, and if the investigator deems continued benefit from the treatment, patients may continue the current therapy. A follow-up imaging assessment, performed at least 6 weeks (±7 days) later, will confirm the PD status. If progression is confirmed, the patient should discontinue the study treatment. If progression is not confirmed, the patient may continue treatme0nt, with imaging evaluations continuing per protocol until radiographic confirmation of PD.

5.2 Rationale for dose selection

5.2.1 Rationale for IBI318 Dose Selection

A dose of 300 mg Q2W is proposed as the recommended regimen for phase Ib studies. This recommendation is based on a comprehensive analysis of phase I data, including safety, efficacy, and pharmacokinetics/receptor occupancy (PK/RO).

Preliminary Safety Data: Across a dose range of 0.3 to 600 mg, 29 patients received IBI318, with only one instance of a grade 3 or higher treatment-related adverse event. No dose-limiting toxicities

(DLTs) were observed (data cutoff: May 6, 2020).

Preliminary Efficacy: Tumor shrinkage of more than 20% was observed in 7 patients treated with doses ranging from 10 mg to 600 mg. Analysis of the relationship between drug concentration and target lesion response supports a target trough concentration of 7.23 μg/mL.

PK/RO Analysis: PK/RO and anti-drug antibody (ADA) data from 34 patients in the phase Ia dose range (0.3 to 1200 mg) indicate that a 300 mg Q2W dosing regimen is expected to maintain target trough concentrations above 7.23 μg/mL in ~ 90% of patients and achieve near-saturation of receptor occupancy. Additionally, the steady-state peak concentration for the 300 mg Q2W regimen is predicted to remain below the peak concentration observed with a single 600 mg dose.

5.2.2 Rationale for lenvatinib dose selection

The dose of lenvatinib was selected based on safety considerations and preliminary results from prior studies in non-small cell lung cancer. The lowest approved dose of 8 mg, from its current indications, was chosen.

6 Selection and withdrawal of subjects

6.1 Inclusion Criteria

Eligible subjects selected for this study must meet all of the following criteria:

1. Sign written informed consent before implementing any trial-related procedures;
2. Age ≥18 years old and ≤75 years old;
3. No limit on the gender;
4. **Cohort A:** Histological or cytological confirmed locally advanced (IIIB-IIIC) or metastatic (stage IV) NSCLC (International Association for the Study of Lung Cancer and Joint Committee on the American Classification of Cancer, TNM Lung cancer 8th edition) without EGFR gene activating mutations, ALK gene fusion or ROS1 gene fusion confirmed by histological specimens, relapse after failure of first-line anti-PD-1 /PD-L1 antibody therapy, as follows:

1) Only one anti-PD-1/PD-L1 antibody monotherapy or combination therapy is received in the advanced stage of the disease, and other immunotherapy is not allowed;

2) Previous anti-PD-1/L1 antibody monotherapy or combination therapy has the best curative effect (according to RECIST 1.1 criteria) as partial response, complete response, or stable disease for ≥6 months (defined as within 6 months from the first medication, no disease progression has occurred);

3) Disease progression confirmed by imaging studies occurred during or after the most recent treatment.

Cohort B: Histological or cytological confirmed locally advanced (IIIB-IIIC) or metastatic (stage IV) NSCLC (International Association for the Study of Lung Cancer and Joint Committee on the American Classification of Cancer, TNM Lung cancer 8th edition) with histologically confirmed EGFR-activating mutations or ALK fusion, relapse after failure of anti-EGFR-TKI or ALK-TKI therapy, as follows:

In patients with EGFR-TKI sensitizing mutations, the specific history of previous EGFR-TKI treatment can be one of the following:

1) There is no T790M mutation in 20 exon after the failure of previous the first or second generations of EGFR-TKI (including gefitinib, erlotinib, icotinib and afatinib);

2) The 20 exon T790M mutation occurred after the treatment failure of the first or second generation EGFR-TKI monotherapy (including gefitinib, erlotinib, icotinib, and afatinib, etc.), and

disease progression recurred after treatment with osimertinib or other third generation EGFR-TKI;

3) Failure of prior osimertinib or other third-generation EGFR-TKI therapy as the first-line therapy (regardless of EGFR T790M mutation status);

4) Those who are allowed to receive neoadjuvant/adjuvant targeted therapy in the early stage and develop drug resistance after subsequent adjuvant targeted therapy, and their drug resistance status meets one of the three requirements of appeal.

5) For patients with ALK fusion NSCLC, disease progression should occur after adequate ALK-TKI treatment, and there is no opportunity for subsequent targeted therapy.

Cohort C: Locally advanced NSCLC that is not suitable for radical surgery or radiotherapy, or that has relapsed without systematic treatment, or that has metastasized without systematic treatment and is negative PD-L1 expression. Patients who have previously received neoadjuvant or adjuvant therapy can also receive neoadjuvant or adjuvant therapy (but neoadjuvant or adjuvant therapy is chemotherapy/radiotherapy, not immunotherapy), and the end of neoadjuvant/adjuvant therapy should be ≥6 months after tumor progression; If the pathological type is adenocarcinoma, the absence of EGFR activating mutations or ALK fusion or ROS1 fusion should be confirmed. Negative expression of PD-L1 was defined as TPS <1% using 22C3 test.

5. According to the evaluation criteria for the efficacy of solid tumors (RECIST v1.1 version), there is at least one imaging measurable lesion. The lesions located in the radiation field of the previous radiotherapy can be regarded as measurable lesions if the progress is confirmed;

6. Subjects with brain metastases asymptomatic or with stable symptoms after local treatment are allowed to be included in the group, as long as the subjects meet the following conditions:

1) There are measurable lesions outside the central nervous system;

2) No symptoms of the central nervous system or no worsening of symptoms within at least 2 weeks;

3) No need for glucocorticoid therapy, or stop glucocorticoid therapy within 7 days before the first administration, or the dosage of glucocorticoid is stable and reduced to less than 10mg/day prednisone (or equivalent dose) within 7 days before the first administration;

7. Subjects are allowed to receive palliative radiotherapy (including craniocerebral radiotherapy for symptomatic brain metastases), but the radiotherapy must be completed at least 1 week before

enrollment, and the radiotherapy-related toxicity should be restored to less than or equal to 1 degree (CTCAE 5.0, except for hair loss).

8. ECOG score 0-1 points;

9. Expected survival time> 3 months;

10. Sufficient organ function, subjects need to meet the following laboratory indicators:

1) The absolute value of neutrophils (ANC) ≥1.5x109/L when no granulocyte colony-stimulating factor is used in the past 14 days;

2) In the case of no blood transfusion in the past 14 days, platelets ≥100×109/L;

3) In the past 14 days without blood transfusion or erythropoietin, hemoglobin>9g/dL;

4) Total bilirubin≤1.5×upper limit of normal (ULN);

5) Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) within ≤2.5×ULN (subjects with liver metastases are allowed to have ALT or AST ≤5×ULN);

6) Serum creatinine ≤1.5×ULN and creatinine clearance rate (calculated by Cockcroft-Gault formula) ≥50ml/min;

7) Good coagulation function, defined as international normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 times ULN;

8) Normal thyroid function is defined as thyroid-stimulating hormone (TSH) within the normal range. If the baseline TSH is out of the normal range, subjects whose total T3 (or FT3) and FT4 are within the normal range can also be included in the group;

9) Myocardial enzyme spectrum is within the normal range (for example, simple laboratory abnormalities that are judged by the investigator to be of no clinical significance are also allowed to be included in the group);

11. For female subjects of childbearing age, a urine or serum pregnancy test and the result should be negative within 3 days before receiving the first study drug administration (day 1 of cycle 1). If the urine pregnancy test result cannot be confirmed as negative, a blood pregnancy test is required. Women of non-bearing age are defined as at least 1 year after menopause, or have undergone surgical sterilization or hysterectomy;

12. If there is a risk of conception, all subjects (whether male or female) need to adopt a low annual failure rate during the entire treatment period until 120 days after the last study drug administration (or 180 days after the last study drug administration) less than 1% of contraceptive measures;

13. Blood pressure can be adequately controlled with or without anti-hypertensive medication, defined as blood pressure ≤ 150/ 90 mm Hg, and blood pressure was under stable control within 1 week before randomization.14.

14. Patients must have recovered from toxicity or complications if they have previously received surgery or radiation > 30Gy.15.

6.2 Criteria for subject withdrawal/discontinuation

Subjects who meet the following criteria cannot be selected for this study:

1. The pathology is small cell lung cancer (SCLC), including lung cancer mixed with SCLC and NSCLC;
2. There is imaging evidence of tumor voids, tumor inclusion or invasion of large vessels. In addition, the proximity of the tumor to the large blood duct should be considered and the risk of severe bleeding associated with tumor shrinkage/necrosis after lenvatinib treatment should be excluded. (The large vessels in the chest include the main pulmonary artery, left pulmonary artery, right pulmonary artery, 4 pulmonary veins, superior vena cava, inferior vena cava and aorta);

a) To cohort A: subjects who have previously used anti-PD-1, PD-L1 or other immunotherapy and meet the following conditions:

b) The toxicity that caused permanent discontinuation occurred before the termination of immunotherapy;

c) Prior to the administration of the study drug, the toxicity of the previous immunotherapy has not recovered or has not recovered to level 0-1. Asymptomatic and stable control of endocrine toxicity level 2 with appropriate replacement therapy is allowed to enter the group;

d) Adverse events that require additional immunosuppressive agents in addition to corticosteroids, or adverse events that still recur in the use of corticosteroids during previous immunotherapy.

3. To cohort B and C: Prior treatment: anti-PD-1, anti-PD-L1, or anti-PD-L2 drugs or drugs that target another stimulating or co-inhibiting T-cell receptor (including but not limited to CTLA-4, OX-40, CD137, etc.); Anti-pd-1, anti-PD-L1, or anti-PD-L2 drugs or drugs that target another stimulating or co-inhibiting T cell receptor (including but not limited to CTLA-4, OX-40, CD137, etc.);

4. Have received the following treatments:

1) Received systemic anti-tumor therapy within 2 weeks before treatment, such as chemotherapy, targeted therapy, immunotherapy (including Chinese herbal medicine with anti-tumor indications), etc.;

2) Previously received lenvatinib, bevacizumab, anlotinib monotherapy, or in combination with anti-PD-1 / PD-L1 drugs

3) Have received any investigational drug treatment within 4 weeks before treatment;

4) Received large doses of immunosuppressive drugs within 4 weeks before treatment (systemic glucocorticoid exceeding 10mg/day prednisone or its equivalent dose);

5) Received live attenuated vaccine within 4 weeks before treatment (or plan to receive live attenuated vaccine during the study period);

6) Have received major surgery (such as open cavity, thoracotomy, or Kaifu surgery), or unhealed surgical wounds, ulcers or fractures within 4 weeks before treatment.

5. Clinically significant cardiovascular damage occurred within 12 months of the first dose of study treatment.

6. Gastrointestinal diseases that may affect oral absorption of study drugs.

7. Prior gastrointestinal or grade ≥ 3 non-gastrointestinal fistula.

8. A history of other malignancies is known, and unless the participant has undergone potentially curative treatment, there is no evidence of disease recurrence in the 3 years since the start of that treatment.

9. Severe allergy to IBI318 and lenvatinib.

10. There is clinically uncontrollable pleural effusion/abdominal effusion (subjects who do not need to drain the effusion or stop drainage for 3 days without a significant increase in effusion can be included in the group);

11. Subjects who have received thoracic radiotherapy of greater than 30 Gy within 6 months before treatment or palliative radiotherapy of 30 Gy or less within 7 days before treatment (allowing palliative treatment of bone lesions or intracranial lesions, radiation therapy);

12. An active autoimmune disease that requires systemic treatment (such as the use of disease-relieving drugs, glucocorticoids, or immunosuppressive agents) occurred within 2 years before the first administration. Alternative therapies (such as thyroxine, insulin, or physiological

glucocorticoids for adrenal or pituitary insufficiency, etc.) are not considered systemic treatments;

13. Known allogeneic organ transplantation (except corneal transplantation) or allogeneic hematopoietic stem cell transplantation;

14. Before starting treatment, have not fully recovered from toxicity and/or complications caused by any intervention (ie, ≤ Grade 1 or reached baseline, excluding fatigue or hair loss);

15. Known history of human immunodeficiency virus (HIV) infection (ie HIV 1/2 antibody positive);

16. Untreated active hepatitis B (defined as HBsAg positive and the number of HBV-DNA copies detected at the same time is greater than the upper limit of the normal value of the laboratory department of the research center);

Note: Hepatitis B subjects who meet the following criteria can also be included in the group:

1) Before the first administration, the HBV viral load is less than 1000 copies/ml (200 IU/ml), and the subject should receive anti-HBV treatment during the entire study chemotherapy drug treatment to avoid viral reactivation;

2) For subjects with anti-HBc (+), HBsAg (-), anti-HBs (-) and HBV viral load (-), there is no need to receive preventive anti-HBV treatment, but close monitoring of virus reactivation is required.

17. Active HCV infected subjects (HCV antibody-positive and HCV-RNA level is higher than the lower limit of detection);

18. Live vaccines have been vaccinated within 30 days before the first administration (cycle 1, day 1); Note: It is allowed to receive inactivated virus vaccine for seasonal influenza injection within 30 days before the first administration; However, it is not allowed to receive live attenuated influenza vaccine for intranasal administration.

19. Pregnant or lactating women;

20. There are any serious or uncontrollable systemic diseases, such as:

1) The resting electrocardiogram has major abnormalities in rhythm, conduction or morphology that are severe and difficult to control, such as complete left bundle branch block, heart block above degree II, ventricular arrhythmia or atrial fibrillation;

2) Left ventricular ejection fraction (LVEF) was lower than normal;

3) QTc interval is extended to more than 480 ms；

4) Unstable angina pectoris, congestive heart failure, chronic heart failure of New York Heart Association (NYHA) grade ≥ 2;

5) Myocardial infarction occurred within 6 months before enrollment;

6) A history of non-infectious pneumonia requiring glucocorticoid treatment within 1 year before the first administration, or current clinically active interstitial lung disease;

7) Active tuberculosis;

8) There is an active or uncontrolled infection that requires systemic treatment;

9) There is clinically active diverticulitis, abdominal abscess, gastrointestinal obstruction;

10) Liver diseases such as liver cirrhosis, decompensated liver disease, acute or chronic active hepatitis;

11) Poor control of diabetes (fasting blood glucose [FBG] > 10mmol/L);

12) Urine routines suggest that urine protein is ≥ ++, and the 24-hour urine protein quantification is confirmed to be greater than 1.0 g;

13) Subjects who have mental disorders and cannot cooperate with treatment;

21. The medical history or disease evidence, abnormal treatment or laboratory test values that may interfere with the test results, prevent the subject from participating in the study, or the investigator believes that it is not suitable for inclusion this research.

6.3 Criteria for subject withdrawal/discontinuation

6.3.1 Discontinuation of study treatment

Discontinuing treatment does not mean withdrawal from the study. Since certain clinical data after treatment cessation may be crucial for the study, these data must still be collected until the participant's final scheduled visit, even if the treatment has stopped.

Participants may stop treatment at any time for any reason, or the investigator may decide to discontinue treatment due to adverse events. Additionally, treatment can be stopped if the participant is unsuitable for therapy, violates the protocol, or if management or safety concerns arise.

The following are mandatory reasons for discontinuing treatment, though participants may still be monitored within the study:

- The participant or their legal representative requests to stop treatment.
- The participant experiences an adverse event that requires treatment discontinuation.
- A new malignancy requiring active treatment is diagnosed.
- A comorbidity occurs that prevents further treatment.

- The investigator decides the participant should leave the study.
- A positive serum pregnancy test is returned.
- The participant shows poor adherence.
- The investigator believes that continuing treatment would pose an unnecessary risk to the participant based on their disease status or personal situation.
- For participants who stop treatment but remain in the study, all visits and procedures listed in the study schedule (Table 1) should be completed.

6.3.2 Withdrawal from the study

If the participant or their legal representative withdraws consent, the participant must leave the study. In this case, they will no longer receive treatment or attend scheduled visits. If the participant agrees, they may still be followed up for survival after withdrawal. Participants who are lost to follow-up must be considered withdrawn.

6.3.3 Clinical criteria for early study termination

The study will be terminated early if the following criteria are met:

- The quality or quantity of data is inaccurate or incomplete.
- There is poor adherence to the study protocol or regulatory requirements.
- The incidence or severity of adverse reactions in this or other studies suggests a risk to participant health.
- The development of the study drug is modified or halted.

In the event that the study drug is no longer provided, participants will be informed in advance to allow for appropriate adjustments to their treatment.

7 Investigational product

7.1 Treatment Regimen

In this study, the investigational drugs are defined as IBI318 and lenvatinib. Administration of the study drugs will begin on Day 1 of Cycle 1 following the pre-administration assessment. For each subsequent cycle, the study drugs will be administered on Day 1. For management reasons, based on the investigator's judgment, administration can occur within three days before or after the scheduled Day 1 of each cycle.

Treatment Regimen

Drug	Dose	Frequency	Route of Administration	Treatment Duration/Period
IBI318	300 mg	Q2W	Intravenous	Q2W, administered on Day 1, continued until disease progression or toxicity, for up to 2 years
Lenvatinib	8 mg	QD	Oral	Administered daily, until disease progression or toxicity, for up to 2 years

7.2 Administration of IBI318

7.2.1 Description of the Investigational Drug

The investigational drug is a recombinant fully human bispecific antibody targeting both programmed cell death receptor 1 (PD-1) and programmed cell death ligand 1 (PD-L1), with the research code IBI318. IBI318 is an injectable formulation, and its main active ingredient is the recombinant fully human bispecific antibody against PD-1 and PD-L1.

Excipients include: 0.85 mg/ml histidine, 1.00 mg/ml histidine hydrochloride, 30.00 mg/ml sorbitol, 7.49 mg/ml methionine, 21.07 mg/ml arginine hydrochloride, 0.20 mg/ml polysorbate 80, and pH adjusted to 6.0.

The drug is supplied as 100 mg (5 ml) per vial. It appears as a clear to slightly opalescent,

colorless to slightly yellow liquid, free from visible particles. Manufacturer: Innovent Biologics, Inc. (Suzhou).

7.2.2 Investigational drug labeling

The smallest packaging unit for IBI318 is a box, containing one vial of IBI318 injection. The box label includes the drug code, batch number, dosage, expiration date, storage conditions, main ingredients, and sponsor information. The vial label mirrors this information, except for the quantity, cautionary statements, and detailed ingredient list.

7.2.3 Storage of investigational drug

The current storage condition for IBI318 is between 2–8°C, protected from light, with a provisional shelf life of 24 months. This may be updated based on the results of long-term stability testing. If the solution shows signs of cloudiness, precipitation, or other quality issues, it should be quarantined, and the sponsor should be notified immediately. All labels on the boxes and vials clearly state, "For clinical trial use only.

7.2.4 Preparation and administration of the investigational drug

Eligible participants who meet the screening criteria will be admitted to the study center before administration. All baseline safety assessments must be completed prior to dosing.

On the day of administration, vital signs will be monitored, and the required blood samples will be collected as per the visit schedule before drug administration begins.

7.2.5 Preparation and infusion procedure for IBI318

The procedure for the preparation and infusion of IBI318 is as follows:

1) Withdraw 15 mL of IBI318 solution.
2) Discard 15 mL of sterile saline from a 0.9% sodium chloride intravenous (IV) infusion bag (a 100 mL saline bag is recommended; the final concentration of IBI318 should range between 1 mg/mL and 10 mg/mL).
3) Add the entire 15 mL of IBI318 solution into the saline bag in one single step (do not add in portions). Record the time of preparation.
4) Gently invert the bag to mix the solution and ensure homogeneity. Avoid vigorous shaking to prevent foam formation.
5) Administer the solution through an in-line filter (0.2–5 μm) within 90 minutes, but no less than 30 minutes. Record the start and end times of the infusion.

Notes:

1) Do not mix different batches of the drug during a single infusion.
2) Avoid vigorous shaking prior to preparation. Let the IBI318 solution sit at room temperature for approximately 5 minutes to ensure it is clear and free from cloudiness or precipitation.
3) Ensure that the time from the first needle puncture of the IBI318 vial to the end of infusion does not exceed 24 hours (store the prepared solution at 2–8°C).
4) Do not mix with other medications.
5) Avoid IV bolus injection.

7.2.6 IBI318 dose adjustments

7.2.6.1 General principles

In the event of adverse events (AEs) during the study, the investigator will first assess which drug is likely responsible and adjust the dosing based on the severity of the most serious adverse event that occurred in the previous treatment cycle. Prior to the administration of each cycle's Day 1 dose, the participant's hematological, liver, and kidney functions must meet the treatment requirements, and all other toxicities must have resolved to CTCAE Grade 0-1 or baseline levels (except for alopecia, fatigue, protocol-specified exceptions, or other conditions deemed clinically insignificant by the investigator).

All reasons for dose adjustments and related actions should be documented in the source medical records and case report forms. Any dose modifications should be recorded, including the reasons and actions taken.

In principle, dose adjustments of IBI318 are not allowed throughout the study.

The table below summarizes the general principles for temporarily or permanently discontinuing IBI318 due to immune-related adverse events (irAEs).

Immune-related Toxicity	**Severity**	**Principles for Temporary or Permanent Discontinuation**
Pulmonary Toxicity (Pneumonitis)	**Grade 1**	Continue unless imaging confirms disease progression.
	Grade 2	Temporarily discontinue until recovery to grade 1 or lower.

Immune-related Toxicity	Severity	Principles for Temporary or Permanent Discontinuation
	Grade 3-4	Permanently discontinue.
Endocrine Toxicity (Adrenal Insufficiency)	**Grade 2-4**	Temporarily discontinue until recovery to baseline levels.
Endocrine System Toxicity (Primary Hypothyroidism)	**Grade 1-4**	Consider temporary discontinuation until the patient is stabilized on hormone replacement therapy.
Hepatitis	**Grade 1-4**	Temporarily discontinue until the patient is stabilized on hormone replacement therapy.
Diabetes	**Grade 1**	No dosage adjustment required, but closely monitor.
	Grade 2-4	Temporarily discontinue until blood glucose levels are stabilized.
Musculoskeletal Toxicity (Inflammatory Arthritis)	**Grade 1**	No dosage adjustment required.
	Grade 2	Temporarily discontinue until symptoms are controlled with prednisone ≤10 mg/day.
	Grade 3-4	Temporarily discontinue. Once symptoms improve to grade 1, taper corticosteroids and decide whether to resume based on clinical assessment.
Myositis	**Grade 1**	No dosage adjustment required.
	Grade 2	Temporarily discontinue until creatine kinase (CK) levels normalize.
	Grade 3-4	Temporarily discontinue until resolved to grade 1. Permanently discontinue if there are signs of heart failure, arrhythmia, or other severe complications.
Immune System Toxicity (Stevens-Johnson Syndrome)	**Grade 1**	No dosage adjustment required.

Immune-related Toxicity	Severity	Principles for Temporary or Permanent Discontinuation
	Grade 2	Consider temporarily discontinuing until symptoms are controlled with prednisone ≤10 mg/day.
	Grade 3-4	Temporarily discontinue. Once resolved to grade 1, taper corticosteroids. Consult specialists to decide whether to resume treatment.
Renal Toxicity (Nephritis)	**Grade 1**	Temporarily discontinue, and evaluate other possible causes in combination with baseline renal function.
	Grade 2	Temporarily discontinue. Permanently discontinue if unresolved.
Nervous System Toxicity (Asymptomatic Neurotoxicity)	**Grade 1 (No symptoms)**	No dosage adjustment required.
	Grade 2	Temporarily discontinue until resolved to baseline.
Guillain-Barré Syndrome	**Grade 1 (No symptoms)**	Permanently discontinue.
Peripheral Neuropathy	**Grade 3-4**	Permanently discontinue after confirmation of the diagnosis within one week. Continued monitoring is required if symptoms persist.
	Grade 2	Temporarily discontinue until symptoms resolve to grade 1 or lower.
	Grade 3-4	Permanently discontinue.
Autonomic Neuropathy	**Grade 1**	Temporarily discontinue and monitor symptoms for 1 week; If symptoms persist, discontinue treatment.
	Grade 2	Temporarily discontinue until symptoms resolve to grade 1 or lower, closely monitor symptoms.

Immune-related Toxicity	Severity	Principles for Temporary or Permanent Discontinuation
	Grade 3-4	Permanently discontinue.
Aseptic Meningitis	**Grade 1-4**	Temporarily discontinue.
Encephalitis	**Grade 1-4**	Temporarily discontinue.
Transverse Myelitis	**Grade 1-4**	Permanently discontinue.
Myocarditis, Pericarditis, Arrhythmia, Heart Failure, Cardiomyopathy, and Vasculitis	**Grade 1**	Temporarily discontinue IBI318.
	Grade 2-4	Permanently discontinue IBI318.
Venous Thrombosis	**Grade 1-3**	No dose adjustment required.
	Grade 4	Permanently discontinue IBI318.
Ocular Toxicity		
Conjunctivitis, Blepharitis	**Grade 1**	No dose adjustment required.
	Grade 2	Temporarily discontinue IBI318 and consult an ophthalmologist.
	Grade 3-4	Permanently discontinue IBI318.
Keratitis	**Grade 1**	No dose adjustment required.
	Grade 2	Temporarily discontinue IBI318 and consult an ophthalmologist.
	Grade 3-4	Permanently discontinue IBI318.

7.2.6.2 Principles for managing irAEs

The mechanism of action of IBI318 involves its dual-targeted approach, utilizing its anti-PD-1 and anti-PD-L1 heavy chains to simultaneously block the PD-1/PD-L1/PD-L2 and PD-L1/CD80 signaling pathways. This blocks all three interactions within the PD axis, restoring T-cell activation and promoting antitumor effects. However, this T-cell proliferation and activation can potentially

result in autoimmune hyperactivity, leading to immune-related adverse events (irAEs) across multiple systems.

Immune checkpoint inhibitors such as Ipilimumab, Nivolumab, Pembrolizumab, and Atezolizumab have been associated with irAEs in clinical practice, including pneumonitis, diarrhea/colitis, renal impairment, rash, hepatitis, myocarditis, endocrine disorders, and peripheral or central neuropathies. If such irAEs occur in participants of this study, their symptoms and signs should be closely monitored, relevant diagnostic tests should be performed, and differential diagnoses should be considered.

If no alternative cause (e.g., disease progression, concomitant medications, or infections) is identified, and treatment with corticosteroids and/or other immunosuppressants is warranted (except for endocrine events such as hyperthyroidism/hypothyroidism, hypophysitis, type 1 diabetes, and adrenal insufficiency, which may not require immunosuppressive therapy but are still considered related to IBI318-induced autoimmune hyperactivity), these events should be considered as immune-related and classified as irAEs.

Guidelines for dose adjustments and toxicity management of potential irAEs are provided in the sponsor's "Management Manual for Immune-Related Adverse Events." Investigators are also required to remain vigilant in monitoring participants for any abnormal clinical signs during treatment to ensure early detection and timely intervention for irAEs.

For additional details, refer to the dose adjustment and toxicity management guidelines in the sponsor-provided manual.

7.2.6.3 Temporary discontinuation of IBI318

IBI318 administration should be temporarily discontinued in the event of the following immune-related toxicities:

Any grade 2 or higher treatment-related non-dermatologic adverse event, with the exception of:

1）Grade 2 treatment-related fatigue.

2）Laboratory abnormalities that do not require treatment discontinuation, as specified in the *Management Guidelines for Immune-Related Adverse Events*.

- Any grade 3 treatment-related dermatologic adverse event.
- Any grade 3 treatment-related laboratory abnormality, except in the following cases:

1) Grade 3 asymptomatic amylase abnormality unrelated to pancreatitis does not require

discontinuation of the study drug.

2) For baseline AST, ALT, or total bilirubin levels, the following criteria apply: a) If the participant's baseline AST, ALT, or total bilirubin levels are within the normal range, IBI318 should be discontinued for any treatment-related grade 2 or higher toxicity. b) If the participant's baseline AST, ALT, or total bilirubin levels are at grade 1 toxicity, IBI318 should be discontinued for any treatment-related grade 3 or higher toxicity.

- Any adverse event, laboratory abnormality, or complication that, in the investigator's judgment, warrants discontinuation of the study drug.

Additional criteria for discontinuation of IBI318 are outlined in Table 5 and the *Management Guidelines for Immune-Related Adverse Events* provided by the sponsor.

Note: The maximum allowable interruption of study drug administration is 12 weeks. If the participant does not recover to a condition allowing the resumption of IBI318 within 12 weeks, the study drug will be permanently discontinued, and the participant will enter the follow-up phase, with the exception of two cases.

7.2.6.4 Resumption of treatment

Treatment may be resumed when immune-related adverse events have resolved to grade 1 or below, or to baseline levels or the specified laboratory values from the screening period, with the following exceptions:

- Participants may resume treatment with grade 2 fatigue.
- Participants who have not experienced a grade 3 treatment-related dermatologic adverse event may resume treatment with grade 2 dermatologic toxicity.
- For participants with baseline AST/ALT or total bilirubin levels at grade 1, if treatment was paused due to a grade 2 event unrelated to AST/ALT or total bilirubin, treatment may be resumed when AST/ALT or total bilirubin levels are at grade 2.
- Participants with pulmonary toxicity, diarrhea, or colitis must return to baseline levels before resuming treatment.
- Treatment-related endocrine toxicity may be managed with hormone replacement therapy, after which treatment can be resumed.

For other criteria regarding treatment resumption, refer to the *Management Guidelines for Immune-Related Adverse Events* provided by the sponsor.

7.2.6.5 Permanent discontinuation of the study drug

The study drug will be permanently discontinued under the following circumstances:

- Any treatment-related grade 2 uveitis, eye pain, or blurred vision that is unresponsive to treatment or fails to resolve to grade 1 with further therapy, or that requires systemic treatment.
- Any non-dermatologic treatment-related grade 3 adverse event persisting for more than 7 days.
- Cardiac dysfunction suspected to be immune-related myocarditis, including:
  - Severe cases (e.g., arrhythmia, abnormal cardiac biomarkers, and echocardiogram findings, but with hemodynamic stability).
  - Life-threatening cases (e.g., malignant arrhythmias, severe cardiomyopathy, or hemodynamic instability).

The following treatment-related laboratory abnormalities also require permanent discontinuation of the study drug:

1. Treatment-related grade 3 thrombocytopenia persisting for more than 7 days or accompanied by bleeding.
2. Any treatment-related liver function abnormalities that meet one of the following criteria:
   - AST or ALT > 8× the upper limit of normal (ULN).
   - Total bilirubin > 5× ULN.
   - AST or ALT > 3× ULN with total bilirubin > 2× ULN.

Participants with concurrent grade 2 AST/ALT and bilirubin abnormalities who meet these criteria should also permanently discontinue the study drug.

- Any treatment-related grade 4 adverse event or laboratory abnormality, with the following exceptions: a) Grade 4 asymptomatic amylase abnormality not related to pancreatitis. b) Isolated grade 4 electrolyte abnormality without lasting effects, resolved with treatment within 72 hours.
- Temporary discontinuation of the study drug exceeding 12 weeks, except in the following cases: c) In cases where corticosteroid treatment for an adverse event (AE) prolongs study drug interruption beyond 12 weeks due to corticosteroid tapering, the decision to resume the study drug should be discussed with the sponsor's medical manager. Tumor imaging assessments will continue as scheduled, regardless of the study drug discontinuation. d) In cases where an AE unrelated to the study drug leads to more than 12 weeks of drug interruption, the decision to resume treatment should be discussed with the sponsor's medical manager. Tumor imaging assessments will continue as

scheduled, regardless of the study drug discontinuation.

- Any adverse event, laboratory abnormality, or complication that, in the investigator's judgment, poses a potential clinical risk to the participant, requiring discontinuation of the study drug.

Additional criteria for permanent discontinuation are detailed in the *Management Guidelines for Immune-Related Adverse Events* provided by the sponsor.

7.2.6.6 Management of infusion reactions

IBI318 contains only human immunoglobulin amino acid sequences, making it less likely to cause infusion reactions or hypersensitivity. However, if such reactions occur, they may manifest as fever, chills, headache, rash, pruritus, arthralgia, hypertension or hypotension, bronchospasm, and other symptoms. All grade 3 and 4 infusion reactions that meet the criteria for serious adverse events (SAEs) must be reported as SAEs within 24 hours. Infusion reactions should be graded according to the NCI CTCAE v5.0 criteria. Symptomatic treatment should be guided by the following recommendations or based on standard clinical practice:

- **Grade 1 symptoms (mild reaction)**: Infusion does not need to be paused. The infusion rate can be reduced by 50%, or the infusion can be temporarily stopped with bedside observation until symptoms resolve before resuming the infusion.
- **Grade 2 symptoms (moderate reaction)**: The infusion should be paused but can be resumed after symptomatic treatment (e.g., antihistamines, NSAIDs, analgesics, corticosteroids, bronchodilators, fluids). Consider adjusting the infusion rate to 50% during subsequent administrations.

If symptoms occur, stop the study drug infusion, begin an infusion of normal saline, and administer 50 mg diphenhydramine (or an equivalent) and/or 325–1000 mg acetaminophen. Bedside observation should continue until symptoms resolve. If necessary, corticosteroids or bronchodilators may be administered. If the infusion is paused, resume it at 50% of the previous infusion rate after symptoms disappear. If there are no further symptoms after 30 minutes, the infusion rate can be increased to 100%, with close monitoring. If symptoms recur, no further study drug should be administered that day, and 50 mg diphenhydramine IV should be given, with continued bedside observation until the symptoms resolve. The amount of study drug infused must be recorded in the eCRF. For future administrations, it is recommended to give prophylactic medications at least 30

minutes before infusion, including 50 mg diphenhydramine (or an equivalent) and/or 325–1000 mg acetaminophen. Corticosteroids (up to 25 mg hydrocortisone IV or an equivalent) can be administered if needed.

- **Grade 3–4 symptoms (severe reaction)**:
  - **Grade 3**: Symptoms are prolonged (do not resolve promptly with symptomatic treatment and/or a brief pause in infusion), recur after improvement, or hospitalization is required due to complications.
  - **Grade 4**: Life-threatening reaction requiring pressor or ventilatory support.

Immediately stop the study drug infusion. Begin an infusion of normal saline and treat as follows: recommend bronchodilators, epinephrine 0.2–1 mg (1:1000) subcutaneously or 0.1–0.25 mg (1:10,000) slow IV, and/or 50 mg diphenhydramine IV with 100 mg methylprednisolone (or equivalent). Continue to observe the participant until the investigator is confident that symptoms will not recur. The study drug must be permanently discontinued. Allergic reactions should be treated according to established guidelines. Continue bedside observation until symptoms resolve. If delayed hypersensitivity reactions occur (e.g., localized or systemic pruritus one week post-treatment), symptomatic treatment should be provided, such as oral antihistamines or corticosteroids.

7.2.6.7 Management of immunotherapy-related cardiovascular adverse events

For patients with immune-related myocarditis, both those with severe conditions (e.g., arrhythmia, elevated myocardial biomarkers, or echocardiographic abnormalities but stable hemodynamics) and those with life-threatening conditions (e.g., malignant arrhythmias, severe cardiomyopathy, or hemodynamic instability), immediate discontinuation of IBI318 therapy is required. Methylprednisolone at 1 g per day should be administered promptly as pulse therapy for 3–5 days, followed by a gradual taper once the condition begins to improve.

In life-threatening cases where there is no improvement within 24 hours after initiating methylprednisolone pulse therapy, additional treatments such as intravenous immunoglobulin (IVIG), antithymocyte globulin, or infliximab may be considered. In some cases, plasma exchange or other biologic agents targeting inflammatory factors may be warranted. For patients with persistent refractory heart failure, in addition to vasoactive medications, intra-aortic balloon pump (IABP) or extracorporeal membrane oxygenation (ECMO) support may be attempted.

For a detailed description of common immune-related cardiac adverse events and their management,

please refer to the guidelines outlined in "Clinical Diagnosis and Management of Immune Checkpoint Inhibitor-Related Cardiac Adverse Events" (**Chinese Journal of Lung Cancer, 2019 Oct 20; 22(10): 627–632).**

Other cancer treatments, including radiotherapy (except palliative radiotherapy), chemotherapy, immunotherapy, targeted therapy, and hormone therapy, are to be excluded.

The use of immunosuppressants and high-dose corticosteroids (i.e., doses exceeding 10 mg/day of prednisone or equivalent, except for the treatment of adverse events) should also be avoided.

Additionally, the administration of immunoglobulin (except for treating adverse events), live attenuated vaccines, and autologous hematopoietic stem cell transplantation are contraindicated.

7.3 Use of lenvatinib

7.3.1 Study Drug Description

Lenvatinib mesylate is supplied in capsule form, with a dosage strength of 4 mg, taken orally. It should be administered at a consistent time each day, either with or without food.

Manufacturer: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

7.3.2 Dose preparation

Lenvatinib is provided as an oral capsule and does not require preparation. If a dose of lenvatinib is missed and cannot be taken within 12 hours of the scheduled time, the participant should skip that dose and take the next scheduled dose at the usual time the following day.

7.3.3 Dose adjustments

Adverse events will be graded using the NCI CTCAE version 5.0. The investigator will assess the likelihood of the event being related to one or both drugs to determine whether dose adjustments are necessary.

If the dose is reduced to below 8 mg/day, consultation with the principal investigator is required. The minimum allowable dose of lenvatinib is 4 mg every other day, with no further reduction permitted. Doses below 4 mg/day in combination with IBI318 have not been studied. Once the lenvatinib dose is reduced, it cannot be increased again unless the reduction was made in error; in such cases, increasing the dose will require sponsor approval.

For the management of hypertension, proteinuria, diarrhea, hepatotoxicity, thromboembolic events, reversible posterior leukoencephalopathy syndrome (PRES/RPLS), hypocalcemia, hemorrhage, and

gastrointestinal perforation or fistula formation, please refer to the relevant sections and the dose adjustment table (Table below). Additionally, overlapping toxicities between pembrolizumab and lenvatinib/placebo should be reviewed.

Furthermore, lenvatinib may increase the risk of QTc prolongation, and caution is advised when administering the drug to participants with a resting heart rate of less than 50 bpm.

Lenvatinib or Placebo Dose Adjustment Guidelines for Related Adverse Events

Toxicity Type	Management	Dose Adjustment
Grade 1 or Tolerable Grade 2	Continue treatment	No dose adjustment
Intolerable Grade 2 or Grade 3	First occurrence: Temporarily discontinue lenvatinib or placebo treatment until recovery to grade 0–1 or tolerable grade 2	Reduce lenvatinib dose to 14 mg QD (reduce by 1 dose level)
	Second occurrence (same toxicity or new toxicity): Temporarily discontinue lenvatinib or placebo treatment until recovery to grade 0–1 or tolerable grade 2	Reduce lenvatinib dose to 10 mg QD (reduce by 1 dose level)
	Third occurrence (same toxicity or new toxicity): Temporarily discontinue lenvatinib or placebo treatment until recovery to grade 0–1 or tolerable grade 2	Reduce lenvatinib dose to 8 mg QD (reduce by 1 dose level)
	Fourth occurrence (same toxicity or new toxicity): Temporarily discontinue lenvatinib or placebo treatment	Permanently discontinue treatment

Grade 4: Permanently Discontinue Lenvatinib/Placebo Treatment

Abbreviations: AE = adverse event; BMI = body mass index; CTCAE = Common Terminology Criteria for Adverse Events.

Notes: For toxicity grading, refer to CTCAE version 4.0. All collected AEs should be graded (including both low and high CTCAE grades).

- If lenvatinib or placebo treatment is interrupted for more than 28 days, permission from the sponsor is required before restarting treatment.
- Before starting lenvatinib or placebo treatment, baseline assessments such as weight, blood pressure, thyroid function, and other relevant parameters should be performed.
- Only treat intolerable Grade 2 or higher adverse events.
- **Weight-based dose reductions**: Participants with a BMI below the normal threshold who require a 1 dose level reduction should maintain the reduced dose for at least 1 week until a stable BMI is achieved. For participants with stable BMI, they may resume treatment at the prior dose level.
- **Resuming treatment**: If the patient has stable weight/BMI for more than 1 week, and the relevant AE has resolved to Grade 1 or lower, treatment can resume. Participants who remain at a stable BMI for more than 1 week may resume treatment at their usual dose or reduced dose level.

7.3.4 Management of hypertension

Hypertension is a known side effect of VEGF signaling inhibition therapies. Investigators must ensure that participants enrolled in the lenvatinib/placebo treatment group have a blood pressure ≤150/90 mm Hg at study entry. If participants have a history of hypertension, they should be on a stable dose of antihypertensive medication for at least one week before starting Cycle 1, Day 1 (C1D1). Early detection and effective management of hypertension are crucial to minimizing the need for treatment interruptions and dose reductions of lenvatinib/placebo.

Blood pressure should be regularly monitored as outlined in the Schedule of Assessments (SoA) in Section 1.3. Hypertension will be graded using the NCI CTCAE Version 4.0, based solely on blood

pressure measurements, not the number of antihypertensive medications. If an initial elevated blood pressure reading is recorded (systolic ≥140 mm Hg or diastolic ≥90 mm Hg), it should be confirmed with a repeat measurement taken at least 5 minutes later.

A single blood pressure evaluation is defined as the average of two readings taken at least 5 minutes apart. If the average of these two measurements shows elevated blood pressure (systolic ≥140 mm Hg or diastolic ≥90 mm Hg), a confirmatory evaluation should be performed after at least 30 minutes, again averaging two readings taken at least 5 minutes apart.

Once elevated blood pressure is confirmed (systolic ≥140 mm Hg or diastolic ≥90 mm Hg) through two evaluations taken at least 30 minutes apart, antihypertensive treatment should be initiated promptly. The choice of antihypertensive therapy should be based on the participant's individual clinical situation, following standard medical practices. For participants with previously normal blood pressure, appropriate antihypertensive therapy should be started upon the first observation of systolic ≥140 mm Hg or diastolic ≥90 mm Hg, confirmed by two evaluations at least 30 minutes apart. For participants already receiving antihypertensive treatment, adjustments to their regimen may be required if hypertension persists.

In cases where participants face an urgent risk of hypertensive crisis or have significant risk factors for severe hypertension-related complications (e.g., BP ≥160/100 mm Hg, major cardiovascular risk factors, intracranial hemorrhage, or other severe comorbidities), lenvatinib/placebo should be temporarily discontinued. Once the participant has been on a stable dose of antihypertensive medication for at least 48 hours and their blood pressure is controlled, lenvatinib/placebo treatment may be resumed according to the protocol.

Note: Participants with systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg must have their blood pressure monitored on Day 15 of the current cycle (or more frequently, as clinically indicated) until systolic BP is ≤150 mm Hg and diastolic BP is ≤95 mm Hg for two consecutive cycles. If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg recurs, participants must undergo reassessment on Day 15 until two consecutive cycles show systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg.

In certain cases, participants may opt for local blood pressure monitoring by healthcare professionals between study visits. Participants will be provided with a diary to record blood pressure measurements between visits, and they will bring these records to each visit. Blood pressure data will be documented in the participant’s chart and eCRF.

For managing systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg confirmed by two evaluations at least 30 minutes apart, the following guidelines should be followed:

- For participants not yet receiving antihypertensive treatment, lenvatinib/placebo may be continued, and antihypertensive therapy should be initiated.
- For participants already on antihypertensive therapy, current medication doses may be increased, or one or more additional antihypertensive agents from different classes should be added. The study intervention may continue without lenvatinib dose adjustment.
- If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg persists despite maximum antihypertensive treatment, lenvatinib/placebo should be temporarily discontinued. Treatment may only be resumed at a reduced dose level once systolic BP is ≤150 mm Hg and diastolic BP is ≤95 mm Hg, with the participant on a stable dose of antihypertensive medication for at least 48 hours.
- If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg recurs despite optimal management with antihypertensive medications during the first lenvatinib/placebo dose reduction, lenvatinib/placebo should be temporarily discontinued. Treatment may be resumed at a further reduced dose level only after systolic BP is ≤150 mm Hg and diastolic BP is ≤95 mm Hg, with the participant on stable antihypertensive therapy for at least 48 hours.
- If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg recurs after the second lenvatinib/placebo dose reduction, lenvatinib/placebo should again be temporarily discontinued. Treatment may only be resumed at a further reduced dose level after systolic BP is ≤150 mm Hg and diastolic BP is ≤95 mm Hg, with the participant on stable antihypertensive therapy for at least 48 hours. If further dose reductions are required, consultation with the sponsor is necessary.

For the management of Grade 4 hypertension (life-threatening consequences), the following guidelines apply:

- Initiate appropriate medical treatment.
- Discontinue lenvatinib treatment permanently.

7.3.5 Management of proteinuria

Proteinuria should be regularly monitored as specified in the Schedule of Assessments (SoA) in Section 1.3. The following guidelines outline the detection and management of proteinuria:

Detection and Confirmation

On Day 1, a dipstick assessment and urinalysis should be performed according to the SoA.

Note: A 24-hour urine collection (or a random urine protein/creatinine ratio [UPCR] test) should be initiated as soon as possible and within 72 hours in the following situations:

- The participant presents with ≥2+ proteinuria for the first time during urinalysis while receiving lenvatinib/placebo.
- The severity of proteinuria increases during subsequent urinalyses at the same lenvatinib/placebo dose level.
- ≥2+ proteinuria occurs during urinalysis after a lenvatinib/placebo dose reduction.

If the UPCR is ≥2.4, a 24-hour urine collection should be performed (as soon as possible and within 72 hours) to confirm the proteinuria grade.

Proteinuria will be graded according to the NCI CTCAE Version 4.0, based on 24-hour urine protein results (if available). The management of lenvatinib/placebo dosing will follow the proteinuria grading in Table 3.

Monitoring

For participants with ≥2+ proteinuria on Day 1 of any cycle, a dipstick test (performed locally) or urinalysis (performed locally) should be conducted on Day 15 (or more frequently, if clinically indicated) until the results show 1+ or negative for two consecutive treatment cycles (see Section 8.3.5.2 for more details).

Proteinuria monitoring may be conducted by local laboratories or at the study center; however, management must be overseen by the study center physician.

If nephrotic syndrome occurs, lenvatinib treatment must be permanently discontinued.

7.3.6 Management of diarrhea

Participants should be advised to have antidiarrheal medications available when beginning the study intervention. They should be instructed and educated to start antidiarrheal treatment at the first sign of loose stools. The choice of antidiarrheal medication should be based on the participant's individual clinical condition and should follow standard medical practice. If diarrhea symptoms persist despite optimal management, follow the guidance in Table 3.

Electrolyte imbalances, such as hypomagnesemia, hypocalcemia, and hypokalemia, caused by diarrhea and related adverse events should be corrected according to institutional guidelines

throughout the study, including the screening period.

7.3.7 Management of hepatotoxicity

Liver function tests (ALT, AST, and bilirubin) should be performed as outlined in the SoA (Section 1.3) and as clinically indicated. If signs or symptoms of liver injury occur, management should follow the guidance in Table 3. Appropriate supportive care and close monitoring should be provided. If liver failure develops, lenvatinib must be discontinued.

7.3.8 Management of thromboembolic events

Participants should be advised to watch for symptoms of venous thromboembolism, including sudden shortness of breath, difficulty breathing, chest pain, coughing, coughing up blood, rapid breathing, tachycardia, cyanosis, or signs of deep vein thrombosis (leg swelling, warmth, or tenderness). If any of these symptoms occur, participants should be instructed to report them to the investigator immediately. If a thromboembolic event is confirmed, follow the instructions in Table 3 for management. Appropriate supportive care and close monitoring should be provided. If a participant experiences a grade 3 or 4 thromboembolic event, including pulmonary embolism, lenvatinib/placebo must be discontinued. Arterial thromboembolic events of any grade (e.g., new or worsening unstable angina, myocardial infarction, transient ischemic attack, or stroke) require discontinuation of lenvatinib/placebo treatment.

7.3.9 Management of Posterior Reversible Encephalopathy Syndrome (PRES)/Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

PRES/RPLS is a neurological disorder that may present with headaches, seizures, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Hypertension may be mild to severe. An MRI scan is needed to confirm the diagnosis of PRES/RPLS. Appropriate measures to control blood pressure should be taken. For participants with signs or symptoms of PRES/RPLS, follow the guidance in Table 3 for management.

7.3.10 Management of hypocalcemia

Serum calcium levels should be monitored according to the SoA (Section 1.3). Corrected serum calcium levels should be calculated using the following formula:

Corrected calcium = ([4 - serum albumin (g/dL)] × 0.8 + serum calcium).

Hypocalcemia should be graded according to NCI CTCAE Version 4.0. If the serum albumin level is normal (>4 g/dL), this formula does not apply, and total (uncorrected) serum calcium should be

used instead.

Hypocalcemia should be treated according to institutional guidelines (e.g., appropriate calcium, magnesium, and vitamin D supplementation) until resolution.

7.3.11 Management of bleeding

Bleeding events should be managed according to the guidance in Table 3. Based on the severity and persistence of bleeding, lenvatinib/placebo treatment should be resumed at a reduced dose or discontinued.

7.3.12 Management of gastrointestinal perforation or fistula formation

Participants who develop gastrointestinal perforation or life-threatening gastrointestinal fistula must discontinue lenvatinib treatment.

7.4 Prohibited treatments

The following treatments are prohibited during the study:

- Radiotherapy (except for palliative radiotherapy), chemotherapy, immunotherapy, targeted therapy, and hormone therapy for cancer.
- Immunosuppressants and high-dose corticosteroids (defined as doses exceeding 10 mg/day of prednisone or equivalent corticosteroids, unless used to treat adverse events).
- Immunoglobulins (unless used to treat adverse events).
- Live attenuated vaccines.
- Autologous hematopoietic stem cell transplantation.

7.5 Permitted treatments

The following treatments are permitted:

- Medications deemed appropriate by the investigator, in accordance with the study protocol (e.g., medications used to treat symptoms related to the disease or to manage various adverse events).
- Participants who require long-term treatment for underlying conditions such as hypertension or diabetes may continue these medications.
- Supportive care to alleviate tumor-related symptoms is allowed.
- The use of topical corticosteroids, such as creams for the skin, eye drops, nasal sprays, or

inhalers, is permitted.

7.6 Drug interactions

There is currently no available data regarding drug interactions with IBI318.

8 Management of study drugs

8.1 Storage and handling of study drugs

IBI318 must be stored at 2–8°C, protected from light, with a shelf life of 24 months. It should be transported to each research center via a cold chain. Lenvatinib must be stored at temperatures not exceeding 30°C. Designated personnel are responsible for the storage and distribution of the study drugs.

Each research center must ensure that a dedicated individual is responsible for receiving the study drugs, maintaining accurate distribution records, and ensuring the proper use and storage of the study medication. Unused drugs should be stored according to the required conditions, with regular checks by assigned staff to ensure compliance with storage guidelines. Upon study completion, unused drugs must be collected, documented, and processed according to Good Clinical Practice (GCP) requirements. All study drugs provided by the sponsor are intended exclusively for use in this study and may not be used for purposes outside the study protocol. Investigators must commit to not providing the study drugs to any unauthorized individuals not involved in the study.

8.2 Drug retrieval and disposal

In this study, used or partially used drug containers, bottles, infusion bags, and syringes may be disposed of on-site according to applicable guidelines and standard operating procedures established by the research center or local institutions.

All unused study drugs must be retrieved and returned to the sponsor for destruction upon study completion/termination or expiration of the drugs' shelf life. The sponsor-appointed clinical monitor will arrange the retrieval of study drugs.

8.3 Drug accountability records

Designated personnel at each research center must maintain detailed records of drug receipt, distribution, usage, inventory, disposal, retrieval, and destruction, in accordance with applicable regulations, guidelines, and the operational procedures of this trial.

9 Study procedures

9.1 Subject screening process

9.1.1 Subject screening

The investigator will enroll subjects following these steps:

1. Obtain informed consent from the participant before conducting any study-related procedures.
2. The principal investigator or a designated individual, who has received appropriate training, will review the inclusion/exclusion criteria to formally confirm the participant's eligibility for the study.

9.1.2 Procedure for handling incorrectly enrolled participants

Strict adherence to the inclusion and exclusion criteria is required. If a participant who does not meet the eligibility criteria is enrolled, the investigator must discuss with the sponsor to determine whether the participant should continue in the study. If the investigator deems it medically appropriate for the participant to continue in the study, and the sponsor agrees with this decision, the participant may remain in the study and receive the study treatment. If the investigator believes it is medically appropriate for the participant to continue but the sponsor disagrees, the participant must be withdrawn from the study. The investigator may only allow the incorrectly enrolled participant to continue in the study after receiving written approval from the sponsor.

10 Study procedures

10.1 Screening period

10.1.1 Subject screening

The investigator will enroll subjects according to the following steps:

1. Obtain the participant's signed informed consent before performing any study-related procedures.
2. The principal investigator or a trained, designated individual will review the inclusion/exclusion criteria to formally confirm the participant's eligibility.

10.1.2 Procedure for handling ineligible enrolled participants

Strict adherence to the inclusion and exclusion criteria is essential. If a participant is enrolled who does not meet the eligibility criteria, the investigator must discuss with the sponsor whether the participant should continue in the study. If the investigator determines that continuing the participant in the study is medically appropriate, and the sponsor agrees, the participant may remain in the study and receive the investigational drug. If the investigator believes the participant should continue, but the sponsor does not agree, the participant must be withdrawn from the study. The investigator may only allow the ineligible participant to continue after receiving written approval from the sponsor.

10.2 Study schedule and timelines

10.2.1 Screening period

The following study procedures must be completed during the screening period (Day -28 to Day -1) to ensure the participant's eligibility:

- Obtain informed consent
- Confirm inclusion/exclusion criteria
- Record demographic data, medical history, and prior lung cancer treatments
- Document prior and concomitant medications
- Record vital signs, height, and weight
- Conduct a physical examination
- Assess ECOG Performance Status (PS)

- Perform a 12-lead electrocardiogram (ECG)
- Complete blood count, blood chemistry, and urinalysis (within 7 days prior to first dose)
- Coagulation tests (within 7 days prior to first dose)
- Pregnancy test (within 3 days prior to first dose)
- Thyroid function tests (within 28 days prior to first dose)
- Cardiac enzyme panel (within 28 days prior to first dose)
- Virology testing for antibodies: HIV, Hepatitis B panel (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb), and Hepatitis C (within 28 days prior to first dose)
- HBV-DNA and HCV-RNA testing (if applicable) (within 28 days prior to first dose)
- Adverse event assessment
- Concomitant medications
- Tumor imaging (within 28 days prior to first dose)
- Archived or fresh tumor tissue samples

10.2.2 Treatment period visits

During the treatment period, the following procedures must be completed:

- Record vital signs and weight
- Assess ECOG Performance Status (PS)
- Perform a 12-lead electrocardiogram (ECG)
- Complete blood count, blood chemistry, and urinalysis
- Thyroid function tests
- Cardiac enzyme panel
- HBV-DNA and/or HCV-RNA testing (if applicable)

10.2.3 Safety follow-up

A safety follow-up visit will be conducted 30 days (±7 days) after the last administration of the study drug or before the initiation of any new anti-tumor treatment, whichever occurs first. This visit will include the following assessments:

- Recording of vital signs
- Body weight
- Physical examination
- ECOG Performance Status (PS)

- 12-lead electrocardiogram (ECG)
- Complete blood count, blood chemistry, and urinalysis
- Coagulation tests
- Thyroid function tests
- Cardiac enzyme panel
- HBV-DNA and/or HCV-RNA testing (if applicable)
- Adverse event assessment
- Documentation of any subsequent anti-tumor treatments (if applicable)

All adverse events occurring before the safety follow-up visit should be recorded until they resolve to Grade 0–1 or baseline levels, or until the investigator deems that no further follow-up is necessary for reasonable medical reasons (e.g., the event is not expected to resolve or has already improved).

10.2.4 Survival follow-up

After the safety follow-up, participants will enter survival follow-up. Every 90 days (±7 days), participants will be contacted (phone contact is acceptable) to gather information on survival and any subsequent systemic anti-tumor treatments. For participants who discontinue study drug treatment for reasons other than disease progression, efforts should be made to collect information related to disease progression. Long-term follow-up will continue until the participant's death or the end of the study.

Note: If a participant does not undergo the 30-day safety follow-up visit, the survival follow-up should be calculated from the date of treatment discontinuation.

10.2.5 Follow-up on subsequent anti-tumor treatments

The investigator or a qualified designee will review all new anti-tumor treatments initiated after the last dose of study medication. If the participant begins a new anti-cancer treatment within 30 days of the last study dose, the safety follow-up visit must be conducted before the first dose of the new treatment. After initiating new anti-cancer therapy, the participant will enter survival follow-up.

10.3 Additional procedures

10.3.1 Discontinuation of treatment/withdrawal from study

Participants who discontinue treatment or withdraw from the study before completing the protocol-specified treatment should be encouraged to continue follow-up and complete all remaining study visits.

At the time of treatment discontinuation or withdrawal, all procedures applicable to treatment completion should be conducted. Any ongoing adverse events at the time of discontinuation or withdrawal should be followed up according to the safety requirements outlined in Section 9.4 (Adverse Event Reporting). If the participant discontinues for reasons other than disease progression, an imaging assessment should be performed at the end of treatment.

10.3.2 Lost to Follow-up

If a participant fails to return to the clinic for required study visits and/or the study site cannot contact the participant, the following steps should be taken:

- The study site must attempt to contact the participant and reschedule the missed visit. If contact is made, the participant should be reminded of the importance of adhering to the scheduled visit plan.
- For each missed visit, the investigator or designated personnel must make every effort to re-establish contact with the participant (e.g., by phone or sending a registered letter to the participant's last known address, or using an equivalent local method). All contact attempts should be documented in the participant's medical records.
- Note: A participant is not considered lost to follow-up until they have missed their final scheduled visit. The amount of missing data for the participant should be managed according to the pre-specified data handling and analysis guidelines.

11 Study assessments

11.1 Efficacy assessments

11.1.1 Tumor imaging and disease assessment

The first tumor imaging assessment during screening must be completed within 28 days prior to the initiation of treatment. Imaging performed as part of routine clinical care may be used for screening if it meets diagnostic quality standards and was conducted within the 28 days before treatment initiation.

The imaging modality used at baseline for tumor burden assessment (CT/MRI) must be consistent with the methods used for all subsequent follow-up assessments. Additional imaging may be performed to evaluate other suspected areas of involvement (e.g., the brain) based on clinical signs and symptoms. PET/CT may be used as a screening method at baseline, and further evaluation is required if abnormalities are detected.

11.1.2 Baseline tumor imaging assessment

The first tumor imaging during the screening period must be completed within 28 days prior to the initiation of treatment. Before treatment begins, the investigator must confirm that the participant has measurable disease in accordance with RECIST 1.1 criteria.

Imaging performed as part of routine clinical care may be used for baseline assessment if it meets diagnostic quality standards and was conducted within 28 days prior to treatment. The method used to assess tumor burden at baseline (CT/MRI) must be used consistently throughout the follow-up assessments. Additional imaging may be conducted based on clinical symptoms or signs to evaluate other suspected areas (e.g., the brain). CT/MRI monitoring will facilitate future assessments.

11.1.3 Tumor imaging assessments during the study

Imaging assessments should be conducted according to the protocol-specified schedule whenever possible. Starting from the first dose, tumor imaging assessments should be performed every 6 weeks (±7 days) for the first 24 weeks, and every 8 weeks (±7 days) thereafter.

For participants showing radiographic evidence of disease progression (PD) based on RECIST 1.1 during initial assessments, if clinical disease is stable, there is no evidence of rapid

radiographic progression, and the investigator believes the participant may still benefit from the study treatment, the participant may continue treatment. In such cases, a follow-up imaging assessment must be performed at least 6 weeks (±7 days) later to confirm PD. If PD is confirmed, the participant should discontinue study treatment; If PD is not confirmed, the participant may continue treatment and be evaluated according to the scheduled imaging assessment intervals until PD is confirmed.

If, after the first radiographic evidence of PD, the participant's clinical condition is unstable, there is no need to wait 6 weeks for confirmation of progression, and study treatment should be discontinued immediately.

According to iRECIST (2017), if follow-up tumor re-evaluation is performed after initial radiographic PD, the tumor burden should be compared with the initial PD findings. Disease progression is confirmed if any of the following criteria are met:

- The sum of the longest diameters of target lesions increases by more than 5 mm
- Non-target lesions show further progression
- New lesions appear, and the sum of their longest diameters increases by more than 5 mm (for target lesions) or further progression is observed (for non-target lesions)
- Additional new lesions appear

If clinical instability occurs during the study, unscheduled imaging assessments may be conducted at any time. Clinical instability is defined as:

- Significant symptoms or signs suggestive of disease progression (including worsening laboratory values)
- Decline in ECOG PS score
- Rapid disease progression
- Tumor progression in critical anatomical locations requiring urgent medical intervention (e.g., spinal cord compression)

For participants discontinuing treatment for reasons other than objective disease progression, an imaging assessment should be performed at the time of treatment discontinuation. Subsequent imaging assessments should continue according to the protocol-specified schedule until any of the following occurs: initiation of new anti-tumor treatment, objective disease progression, loss to follow-up, death, or withdrawal of informed consent (ICF), whichever

comes first.

If clinical instability occurs after the first radiographic PD, confirmation of progression is not required 4-6 weeks later, and study treatment should be discontinued.

For participants who discontinue treatment for reasons other than radiographic disease progression, an imaging assessment should be performed at the time of treatment discontinuation, followed by scheduled imaging assessments until one of the following occurs: initiation of new anti-tumor treatment, objective disease progression, withdrawal of ICF, loss to follow-up, or death.

Participants known or suspected to have brain metastases at screening must undergo baseline brain CT/MRI prior to starting study treatment. During the study, these participants should undergo regular brain CT/MRI evaluations, and brain metastases will be evaluated as non-target lesions.

If the investigator is uncertain about disease progression, particularly in the case of non-target or new lesions, the participant may continue treatment until clinical symptoms arise or until the next scheduled imaging assessment, at which time disease progression can be reassessed. If progression is confirmed, the date of progression should be recorded as the date of the initial finding.

Tumor imaging assessments for this study will be conducted based on RECIST 1.1 criteria, as detailed in **Appendix 3**.

11.1.4 Tumor imaging at end of treatment and during follow-up

For participants who complete treatment or discontinue treatment for reasons other than disease progression, a tumor imaging assessment should be performed at the time of treatment completion or discontinuation. Subsequent imaging assessments should continue according to the protocol-specified schedule until one of the following occurs: initiation of new anti-tumor treatment, objective disease progression, death, or the end of the study, whichever comes first.

11.2 Safety assessments

The investigator or a qualified designee will assess adverse events (AEs) for each participant during the study and follow-up periods according to the study schedule. Adverse events will be graded and recorded based on the NCI CTCAE (version 5.0). The characteristics of each AE

will be determined by its severity, causality, toxicity grade, and the actions taken regarding the study treatment.

All AEs of unknown etiology occurring during the study treatment should be evaluated to determine if they are immune-related adverse events (irAEs).

11.2.1 Physical examination

11.2.1.1Comprehensive physical examination

A comprehensive physical examination will be conducted by the investigator or a qualified designee during the screening period, and any clinically significant abnormalities will be recorded. Additional comprehensive physical exams will be performed as outlined in the study schedule. Any new clinically significant findings after the first dose of the study treatment will be recorded as AEs.

11.2.1.2Targeted physical examination

For treatment cycles where a comprehensive physical examination is not required, the investigator or a qualified designee will conduct a targeted physical examination based on clinical indications. These examinations will occur before dosing on Day 1 of each treatment cycle. Any new clinically significant abnormalities will be recorded as AEs.

11.2.1.3Height, weight, and vital signs

The investigator or a qualified designee will record vital signs at screening, before each study treatment administration, and at treatment discontinuation, as specified in the study schedule. Height will only be measured at baseline. Vital signs include body temperature, pulse rate, respiratory rate, and blood pressure.

11.2.1.412-Lead Electrocardiogram (ECG)

A standard 12-lead ECG will be recorded during the screening period according to local standard procedures, and any clinically significant abnormalities will be documented. Additional ECGs may be performed at other time points based on clinical need.

11.2.1.5Eastern Cooperative Oncology Group (ECOG) performance status

The investigator or a qualified designee will assess ECOG performance status at screening, before dosing on Day 1 of each treatment cycle, at treatment discontinuation, and during safety follow-up, in accordance with the study schedule. Detailed instructions for the assessment and documentation of ECOG performance status are provided in Section 10.

11.2.2 Laboratory assessments

The laboratory assessments are detailed below, and the procedures for fluid sample collection are provided in the Study Procedure Manual. The timing of laboratory assessments is specified in the study schedule.

11.2.2.1Laboratory safety evaluations (hematology, coagulation, urinalysis, biochemistry)

The laboratory safety evaluations, including hematology, coagulation, urinalysis, and biochemistry analyses, are listed in the table below.

Laboratory Evaluations

Hematology/Coagulation	Biochemistry	Urinalysis	Others
Hemoglobin	Albumin	pH	Pregnancy test (blood or urine)
Platelet count	Alkaline phosphatase	Glucose	FT3, FT4, and TSH
WBC (total and differential)	Aspartate aminotransferase (AST)	Protein	HCV antibodies
RBC	Alanine aminotransferase (ALT)	Specific gravity	HCV-RNA
Hematocrit	Creatinine	Red blood cells (RBC)	HBsAg
INR	Blood urea nitrogen (BUN)	White blood cells (WBC)	HBV-DNA
PT	Glucose		HBsAb
	Calcium		HBcAb
	Phosphorus		HBeAg
	Magnesium		HBeAb
	Sodium		HIV antibodies

	Potassium	Cardiac troponin
	Total bilirubin	
	Direct bilirubin	
	Total protein	
	Blood uric acid	
	Lactate dehydrogenase (LDH)	
	Gamma-glutamyl transferase (γ-GT)	
	Creatine kinase (CK)	

Laboratory tests for screening should be conducted within 7 days prior to the first dose of study treatment. Exceptions include hepatitis and thyroid serology, which can be conducted within 28 days before the first dose. After Cycle 1, pre-dose safety laboratory tests may be performed within 3 days prior to dosing, unless otherwise specified in the protocol schedule.

Before each study treatment administration, laboratory results must be reviewed by the investigator or a qualified designee to ensure they are acceptable, unless otherwise specified in the protocol schedule. Any unresolved laboratory abnormalities related to treatment must be followed until resolution. After the end of treatment, if laboratory results are within normal ranges, repeat testing is not necessary.

11.2.2.2Pregnancy test

All female participants who are considered for the study and are neither surgically sterile nor postmenopausal must undergo a pregnancy test within 3 days prior to the first dose of the study drug. If the urine test result is inconclusive, a serum test is required. Participants with a positive or borderline positive test result must be excluded from the study or withdrawn from further participation.

11.2.2.3Central laboratory testing for biomarker samples

For details on the collection, storage, and transportation of biomarker samples (such as PD-L1, TMB, etc.), refer to the Study Procedure Manual.

11.2.3 Biomarker analysis (Optional by investigator)

11.2.3.1Tissue biomarkers:

At the investigator's discretion and with ethics committee approval, participants meeting the eligibility criteria will provide tumor tissue samples (either formalin-fixed paraffin-embedded blocks or unstained slides) at baseline for analysis of biomarkers such as PD-L1 expression by immunohistochemistry. The following types of tissue samples are acceptable:

1. Archived tumor tissue, meeting pathology department quality control standards.
2. Newly collected tumor tissue during the screening period.

   A minimum of 5-15 unstained slides with a thickness of 4-5 microns is required. For sampling requirements, storage, transportation, and analysis of the samples, refer to the Laboratory Manual.

11.2.3.2Blood biomarkers:

At the investigator's discretion and with ethics committee approval, participants will provide 10 ml of whole blood at the following time points: prior to the first dose of the study drug, during each treatment cycle when efficacy is evaluated, and before the next treatment begins. Biomarker research may include, but is not limited to, TCR sequencing analysis. For details on sampling methods, storage, transportation, and analysis, refer to the Laboratory Manual.

11.2.3.3Storage and disposal of biological samples:

Biological samples will be handled or destroyed with anonymization and aggregation. Additional analyses may be performed on anonymized, aggregated samples to further evaluate and validate analytical methods. Any results obtained from these analyses may be reported separately from the clinical study report (CSR).

Reproducibility analyses of samples, if conducted, will be performed concurrently with the bioanalytical testing of the study samples. These results will be documented in a separate bioanalytical report, rather than the clinical study report.

12 Safety reporting and adverse event management

12.1 Definition of adverse events

An adverse event (AE) is defined as any unfavorable and unintended medical occurrence in a participant of a clinical trial, starting from the time the informed consent form is signed, regardless of whether there is a causal relationship with the study drug. Adverse events include, but are not limited to, the following scenarios:

- Worsening of pre-existing medical conditions or diseases (including worsening of symptoms, signs, or abnormal laboratory results).
- The occurrence of any new medical condition (including symptoms, signs, or newly diagnosed diseases).
- Clinically significant abnormal laboratory results.

12.2 Definition of serious adverse events

A serious adverse event (SAE) is defined as an adverse event that meets at least one of the following criteria:

- Results in death, excluding death caused by the progression of the disease under study.
- Is life-threatening (the term “life-threatening” refers to an AE where the participant is at immediate risk of death at the time of the event; it does not refer to an AE that could potentially cause death if it worsens).
- Requires inpatient hospitalization or prolongs existing hospitalization, excluding the following situations:
    - Admission to a rehabilitation center.
    - Admission to a nursing home.
    - Routine emergency room visits.
    - Same-day surgeries (e.g., outpatient/day surgery/non-overnight procedures).
    - Hospitalization not related to AE worsening or extended hospitalization without a new AE or worsening of an existing condition (e.g., hospitalizations due to pre-existing conditions without new adverse events, or routine hospital admissions like annual check-ups).

- Hospitalization specified by the clinical trial protocol (e.g., protocol-mandated procedures).
- Elective hospitalizations unrelated to AE worsening (e.g., elective surgeries).
- Hospitalization solely for the administration of blood products.

- Results in permanent or significant disability/incapacity.
- Causes congenital anomalies or birth defects.
- Any other important medical event: defined as events that pose a risk to the participant or require medical intervention to prevent any of the above outcomes.

12.3 AE assessment

The investigator will assess all AEs according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Any AE that results in a change of CTCAE grade will be recorded in the case report form (CRF) or worksheet.

All AEs, regardless of their CTCAE grade, must be evaluated to determine whether they qualify as SAEs.

12.4 Recording of AEs

The investigator should use medical terminology/concepts to record AEs or serious adverse events (SAEs). Colloquial language and abbreviations should be avoided. All AEs (including SAEs) must be recorded in the adverse event section of the CRF.

12.4.1 Adverse event collection period

The investigator will gather information on AEs by asking non-leading questions to the participant.

From the time the informed consent form is signed until 30 days after the last dose, all AEs, including SAEs, must be collected, whether observed by the investigator or spontaneously reported by the participant.

Between 30 days and 90 days after the last dose, the investigator must report all SAEs as well as AEs related to the study drug or study procedures.

After 90 days following the last dose, only SAEs considered related to the study drug or procedures must be reported.

If a new anti-tumor treatment is initiated within 90 days of the last dose, only SAEs related to the study drug need to be recorded thereafter.

12.4.2 Follow-up of adverse events

AEs should be followed until they return to baseline, resolve to Grade 0–1, or the investigator determines that follow-up is no longer needed for justified reasons (e.g., the AE is irreversible or has improved). If an AE does not resolve, the investigator must document a reasonable explanation in the CRF. Regardless of the relationship to the study drug, the resolution and date of resolution for all AEs or SAEs must be documented in the electronic CRF (eCRF) and medical records.

12.4.3 Content of adverse event records

The investigator must fully document each AE, including the diagnosis (or if unavailable, symptoms, signs, or abnormal laboratory results), start and end dates/times (if applicable), CTCAE severity grade and changes (for Grade 3 or higher events), SAE status, action taken regarding the study drug, treatments provided for the AE, and the outcome. The relationship between the AE and the study drug must also be noted.

For SAEs, the investigator must also provide the date the AE met SAE criteria, the date the investigator became aware of the SAE, the reason the AE is considered an SAE, hospitalization and discharge dates (if applicable), possible cause of death (if applicable), date of death, autopsy results (if performed), and causality assessments for both the study drug and other medications. The investigator must also provide the rationale for their causality assessment and a detailed description of the SAE. This description should include the participant's ID, age, gender, height, weight, the indication for study treatment and disease stage, as well as the participant’s general health status. A detailed clinical course of the SAE should also be included, as well as relevant laboratory test results (including date, unit, and reference range), relevant medical history, comorbidities (including their duration), medication history, concomitant medications (including dosage and duration), and detailed information on study drug treatment (start date, duration, and dosage).

Details of AE recording:

Diagnosis, symptoms, and signs

If a diagnosis is available, the diagnosis should be recorded in the CRF rather than individual

symptoms and signs (e.g., "hepatic failure" instead of "jaundice," "elevated transaminases," or "asterixis"). If symptoms and signs cannot be attributed to a diagnosis at the time of reporting, they should be recorded as separate AEs/SAEs. Once a diagnosis is confirmed, only the diagnosis should be recorded, with symptoms and signs included in the diagnosis. AEs should have symptoms/signs removed from records, while SAEs require a follow-up report.

AEs secondary to other events

Typically, AEs secondary to other events (e.g., caused by another event or clinical sequelae) should be recorded under the primary event unless the secondary event is severe or qualifies as an SAE. However, if the secondary event is of significant clinical importance and occurs at a different time from the primary event, it should be recorded as an independent AE in the CRF. If the relationship between events is unclear, they should be recorded separately in the CRF.

Persistent or recurrent adverse events

A persistent AE is one that remains unresolved between two evaluation points. This type of AE should only be recorded once in the CRF. The initial severity of the event should be documented, and updates should be made if the severity increases.

A recurrent AE is one that resolves between two evaluation points and then reoccurs. Each occurrence of a recurrent AE should be recorded separately in the CRF.

Laboratory abnormalities

Clinically significant abnormal laboratory results should be reported as AEs. The investigator is responsible for reviewing all laboratory results and making a medical judgment as to whether each abnormal result should be reported as an AE.

Death

All deaths occurring during the trial, including during the 90-day follow-up period after the last dose, must be recorded in the death section of the eCRF and promptly reported to the sponsor, regardless of the relationship to the study drug.

If the cause of death is known, the cause should be recorded as an AE, with the outcome being death, and reported as an SAE. (Deaths due to disease progression are not reported as AE/SAEs but should be documented in the CRF death report and promptly reported to the sponsor.) If the cause of death is unknown at the time of reporting, it should be recorded in the CRF as "death of unknown cause" and reported as an SAE. Further investigation into the cause of death should

be conducted.

Pre-existing medical conditions

Pre-existing symptoms or signs present at screening should only be recorded and reported as AEs if there is an increase in severity, frequency, or nature (excluding worsening of the disease under investigation). The change from the pre-existing state should be reflected in the record, for example, "increased frequency of headaches."

Disease progression

Disease progression refers to worsening of the participant's condition due to the primary tumor targeted by the investigational drug, including the appearance of new lesions or progression of existing lesions. Expected disease progression is not reported as an AE. Symptoms or signs due to expected disease progression, even if they lead to death, hospitalization, or significant disability, are not reported as SAEs.

New anti-tumor treatment

If the participant starts a new anti-tumor treatment within 90 days of the last dose, only SAEs related to the study drug need to be recorded and reported.

12.5 SAE and pregnancy expedited reporting

SAE reporting:

The reporting period for SAEs starts from the signing of the informed consent form and extends to 90 days after the last dose of study treatment (including the 90th day). In the event of an SAE, the investigator must immediately complete the Serious Adverse Event Report Form and notify the sponsor within 24 hours of becoming aware of the event. The event must also be reported to the national regulatory authority and the ethics committee as per Chinese regulations. Additionally, the SAE must be reported to Innovent within 24 hours at: drugsafety@innoventbio.com.

If an SAE occurs outside of this reporting period and is deemed related to the study drug, it must also be reported.

Pregnancy:

Given the potential risk of embryotoxicity associated with similar drugs, all participants of childbearing potential in this clinical trial must use effective contraception.

If a female participant becomes pregnant during the study while exposed to the study drug, she must discontinue the trial, and the pregnancy must be reported to the sponsor within 24 hours of the investigator becoming aware of it. The "Innovent Clinical Trial Pregnancy Report/Follow-up Form" must be completed.

If a male participant's partner becomes pregnant while the participant is exposed to the study drug, the participant may continue in the trial, but the pregnancy must also be reported to the sponsor within 24 hours, and the same pregnancy report/follow-up form must be completed.

The investigator must monitor the pregnant participant throughout the pregnancy and follow up on the pregnancy outcome until 8 weeks after delivery, with the results reported to the sponsor.

If the pregnancy results in stillbirth, spontaneous abortion, fetal malformation (any congenital anomaly/birth defect), or medically indicated abortion, it will be considered an SAE and must be reported following the SAE reporting process and timelines.

If the participant experiences an SAE during pregnancy, the SAE must be reported according to the SAE reporting procedures.

12.6 Immune-related adverse events

Due to the mechanism of action of sintilimab, which involves T-cell activation and proliferation, immune-related adverse events (irAEs) may be observed during the study. Participants should be monitored for signs and symptoms of irAEs. If no clear alternative cause (e.g., infection) is identified, it should be considered that the participant's signs or symptoms are related to the immune system.

13 Statistical analyses

13.1 Sample size calculation

This investigation was designed to be a study with a fixed sample size (n = 40 in each cohort).

For cohort A: Historical data indicate that the ORR for chemotherapy as second-line therapy is approximately 12%.[1] This trial aims to detect an improvement of about 18 percentage points, achieving an ORR of 30%. Based on a power of 80%, an alpha of 0.05, and accounting for a 15% dropout rate, the required sample size is 40 patients. Sample size was calculated using PASS software (version 15.0, NCSS LLC, Kaysville, Utah, USA).

13.2 Analysis sets

Full analysis set (FAS):

The FAS will include all patients enrolled and receive at least one cycle of the study treatment. The primary and secondary efficacy analysis will be conducted in the FAS. Additionally, demographic information and baseline characteristics will be summarized for this population.

Per-Protocol Set (PPS):

The PPS is a subset of the FAS. It will include patients who have any major protocol deviations that could impact efficacy evaluation, as well as those who were enrolled but did not receive treatment.

Safety Analysis Set:

The safety analysis set population will include all patients who have received at least one dose of the study medication. This set will be used for the analysis of safety endpoints.

13.3 Statistical analysis methods

13.3.1 General statistical analysis methods

Continuous variables will be summarized using the median (minimum, maximum). Categorical variables will be summarized using frequency (percentage).

13.4 Efficacy analysis

13.4.1 Primary endpoint analysis

12-week Objective response rate (ORR)

12-weel ORR is defined as the proportion of participants who achieve CR or PR as assessed by the investigator based on RECIST 1.1 evaluated around 12 weeks. ORR will be calculated as (number of CR + PR participants) / total number of participants * 100%. The ORR at 12 weeks was summarized with exact 95% CIs derived from the Clopper–Pearson method.

13.4.2 Secondary endpoint analysis

Best overall response (BOR)

BOR is defined as the proportion of participants who achieve a CR or PR as part of their best treatment assessment. Response evaluation will be conducted by the investigator in accordance with RECIST v1.1 criteria. The BOR was calculated, and the corresponding exact 95% confidence intervals were obtained using the Clopper–Pearson method.

Progression-free survival (PFS)

PFS is defined as the time from the start of treatment to the first occurrence of radiographic disease progression or death (whichever occurs first). Disease progression will be determined by the investigator based on the RECIST v1.1 criteria. Participants without documented disease progression or death at the time of analysis will be censored at the date of their last tumor assessment. The median PFS and its 95% confidence interval (CI) will be estimated using the Kaplan-Meier method, and a survival curve will be plotted. Hazard ratios (HRs) with 95% CIs were estimated using Cox proportional hazards regression models.

Overall survival (OS)

OS is defined as the time from the start of treatment to death from any cause. Participants still alive at the end of the study will be censored at the date of their last known survival status. A survival curve will be plotted. The Kaplan–Meier approach was employed to estimate OS, and the median OS together with its 95% CI was documented. Cox proportional hazards regression was applied to estimate HRs and corresponding 95% CIs.

Disease control rate (DCR)

DCR is defined as the proportion of participants achieving CR, PR, or stable disease (SD). DCR will be calculated as (number of CR + PR + SD participants) / total number of participants * 100%. The analysis of the DCR included exact 95% confidence intervals, derived through the Clopper–Pearson procedure. HRs with 95% CIs were estimated using Cox proportional hazards regression models.

Duration of response (DOR)

DOR is defined as the time from the first documented response (CR or PR) to disease progression or death (whichever occurs first). The median DOR will be estimated using the Kaplan-Meier method, and a survival curve will be plotted. The DOR was analyzed with exact 95% confidence intervals estimated using the Clopper–Pearson method.

13.4.3 Cox Proportional Hazards Regression Analysis

In this study, exploratory analyses of potential prognostic and predictive factors for survival outcomes will be conducted using Cox proportional hazards regression models. The primary endpoints of interest for these analyses are PFS and OS, defined respectively as the time from first treatment to documented disease progression or death, and the time from first treatment to death from any cause. Baseline demographic and clinical variables, including but not limited to age (<60 vs ⩾60 years), sex (male vs female), smoking status (never vs ever), tumor histology (LUAD vs LUSC), Eastern Cooperative Oncology Group performance status (0 vs 1), presence of liver, brain, or bone metastases (yes vs no), and PD-L1 tumor proportion score (<1%, 1–49%, ⩾50%, unknown), will be examined. Initially, univariate Cox models will be fitted for each variable individually, and hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) and p-values will be presented. Subsequently, multivariate Cox regression models will be performed to adjust for potential confounding among clinically relevant factors; covariates selected a priori (e.g., age, sex, ECOG PS, metastatic sites, PD-L1 expression) will be included regardless of univariate significance, while variables demonstrating signals of association in univariate analyses may also be considered. The proportional hazards assumption will be tested using Schoenfeld residuals and alternative approaches such as stratified or time-varying covariates will be applied if violations are detected.

13.5 Safety analysis

Safety analyses will be performed on the safety set (SS), and safety data will include AEs, laboratory results, vital signs, electrocardiograms (ECGs), and other safety assessments.

13.5.1 Adverse event analysis

AEs, adverse reactions, immune-related AEs/adverse reactions, serious AEs/adverse reactions,

AEs/adverse reactions leading to dose reduction or treatment interruption, AEs/adverse reactions leading to study withdrawal, and AEs/adverse reactions resulting in death will be summarized for each treatment group. The severity of AEs and adverse reactions will be graded according to NCI CTCAE version 5.0. All AEs and adverse reactions will also be summarized by system organ class (SOC) and preferred term (PT). Data will be summarized for each treatment group, and overall summaries of AEs will also be provided.

13.5.2 Baseline characteristics of participants

Descriptive statistics will be provided for demographic characteristics (e.g., gender, age), disease information related to the indication (e.g., tumor type, pathological diagnosis, clinical stage, prior treatments), baseline tumor assessments (e.g., number and location of target and non-target lesions, total lesion length), and other baseline information such as height, weight (body mass index, body surface area), vital signs, ECOG performance status, laboratory tests, and past/concomitant medications.

14 Quality assurance and quality control

In accordance with Good Clinical Practice (GCP) guidelines, the sponsor is responsible for implementing and maintaining a quality assurance and quality control system based on standard operating procedures. This ensures that the conduct of the clinical trial, as well as the collection, recording, and reporting of data, adheres to the protocol, GCP standards, and applicable regulatory requirements.

15 Ethics

15.1 Ethics committee

The sponsor or its designated representative will prepare the relevant documents for submission to the site's ethics committee (EC). These documents include the study protocol, informed consent form (ICF), investigator's brochure, recruitment materials or advertisements, and any other documents required by regulations. Approval from the EC must be obtained in writing before the study can begin, and a copy must be provided to the sponsor. The approval document should clearly state the protocol title, identification number, version number, and version numbers of other documents (e.g., ICF) along with the approval date. The investigator must notify the sponsor of any delays, suspensions, or re-approvals issued by the EC.

The study site must comply with the EC requirements, which may include protocol amendments, ICF amendments, recruitment materials revisions, local safety reporting requirements, and submission of periodic reports and final study reports as required by the EC. All documents and EC approvals must be provided to the sponsor or its designee.

15.2 Study ethics

The study procedures and the informed consent process must adhere to the Declaration of Helsinki, relevant GCP requirements, and applicable Chinese laws and regulations on drug use and data protection.

GCP provides internationally recognized ethical and scientific quality standards for the design, conduct, recording, and reporting of clinical trials involving human subjects. This study will comply with GCP and relevant national regulations and will follow the ethical principles outlined in the Declaration of Helsinki to protect the rights, safety, and well-being of participants.

Investigators must follow the protocol procedures and cannot make changes without sponsor approval. Any protocol deviations will be reported to the EC, the sponsor, or regulatory authorities.

15.3 Participant information and informed consent

Before any study-related procedures begin, potential participants must be informed of the

potential risks and benefits of the study using an ICF. The language of the ICF should be simple and easy to understand. The ICF must clearly state that participation is voluntary and outline the potential risks and benefits of participation, as well as the participant's right to withdraw from the study at any time.

The investigator may only enroll participants after fully explaining the study, addressing all participant questions, and allowing sufficient time for consideration. Written consent from the participant or their legal representative must be obtained. All signed ICFs must be stored in the investigator’s or participant’s study file.

The investigator is responsible for explaining the ICF content to participants and obtaining signed, dated consent from the participant or their legal representative before the study begins. After signing, a copy of the signed ICF must be provided to the participant, and the consent process must be documented in the trial’s source documents.

15.4 Participant data protection

The ICF will include information on data and privacy protection (or in some cases, separate documentation may be used).

Precautions must be taken to ensure the confidentiality of the data and to prevent participant identification. However, under certain circumstances, specific individuals may have access to a participant’s genetic data and personal identifiers, such as in a medical emergency. The sponsor, its medical representatives, or investigators may have access to participant identification codes and genetic data. Additionally, regulatory authorities may require access to relevant records.

16 Study management

16.1 Data handling and record retention

Study documents (e.g., protocols and amendments, completed CRFs, signed ICFs) must be retained and managed according to GCP requirements. The study site must retain these documents for five years after the study's completion.

Study documents must be stored appropriately to allow for future access or data traceability. Security and environmental risks should be considered when storing these documents.

16.2 Access to source data/documents

The investigator agrees to provide relevant regulatory authorities direct access to all study-related documents, including participant medical records.

16.3 Protocol amendments

Any amendments to the protocol during the study will be communicated and agreed upon by the sponsor and investigator.

All protocol amendments must be documented as protocol addenda. Any changes to the protocol must be submitted to the EC for approval or filing, as required by the EC regulations.

16.4 Investigator responsibilities

The investigator will conduct the study in compliance with the protocol, the ethical principles outlined in the Declaration of Helsinki, Chinese GCP, and applicable regulatory requirements. The investigator's specific responsibilities are detailed in Chapter 5 (Responsibilities of the Investigator) of Chinese GCP (Order No. 3).

16.5 Publication policy

All data generated by this study are the sponsor's confidential information. The sponsor holds the right to publish the study results. Details regarding the publication policy between the sponsor and the investigator are described in the clinical trial agreement.

All information related to this study (e.g., protocol, investigator's brochure) must be treated as strictly confidential. Investigators should recognize that scientific or medical information

obtained from this study may have commercial value to the sponsor. Investigators are required to maintain the confidentiality of all information and data related to this study and must seek the sponsor's prior written approval before publishing or presenting any results from the study. To protect its interests, the sponsor may request that no information about the study be published until the study product has received marketing approval.

The sponsor retains the right to publish or report study-related information or data or to submit it to regulatory authorities. If the sponsor wishes to include the investigator's name in any publication, advertisement, or report, the investigator's consent must be obtained.

16.6 Finance and insurance

The sponsor will provide insurance for study participants, in accordance with local laws and minimum requirements. The insurance terms will be retained in the study documentation.

17 References

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18 Appendix files

Appendix I Performance Status Scale (Eastern Cooperative Oncology Group)

Grade	Description
0	Asymptomatic, fully active, able to carry on all pre-disease performance without restriction.
1	Symptomatic, restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Symptomatic, ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Symptomatic, capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair.
5	Dead

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

Response Evaluation Criteria in Solid Tumors Version 1.1 (Excerpt)

1 Background

Omitted

1 Purpose

Omitted

3 Measurability of Tumor at Baseline

3.1 Definitions

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

3.1.1 Measurable lesions

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

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm);
- 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as non-measurable);
- 20 mm by chest X-ray;
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 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.

3.1.2 Non-measurable lesions

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

3.1.3 Special considerations regarding lesion measurability

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

comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions;
- Lytic lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above;
- Blastic bone lesions are non-measurable lesions.

Cystic lesions:

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

Lesions with prior local treatment:

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

3.2 Specifications by methods of measurements

3.2.1 Measurement of lesions

All measurements should be recorded in metric notation during clinical evaluation. All baseline evaluations should be performed as close as possible to the treatment start and never more than 28 days (4 weeks) before the beginning of the treatment.

3.2.2 Method of assessment

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

should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

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

Chest X-ray: Chest CT is preferred over chest X-ray, especially when tumor progression is an important clinical 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 display clear borders and are surrounded by aerated lung.

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

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

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete pathological 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 normal limit, 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 protocols on a disease specific basis. Specific criteria for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology/histology: These techniques can be used to differentiate between PR and CR if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors may remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met the criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

4 Tumor response evaluation

4.1 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 protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

4.2 Baseline documentation of target and non-target lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where 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, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

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

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

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present”, “absent”, or in rare cases “unequivocal progression”. In addition, it is possible to record multiple nontarget 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).

4.3 Response criteria

4.3.1 Evaluation of target lesions

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

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

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition, the sum must also demonstrate an absolute increase of at least 5 mm (Note: the appearance of one or more new lesions is also considered progressive disease).

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

4.3.2 Special notes on the assessment of target lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. 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 achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become too small to measure: While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, it should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen, and an accurate measurement value cannot be given, a default value of 5 mm can 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 of 5 mm is derived from the CT slice thickness (but this value should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

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

4.3.3 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 need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

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

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

Progressive disease: Unequivocal progression of existing non-target lesions. Note: Appearance of one or more new lesions is also considered progression.

4.3.4 Special notes on evaluation of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows: When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial

worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable non-target lesions: This circumstance arises in some phase 3 trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target lesions cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-target lesions is comparable in magnitude to the increase that would be required to declare progressive disease for target lesions: i.e., an increasing tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase diameter in a measurable lesion) Examples include an increase in a pleural effusion from "trace" to "large", an increase in lymphangitic disease from "localized" to "widespread", or may be described in protocols as "sufficient to require a change in treatment". Or an increase in a pleural effusion from trace to large, lymphatic involvement spreading from the primary site to distant sites, or may be described in protocols as "a change in treatment is necessary". 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 non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

4.3.5 New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are very 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 tumor (for example, some new

bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a new cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of thesis the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

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

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

Negative FDG-PET at baseline, with a positive FDG-PET scan at follow-up is a sign of PD based on a new lesion.

No FDG-PET at baseline and a positive FDG-PET at follow-up:

If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

4.4 Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a

response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement.

4.4.1 Time point response

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

Table 1 Time Point Response: Patients with Target (± Non-target) Lesions

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

CR = complete response, **PR** = partial response, **SD** = stable disease, **PD** = progressive disease, and **NE** = in evaluable.

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

Table 2 Time Point Response - Patients with Non-Target Lesions Only

Non-target lesions	New lesions	Overall response
CR	No	CR

Non-target lesions	New lesions	Overall response
Non-CR or non-PD	No	Non-CR or non-PD*
Not all evaluated	No	NE
Equivocal PD	Yes or No	PD
Any	Yes	PD

*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, so to assign this category when no lesions can be measured is not advised.

4.4.2 Missing assessments and in evaluable designation

When no imaging/measurement is done at all 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 contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example: For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

4.4.3 Best overall response: all time points

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

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

4.4.4 Special notes on response assessment

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

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 description of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1 to 2.

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

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by specialist medical literature for this situation. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

4.5 Frequency of tumor re-evaluation

Frequency of tumor re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase 2 studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumor type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected. After the end of the treatment, the need for repetitive tumor evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If time to an event (e.g., time to progression, disease-free survival, progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomized comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.2

4.6 Confirmatory measurement/duration of response

4.6.1 Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, i.e., in randomized trials (phase 2 or 3) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6-8 weeks) that is defined in the study protocol.

4.6.2 Duration of overall response

2 Disease free survival

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first measured) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study). The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent or progressive disease is objectively documented.

4.6.3 Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD). The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of 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 determination of stable disease.

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