A Randomized, Double-blind, Positive-controlled, Multicenter Phase III Clinical Study of Alflutinib Mesylate (AST2818) versus Gefitinib as First-line Treatment in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer with EGFR Sensitive Mutation

Test Protocol

Study Drug	Alflutinib Mesylate Tablets (AST2818)
CFDA Approval No.	2016L07983
Protocol No.	ALSC006AST2818
Version No.	4.0
Version date	Sunday, May 3, 2020
PI	Professor Shi Yuankai
Company of the team leader	Cancer Hospital Chinese Academy of Medical Sciences
Unit for statistical analysis	Nanjing Ackerman Information Technology Co., Ltd.
Sponsor	Shanghai Allist Pharmaceutical Technology Co., Ltd.

Signature Page (Sponsor)

I will conduct conscientiously fulfill the responsibilities of the sponsor according to Chinese Good Clinical Practice regulations and be responsible for initiation, application, organization, funding and monitoring of this clinical study; in accordance with the provisions in national relevant laws and regulations, the subjects with serious adverse events related to the study drug during the clinical study will be given active treatment and corresponding cost of treatment, rational economic compensation will be provided for the damage induced by the serious adverse reaction that is determined to be related to the study drug. I agree to conduct this clinical study in accordance with the design and provisions in the protocol.

Sponsor: Shanghai Allist Pharmaceutical Technology Co., Ltd.

Signature by Sponsor Representative: _____

Signature Date:_____

Signature Page (Study Unit)

I will earnestly fulfill the responsibilities of the investigator in accordance with the provisions in Chinese Good Clinical Practice.

I have read this protocol and will conduct this clinical study in accordance with the moral, ethical and scientific principles in the Declaration of Helsinki and Chinese Good Clinical Practice. I agree to conduct this clinical study in accordance with the design and provisions in the protocol.

As the principal investigator, I will provide all the relevant materials of this protocol to the investigators participating in this trial, and I will discuss these materials with them to ensure that they fully understand the study drug and how to carry out the clinical study.

I will be responsible for making medical decisions related with clinical practice, as to ensure prompt and appropriate treatment for subjects when any adverse event occurs during the study, and am aware of the requirement of proper reporting of serious adverse event, will record and report these events in accordance with the requirement.

I will make sure the data will be entered in the case report form authentically, accurately, completely, promptly and legally. I will accept the audit and inspection by the monitors and auditors sent by the sponsor, and the drug regulatory authorities, as to make sure the quality of the clinical study.

If the contact information of the investigator changes during the trial, the sponsor will be informed in a written form, and there will be no more supplement in the protocol.

Study unit:_____

Investigator Signature:_____

Signature Date:_____

Ethical requirements

1. Documents to be followed

The study must be conducted in accordance with the standard operating procedures of the clinical study site and shall comply with the study protocol. The study protocol is designed in accordance with the following documents:

Declaration of Helsinki

Drug Administration Law of The People's Republic of China

Measures for the Administration of Drug Registration

Good Clinical Practice

Biostatistical Technical Guidelines for Clinical Trials of Chemical Drugs And Biological Products

2. Institutional Review Board and Ethics Committee

Before the initiation of the trial, the investigator should submit the study protocol, informed consent form, approval letter from relevant authorities and drug test report as well as any advertisement recruiting subjects to the Institutional Review Board, Ethics Committee or other organization with the same power for review and approval. Any amendment to the study protocol should be approved by the ethics committee.

3. Informed consent forms

The informed consent forms should be submitted to the relevant Ethics Committee for review and approval. Each informed consent forms must include all relevant contents.

Before each potential subject participates in any study-related activities, the investigator must explain to each subject the nature, purpose, related procedures, expected time, potential risks and inclusion benefits, and any discomfort that may occur. Each subject must be aware that participation in the study is voluntary and that he/she can withdraw from the study and withdraw consent at any time without affecting his/her subsequent care or relationship with the treating physician. After the basic contents related to the study have been explained and the investigator has confirmed that each subject who will participate in the trial understands the purpose of the study, each subject who will

participate in the trial shall be required to sign the name and date on the informed consent form. This consent form should be given in a standard written format and in lay language. Subjects should read and consider their statements before signing and dating and should be given a copy of the signed document. The subjects can not be enrolled without the informed consent.

Protocol Revision Control

Version # (Version Date)	Affected Sections
2.0 (December 06, 2018)	None (new protocol)
3.0 (November 15, 2019)	1. Table of contents and list of tables were updated. 2. On Page 1, the version number/date of the protocol abstract **is modified** to "3.0/15-Nov-2019", and the header is modified accordingly. 3. On Page 3 and 34, "When 240 subjects are observed to be enrolled (accounting for about 2/3 of the planned participants)" **is modified** to "When 1/3 of PFS events (about 64 PFS events) is observed". 4. On Page 3, 34 and 36, "Subjects who have withdrew will ... through blood samples" **is modified** to "Subjects who have progressed, discontinued study drug and withdrew will ... through blood samples". 5. On Page 4, the number of study sites "40-50" is modified to "about 55". 6. On Page 4 and 37, for inclusion criteria No. 4, "Histopathologically confirmed … (for example, it can be …, can also be a newly diagnosed stage IIIB/IV tumors)"**is modified** to" Histopathologically confirmed … (for example, it can be …, can also be newly diagnosed stage IIIB/IIIC/IV tumors)". 7. On Page 4 and 37, for inclusion Criteria No. 8, "… also not used for study screening biopsy (if there is only one target lesion and a tissue biopsy is required, an extreme tumor assessment is required at least 14 days after the screening biopsy is performed) and at baseline … " **is modified**"… also not used for study screening biopsy (if there is only one target lesion and tissue biopsy is required, and there is no imaging test eligible for exemption from screening, baseline tumor assessment should be performed at least 14 days after screening biopsy; if there is imaging test eligible for exemption from screening as baseline tumor assessment, baseline assessment can be performed again after biopsy at the investigator's discretion based on the condition of the lesion), and at baseline …". 8. On Page 5 and 37, Inclusion Criterion No. 9 "Male patients and females of childbearing potential … Adequate contraception must be carried out within 3 months after the last administration of study drug" **is modified** to "Male patients and women of childbearing potential … Adequate contraception must be carried out within 6 months after the last administration of study drug." 9. On Page 7 and 39, "HBsAg positive and HBV DNA ≥1000cps/ml (or 200IU/ml)"**is modified**to" HBsAg positive and HBV DNA ≥1000cps/ml (or 200IU/ml) or HBV DNA below the minimum detection limit (if the lower limit of HBV DNA detection value of the study center is above 1000cps/ml)".

	10. On Page 8, 59, 60 and 61, for Quality of Life Score, "The subject comes to the site and completes the questionnaire independently before communicating with the health care professional" **is modified** to "The subject comes to the site and completes the questionnaire independently or with the support of his/her relative (illiterate subject) before communicating with the health care professional". 11. On Page 12 and 74, for Full Analysis Set, "… all subjects who have been enrolled and have at least one evaluation will be included in the full analysis set" **is modified** to" … all subjects who have been enrolled and take at least one dose of study drug will be included in the full analysis set". "The per protocol set includes all subjects who complete the protocol-specified treatment …" **is modified** "The per protocol set is a subset of the FAS set, including subjects who meet the definition of the FAS set, all of whom complete protocol-specified treatment …". 12. On pages 13 and 75, "The difference between two groups is tested using the chi-square test or Fisher Exact Test" **is modified** to "The difference between two groups is tested using the Cochran-Mantel-Haenszel (CMH) test, the chi-square test or Fisher Exact Test". 13. On Page 18, add "HR, Hazard ratio" to abbreviation. 14. On Page 23, "EGFR gene amplification, bypass signaling pathways (e.g. MET, HER2, and PIK3CA) epithelial-to-mesenchymal transition …" **is modified** to "EGFR gene amplification, bypass signaling pathways (e.g., MET, HER2 and PIK3CA, epithelial-to-mesenchymal) transition …". 15. On page 28, in section 1.4.1, "alflutinib mesylate tablets 80 mg dose is selected for single-arm study in this trial" **is modified** to "alflutinib mesylate tablets 80 mg dose is selected for double-blind study in this trial". 16. On Page 31, for hepatorenal toxicity event, "the drug may cause liver injury (mainly ALT decreased, AST decreased, etc. caused by liver injury)" **is modified** to "the drug may cause liver injury (mainly ALT increased, AST increased, etc. caused by liver injury)". 17. On page 34, for the primary endpoint, "Progression-free survival (PFS) assessed by independent imaging committee: the time from drug administration to tumor progression or death of the subject" **is modified** to "Progression-free survival (PFS) assessed by independent imaging committee: the time from randomization to tumor progression or death of the subject". 18. On Page 38, for Exclusion Criteria No. 2, " … Alopecia or chemotherapy-induced … liver and kidney organ function, please refer to the exclusion criteria 6" **is modified** to "… Alopecia or chemotherapy-induced... liver and kidney organ function, please refer to the exclusion criteria 7 ". 19. On Page 40 and 41, in section 3.6, "Menopause" **is modified** to "Menopause". " Menopause is defined as 12 months of amenorrhea

	in women over 45 years of age in the absence of other biological or physiological causes. In addition, menopause can only be confirmed by serum follicle stimulating hormone (FSH) level > 40mIU/mL in women under 55 years old. "**is modified** to "Menopause includes: at least 12 months of spontaneous amenorrhea, not including those due to medical causes (e.g., caused by diseases such as anorexia nervosa), and not taking medications that cause amenorrhea (e.g., oral contraceptives, hormones, gonadotropin-releasing hormone, antiestrogens, selective estrogen receptor modulators, or chemotherapy) during the amenorrhea period; 6 to 12 months of spontaneous amenorrhea, and follicle stimulating hormone levels > 40 mlU/mL". 20. On Page 41, "Subjects of childbearing potential … adequate contraception is required within 3 months after the last dose of the drug" is modified to "subjects of childbearing potential... Adequate contraception is required within 6 months after the last dose of the drug". 21. On page 42, for the criterion for discontinuation of study drug, "the patient can not recover to… within 21 days after dose interruption due to toxicity" **is modified** to "the patient can not recover to … within more than 14 days after dose interruption due to intolerable diarrhea or adverse skin reactions or within more than 21 days after dose interruption due to other conditions". 22. On page 43, "subjects should take the drug orally on an empty stomach every morning with about 240 mL warm water" **is modified** to "Subjects should take the drug orally on an empty stomach every morning. Two drugs in each group should be taken at the same time, usually with warm water". 23. On Page 47, in Section 4.7.2, for antiemetic therapy, **Delete** "e.g., tropisetron hydrochloride". 24. On page 48, "The single discontinuation time should not exceed 21 days. If it exceeds 21 days, it is recommended that the patient withdraw from the study "**is modified** to " When there are intolerable diarrhea or skin adverse reactions, the treatment should be suspended for up to 14 days, and the single discontinuation time for other adverse reactions should not exceed 21 days. If the single discontinuation time exceeds more than 14 days for intolerable diarrhoea or skin adverse reactions or exceeds more than 21 days for the other conditions, the patient is advised to withdraw from the study ". "First occurrence of CTCAE grade 3 and above or intolerable toxicity (any grade); if it can be recovered to CTCAE grade 1 or baseline level within 21 days …" **is modified** to "suspend the dose for the first occurrence of CTCAE grade 3 and above or intolerable toxicity (any grade); if recovered to CTCAE grade 1 or baseline within 14/21 days …". "If there is the second occurrence of CTCAE grade 3 and above or intolerable toxicity (any grade) of the same class, reduce the dose by one dose (except for CTCAE grade 3 diarrhea)" **is modified** to "If there is the second occurrence of CTCAE grade 3 and above or intolerable toxicity (any grade) of the

	same class, suspend the dose; if the toxicity recovers to CTCAE grade 1 or baseline within 14/21 days, permanently discontinue the drug or the investigator assessed whether the original dose is resumed or reduced depending on the patient's condition (except for CTCAE grade 3 diarrhea)". 25. On page 49, "Table 3 Treatment of toxic and side effects and dose adjustment table" **is modified** to "Treatment of special toxic and side effects and dose adjustment table". 26. On page 49, under "Other" in Table 3, for dose interruption of "Dehydration with risk of kidney failure, acute/worsening eye disease", "if 21 days …" **is modified** to "If 14/21 days …". For dose interruption of "Serious bullous, blistering, or exfoliative skin disease, serious diarrhea, ineffective use of loperamide or dehydration", "If 21 days …" **is modified**to "If 14 days …" 27. On page 51, **add** Section 4.10 " Treatment of Study Drug Overdose". 28. On Page 53, trial flowchart **delete** 12-lead ECG examination during visit 28 days after the last administration. Trial flowchart Note No. 9, **Delete** "Serum Lipase ", **Add** " Creatinine Clearance is not required for C1D8". 29. On Page 54, for trial flowchart Note No. 11, " prothrombin time (PT) or the PT international normalized ratio (PT-INR), partial prothrombin time (PTT)" **is modified** to" including prothrombin time (PT) , international normalized ratio (INR), activated partial thromboplastin time (APTT)" .Trial flowchart Note No. 15, " onC1D1" **is modified** to" C1D0", "Each interval is about 5 minutes" **is modified**"Each interval is about 5-30 minutes" .Trial flowchart Note No. 16, "If the HBsAg test result is positive, HBV DNA test should be performed; if the HCV antibody test result is positive...; **is modified** to "If the HBsAg test is positive, HBV DNA testing is required, and HBV DNA testing needs to be repeated every 3 months during the study; if the HCV antibody test is positive...". 30. On page 55, trial flow chart Note No. 25, and page 56, "If the results of hematology, blood biochemistry and urinalysis within 7 days before discontinuation are normal as assessed by the investigator, these tests may be exempted at discontinuation visit" **is modified** to "If the results of hematology, blood biochemistry and urinalysis within 7 days before discontinuation are normal or abnormal without clinical significance as assessed by the investigator, these tests may be exempted at discontinuation visit". 31. On Page 55, for trial flowchart Note No. 31, " Patients need to provide tumor tissue or blood samples after disease progression … " **is modified** to "Patients need to provide tumor tissue or blood samples after patient has progressed and study medication has been discontinued …". 32. On Page 58, "HBV, HCV and HIV tests …and contain HBsAg, HBV DNA, HCV antibodies in the normal range. "**is modified** to "HBV,

	HCV and HIV tests …and contain HBsAg, HBsAb, HBeAg, HBeAb, HBcAb, HBV DNA, HCV antibodies in the normal range.". 33. On Page 59 and 64, for 12 lead ECG, "…. Each interval is about 5 minutes. "**is modified** to" …. Each interval is about 5-30 minutes". 34. On Page 61, "laboratory tests … and these tests can be exempted they are abnormal without clinical significance as judged by the investigator"**is modified** to"laboratory tests... and these tests can be exempted if they are normal or abnormal without clinical significance as judged by the investigator". 35. On page 63, in the penultimate paragraph, "When the best response is partial response (PR) or complete response (CR), the same imaging method should be used for response confirmation 6 weeks (± 7 days) after the first record" **is removed**. 36. On page 64, for 12-lead electrocardiogram, "Include heart rate... On C1D1, the examination needs to be repeated three times, approximately 5-30 minutes apart, before the first drug administration " **is modified** to" Include heart rate … On C1D0, tests need to be repeated three times, 5-30 minutes apart, before the first administration". 37. On Page 65, under blood biochemical examination,**delete**" serum lipase", and "…urea / urea nitrogen, creatinine clearance, uric acid"**is modified**to " urea / urea nitrogen, creatinine clearance rate (no testing required for C1D8), uric acid". Under the item of urine test, "Specific gravity, PH, urine glucose, protein, cast (transparent cast, etc.), urine ketone body" **is modified** to "Specific gravity, PH, urine glucose, protein, urine ketone body". 38. On Page 73, "New cancer should belong to AE, and meet at least one SAE criteria"**is modified**to "New cancer belongs to SAE". 39. On Page 78, for 11.1 Signature of Informed Consent Form "Informed Consent Form … language expressions that can be read and understood" **is modified** to"Informed Consent Form … language expressions that can be read or understood".
4.0 (Sunday, May 3, 2020)	1. Update table of contents, table of tables, and table numbers. 2. On Page 1, the version number/date of protocol abstract is modified to "4.0/03-May-2020", and the header is modified accordingly. 3. **Modify** the Roman alphabet font to "Times New Roman" 4. On Page 1, 2, 13, 22, 55, 56, and 101, "Shanghai Allist Pharmaceutical Technology Ltd."**is modified** to "Shanghai Allist Pharmaceutical Technology Co., Ltd.". 5. On page 13, "Jiang Yong" **is modified** to "Li Ling". 6. On page 14 and 45, **add** "6. To compare the efficacy of first-line treatment with alflutinib mesylate versus gefitinib in the population with locally advanced or metastatic non-small cell lung cancer with brain metastases respectively.". 7. On Page 14 and 47, **add** "Central Nervous System Progress Free Survial (CNS PFS), Central Nervous System Depth of Release (CNS DoR), Central Nervous System Objective Response Rate (CNS

	ORR), 6 weeks Central Nervous System Disease Control Rate CNS DCR_{6W} and 12 weeks Central Nervous System Disease Control Rate CNS DCR_{12W} are assessed by the Independent Imaging Committee according to RECIST 1.1 in Chinese patients with naive locally advanced or metastatic non-small cell lung cancer with brain metastasis, respectively". 8. On page 23, "The median PFS equals 17 months in the test group (the alflutinib group); 11 months in the control group (gefitinib group)." **is modified** to "The median PFS equals 16 months in the test group (the alflutinib group) and 11 months in the control group (gefitinib group).". 9. On Page 15 and 46, "When 1/3 of PFS events (about 64 PFS events) are observed"**is modified**to "When 1/3 of PFS events (about 64 PFS events out of 192 target PFS events) according to the protocol version 3.0". 10. On Page 15 and 46, **add** "The target number of events will be adjusted based on the median PFS result and blind sample size from protocol version 3.0, and an Independent Data Monitoring Committee (IDMC) will be established to plan 1 interim analysis as detailed in the Sample Size and Interim Analysis section." 11. On Page 15, 46 and 48, **add** "For patients who are tested and confirmed to be negative for the T790M mutation, the investigator can discuss with the sponsor medical personnel whether the unblinding can be performed when it may affect the next treatment strategy." 12. On page 15 and 46, "The final analysis for primary endpoint PFS will be performed after at least 192 PFS events are observed. The safety and efficacy results including OS from the final analysis will be submitted to regulatory authorities as part of the new drug application." **is modified** to "The primary analysis for primary endpoint PFS will be performed after at least 238 PFS events are observed. The safety and efficacy results including OS from the final analysis will be submitted to regulatory authorities as part of the new drug application.". 13. On Page 15 and 46, "The end of the study is set at 12 months after the completion of 192 PFS events. OS follow-up will continue to be collected for OS data in this 12-month study. The database is locked for the analysis of OS after the end of follow-up for OS. The results of the final follow-up OS analysis are submitted to CDE as supplementary materials." **is modified** to "The end of the study is set at the completion of 238 PFS events and continued OS follow-up to collect OS data until about 60% of deaths are observed. The database is locked for the analysis of OS after the end of follow-up for OS. The results of the final follow-up OS analysis are submitted to CDE as supplementary materials." 14. On Page 17 and 50, "Patients who are receiving drugs known to prolong the QTc interval or potentially cause torsade de pointes and who need to continue treatment with these medications during the

	study" **is modified** to "Patients who are receiving medications known to prolong the QTc interval and who need to continue treatment with these medications during the study". 15. On Page 18 and 51, "various Clinically Significant rhythms…"**is modified** to "various clinically significant and important rhythms...". 16. On Page 19 and 51, "HBsAg positive and HBV DNA ≥1000cps/ml (or 200 IU/ml) or HBV DNA below the minimum detection limit"**is modified** to "HBsAg positive and HBV DNA ≥1000cps/ml (or 200 IU/ml) or HBV DNA above the minimum detection limit". 17. On Page 22 and 73, "treatment termination visit (last administration + 7 Days)"**is modified** to "treatment termination visit (within 7 days after the last administration)". 18. On Page 23, 45, 54, 66, 67, 74 and 75, **add**"initiation of new antineoplastic therapy,". 19. On page 23, **add**"Central Nervous System Progress Free Survial (CNS PFS), Central Nervous System Depth of Release (CNS DoR), Central Nervous System Objective Response Rate (CNS ORR), 6 weeks Central Nervous System Disease Control Rate CNS DCR_{6W} and 12 weeks Central Nervous System Disease Control Rate CNS DCR_{12W},". **20.** On page 24 and 86, "Referring to the Flaura study, it is assumed that the PFS equals 17 months in the test group (the alflutinib group) and 11 months in the control group (the gefitinib group); the hazard ratio (HR) is 0.647 in the tets group (the gefitinib group) relative to the control group. Assuming $\alpha = 0.025$ for one-sided and $\beta = 0.20$, and subjects are randomized into either the test group or the control group at the ratio of 1:1, a total of 192 target events and 304 subjects are required; if the dropout rate was expected as 15%, a total of 358 subjects will required. The duration of this trial is expected to be approximately 8 months with a minimum follow-up of 12 months." **is modified** to "The primary efficacy variable is PFS. Based on the results of the blinded data at the time of the 66 investigator-PFS events, the sponsor considers an adjustment to the protocol hypothesis to increase the number of events. When the first 358 subjects have been 1:1 enrolled within 6.5 months, assuming the median PFS of 16 months for Alflutinib and 11 months in gefitinib control group; the hazard ratio HR is 0.688 for the trial group versus control group and α is two-sided 0.05, a total of 238 target events are needed to provide at least 80% power to detect intergroup difference. After enrollment of 358 subjects in the study, the follow-up is expected to be at least 17 months, as to acquire 238 target events. 21. On page 24 and 86, **add** "Brain metastasis analysis population" 22. On page 24 and 86, **add** "Craniocerebral Full Analysis Set (cFAS): A subset of FAS, which includes subjects who meet the definition of FAS and have measurable or unmeasurable brain lesions assessed by the independent imaging review committee (IRC) at screening visit.

	This analysis set is used for the subgroup analysis of the validity of the independent imaging review committee (IRC) reading assessments." 23. On page 24 and 86, **add** "Craniocerebral Evaluable for Response Set (cEFR): A subset of cFAS, which includes all the subjects with at least one measurable lesion in the brain during the screening visit assessed by the independent imaging review committee (IRC) who meet the definition of FAS. This analysis set is used for efficacy analysis based on measurable lesions reading in subjects with brain metastases as assessed by the independent imaging review committee (IRC)." 24. On page 24 and 86, **add** "Craniocerebral Metastases Set (cMTS): A subset of the FAS, which includes all subjects with target and/or non-target brain lesions assessed by the investigator during the screening visit who meet the definition of the FAS. This analysis set will be generated by programming subjects with both target and non-target brain lesions from the screening investigator reading data. This analysis set is used for the subgroup analysis of the validity of the investigator reading assessments." 25. On Page 24, 25, 26, 87 and 88, "Log-rank Test"**is modified** to"Stratified Log-rank Test". 26. On Page 26, 88, "comparison by treatment group using analysis of covariance"**is modified** to"comparison by treatment group using Mixed Model for Repeated Measurements (MMRM) or analysis of covariance". 27. On Page 26 and 88, "Calculate unmodified mean by visit" **is modified** to "Calculate unmodified mean change from baseline in standard scores by visit". 28. On Page 26 and 88, **add** "An independent imaging review committee (IRC) will provide an overall response assessment based on the assessment of brain measurable and non-measurable lesions and analyze the following efficacy measures: CNS PFS (central nervous system progression-free survival): it is defined as the time from randomization to brain disease progression or death. CNS DoR (central nervous system duration of response): it is defined as the time from objective response (CR or PR) of measurable or non-measurable lesion in brain to brain disease progression or death. CNS ORR (central nervous system objective response rate): it is defined as the proportion of subjects with objective response (CR or PR) of measurable or non-measurable lesion in brain. CNS DCR_{6W} (central nervous system disease control rate at 6 weeks):it is defined as the proportion of subjects with disease control (duration of CR or PR or SD ≥ 6 weeks) of measurable or non-measurable lesion in brain. CNS DCR_{12W} (central nervous system disease control rate at 12

	weeks):it is defined as the proportion of subjects with disease control (duration of CR or PR or SD ≥ 12 weeks) of measurable or non-measurable lesion in brain. The analysis sets for the efficacy endpoints for aforementioned central nervous system metastasis are cFAS and cEFR, which are analyzed using the same analysis method for the overall efficacy endpoints (window period is taken into account for the calculation), and more detailed analysis methods will be described in the statistical analysis plan." 29. On page 28, abbreviations **add** "CNS DoR, Central Nervous System Depth of Release", "CNS DCR_{6W}, 6 weeks Central Nervous System Disease Control Rate", "CNS DCR_{12W}, 12 weeks Central Nervous System Disease Control Rate", "CNS ORR, Central Nervous System Objective Response Rate", "CNS PFS, Central Nervous System Progress Free Survial", "cEFR, Craniocerebral Evaluable for Response Set" 30. On Page 29, abbreviations **add** "cFAS, Craniocerebral Full Analysis Set", "IDMC, Independent Data Monitoring Committee" 31. On Page 29, abbreviation "Independent Review Central" **is modified** to "Independent Review Committee". 32. On Page 29, abbreviations **add** "MMRM, Mixed Model for Repeated Measurements", "cMTS, Craniocerebral Metastases Set", "NMPA, National Medical Products Administration" 33. On Page 32, 34 and 58, "CFDA" **is modified** to "NMPA". 34. On page 39, "All subjects will be enrolled recently " **is modified** to "All subjects have been enrolled" 35. On page 45 and 66, "When the best response is partial response (PR) or complete response (CR), the same imaging method should be used for response confirmation 6 weeks (± 7 days) after the first record." **is removed**. 36. On page 48, "This study is a double-blind trial in which the sponsor, investigators and subjects are blinded until the primary analysis (except for those meeting the conditions for emergency unblinding), and any of the subject information and grouping shall not be disclosed." **is modified** to "This study is a double-blind trial in which the sponsor, investigators and subjects are blinded until the primary analysis of the primary endpoint PFS (except for those meeting the conditions for study defined unblinding), and any of the subject information and grouping shall not be disclosed". 37. On page 54, **add** "When the tumor assessment is disease progression by investigator, he/she should continue to receive the study drug treatment, and the decision to terminate the study drug treatment can only be made after feedback from the independent imaging review committee results. "." 38. On page 54, "patient is confirmed as disease progression by investigator"**is modified** to "patient is confirmed as disease progression by both investigator and IRC".

39. On Page 55, "Both groups are administered the study drug orally once daily and the dosing regimen is performed as per the table below"**is modified** to "Both groups are administered the study drug orally once daily during the double-blind study phase and the dosing regimen is performed as per the table below".
40. On page 55, "Table 2 Dosing Regimen"**is modified** to "Table 2 Dosing Regimen for Double-Blind Study Phase"
41. On page 56, **add** "Table 3 Dosing regimens following the primary analysis

Dose regimen		
	Test group (AST2818 group)	**Control group (Gefitinib group)**
Standard treatment		
Dose	80mg/day	250mg/day
Medicinal product(s)	AST2818 (40 mg/tablet), 2 tablets;	Gefitinib, 250 mg/tablet, 1 tablet;
Usage	once daily, oral, on an empty stomach	once daily, oral, on an empty stomach
Reduced Dose		
Dose	40mg/day	NA
Drug(s)	AST2818 (40 mg/tablet), 1 tablets;	
Usage	once daily, oral, on an empty stomach	

The subject should take the drug orally on an empty stomach every morning with warm water, and the remaining precautions are the same as those for double-blind administration."

42. On Page 56, "This study prepares the following two types of drug packaging boxes"**is modified** to "The drug packaging during blind administration is as follows, trial group (AST2818 group): each box contains 48 tablets of AST2818 and 24 tablets of gefitinib simulation for one patient for 24 days;

    Control group (gefitinib group): each box contains 24 tablets of gefitinib and 48 tablets of AST2818 simulation for one patient for 24 days."
43. On Page 56, **add** "After the primary analysis of the primary endpoint PFS, the following drug packaging will be used: trial group (AST2818 group): 8 tablets/plate, 3 plates/box, each box contains 12-day doses for one patient. Control group (gefitinib group): 10 tablets/plate, 1 plate/box (commercially available package), each small box contains 10-day doses for one patient."
44. On page 56, **add**"After the primary analysis of the primary endpoint PFS is completed and the original blinded drug is dispensed, the drug will no longer be blinded and will be dispensed by study site by group."
45. On Page 58, "drugs known to prolong the QTc interval (Known Risk

	of TdP [KR]) and drugs that may cause torsade de pointes (Possible Risk of TdP [PR])"**is modified** to"drugs known to prolong the QTc interval (Known Risk of TdP [KR])" 46. On page 59, "The following drugs should be avoided as much as possible: sedative hypnotics, erythropoietin, and estrogen-containing therapies that may increase the risk of thromboembolism. If erythropoietin therapy is initiated prior to recruitment (not permitted within 14 days prior to blood drawing for enrollment laboratory tests), treatment can be maintained." **is modified** to "The following drugs should be avoided as much as possible: sedative hypnotics, erythropoietin and estrogen-containing therapies that may increase the risk of thromboembolism, and drugs that may cause torsade de pointes (Possible Risk of TdP [PR]). If erythropoietin therapy is initiated prior to recruitment (not permitted within 14 days prior to blood drawing for enrollment laboratory tests), treatment can be maintained." 47. On page 59, **add** "If a patient has steadily used the drugs that may cause torsade de pointes (Possible Risk of TdP [PR]) before the first dose, continuation of this drugs is required during the study, and there are no remaining use contraindications, continuation of these medications may be considered by the investigator, and patients receiving concomitant medications should be closely monitored. Refer to Appendix 7 for time requirements of stable use." 48. On page 61, "QTc prolongation (QTc ≥500 ms or 60 ms increase from baseline) is detected" **is modified** to "QTcF prolongation (QTcF ≥500 ms or 60 ms increase from baseline) is detected, and during the study, QTcF prolongation is noted on electrocardiography, and the electrocardiogram examination should be repeated for three times, with each interval of 5-30min, to calculate the mean QTcF interval of the three electrocardiograms." 49. On page 61, "suspend the drug until QTc interval is less than 450 ms or returns to baseline level (whichever is higher; resume at low dose)" **is modified** to "suspend the drug until QTcF interval is less than 450 ms or returns to baseline level [1] (resume at low dose or original dose). Permanently discontinue drug if QTcF prolongation develops a second time" 50. On page 61, **add** "1. use the criteria for judging the discontinuation to decide whether the medication resumption criteria is met, e.g., the mean baseline QTcF is 357 ms, the mean QTcF at the visit is 420 ms, which is greater than 60 ms from the baseline, and 420 ms is less than 450 ms. In this particular case, the resumption criteria are: QTcF interval prolongation < 60 ms from baseline, resume at low dose or original dose. " 51. On Page 62, "QTC prolongation" **is modified** to "QTcF prolongation". 52. On page 62, **add** "during the study, QTcF prolongation is noted on electrocardiography, and the electrocardiogram examination should be repeated for three times, with each interval of 5-30min, to

	calculate the mean QTcF interval of the three electrocardiograms." 53. On page 66, "HBV DNA is re-examed every 3 months" **is modified** to "HBV DNA is re-examed every 12 weeks ± 7 days" 54. On page 66, footnote "18. Adverse event (AE) collection: All AEs will be recorded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 during each visit. For SAEs, the active reporting period to the sponsor or its designated representative begins when the patient signs informed consent and ends 28 ± 7 days after the last dose of study drug. If a patient receives a new anticancer therapy, no new AEs/SAEs will be reported." is modified to "Adverse event (AE) collection: All AEs will be recorded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 during each visit. For SAEs, the active reporting period to the sponsor or its designated representative begins when the patient signs informed consent and ends 28 days after the last dose of study drug. If a patient receives a new anticancer therapy, no new AEs/SAEs will be reported". 55. On Page 70, "and subsequent retest of HBV DNA every three months" **is modified** to "and subsequent retest of HBV DNA every 12 weeks ± 7 days from C1D1" 56. On page 75, **add** "If the tumor assessment is progressive disease by investigator, IRC confirmation is required. If disease progression is not confirmed by the IRC, tumor imaging continues as described above until disease progression is confirmed by the IRC, or the start of new antineoplastic therapy, withdrawal of patient consent, lost to follow-up, death, or study termination, whichever occurs first. " 57. On Page 75, "Tumor response and treatment decisions in this study will be based on tumor assessments by the local investigator and … will be collected" **is modified** to "… will be collected in addition to the local investigator's tumor assessments in this study" 58. On Page 76, "and a single electrocardiogram is performed when the investigator increases the frequency of examination according to clinical signs during the study" **is modified** to "and electrocardiogram is performed when the investigator increases the frequency of examination according to clinical signs during the study" 59. On Page 85, **add** "8.2 Independent Data Monitoring Committee (IDMC) An Independent Data Monitoring Committee (IDMC) will be established for this study. IDMC is an important component for ensuring the protection of subjects and the integrity of data. At the initation of IDMC and for data monitoring, a meeting is held by IDMC. IDMC mainly aims to periodically monitor the data of efficacy and safety in each treatment group of this study; meanwhile, IDMC also raises formal suggestions, such as whether study protocol needs be revised and whether the study is continued or terminated. Detailed operation procedures refer to Independent Data Monitoring Committees Charter."

	60. On Page 86, **add** "9.3 Interim Analysis One interim analysis (performed by IDMC) is planned for this trial. Through O'Brien-Fleming border concomitant in Lan-DeMets α consumption function, interim analysis is made when about 50% of PFS events (i.e. about 119 cases of PFS events) are found. According to the number of confirmed PFS events, endopoint border of interim analysis and primary analysis is obtained. When about 119 cases of PFS events (i.e. about 50% of target events) are found, interim analysis is made; in order to control the error of Class I in whole study as 0.05 (two-sided), α consumption of interim analysis is set as 0.00306 (two-sided) according to the Lan-DeMets method for α consumption. Actual α consumption of interim analysis is determined according to the number of events found at actual interim analysis. If P value of interim analysis is ≤0.00306 (two-sided), the efficacy of study drug is considered as significantly superior to that of control drug. If the study is still continued after the interim analysis, there are just 238 cases of PFS events in the database locked at primary analysis of PFS. If P value of Log-rank test (two-sided) is ≤0.049 (two-sided), H0 is refused. If the number of final events exceeds the number stipulated in the study protocol, all events recorded in the database at locking are used; and the information renewed at interim analysis is not used to calculate final border again. The IDMC will consider whether the sponsor is recommended to re-estimate the sample size based on the efficacy assessment at the interim analysis. " 61. On page 86, **add** "9.4 Independent Data Monitoring Committee (IDMC) The data of efficacy and safety are periodically reviewed by IDMC, so as to protect the rights and interests of subjects for ethics and safety. IDMC is comprised of clinical oncologists and statistician who are independent on the sponsor and have no major conflict of interest with the sponsor. IDMC is responsible to periodically review study data, and raise the suggestions for study (such as continuation as schedule, protocol adjustment and termination). Decided by Shanghai Allist Pharmaceutical Technology Co., Ltd. finally. Refer to the IDMC Charter for this study for the operational process of the IDMC. " 62. On Page 87, **add** "Response assessment using RECIST v1.1 criteria, see Appendix 1 for CR, PR, SD and PD definitions." 63. On page 87, **add** title "9.9.1 Analysis of primary endpoint" 64. On page 87, **add** title "9.9.2 Analyses of secondary efficacy endpoints" 65. On Page 88, **add** title "9.9.3 Central Nervous System Metastasis Efficacy Analysis"

	66. On page 88, **add** title "9.9.4 Subgroup analyses" 67. Page 88, **add** title "9.9.5 Analysis of Quality of Life Scores" 68. On page 87, "The analysis of primary efficacy endpoint will be based on FAS and PPS, respectively, with FAS as the primary analysis set. The analysis of secondary efficacy parameters will be based on FAS." **is removed**. 69. On page 115, **Split** "Appendix 8 Drugs Known to Prolong QTc Interval (Known Risk of TdP [KR]) or Potentially Cause Torsade de Pointes (TdP) (Possible Risk of TdP [PR])" and **add** the column "Time of stable use before initiation of the study drug" 70. On Page 116, **add** "Appendix 12. Hy's Law Criteria A drug-induced liver injury (DILI) event meeting Hy's Law criteria is defined as an elevation of ALT or AST of at least 3 times the upper limit of normal (ULN) accompanied by an elevation of total serum bilirubin of more than 2 times the ULN, without cholestasis (defined as serum alkaline phosphatase activity of less than 2 × ULN), and without alternative explanation, such as viral hepatitis, cancer progression, alcoholism, ischemia, previous liver disease, or other drugs (FDA, 2009)."

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Synopsis

Protocol number	ALSC006AST2818	
Title	A Phase III, Randomized, Double-blind, Positive-controlled, Multicenter Clinical Study to Compare Alflutinib Mesylate (AST2818) with Gefitinib as First-line Treatment in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer with EGFR Sensitive Mutation	
Version Number/Date	4.0 / Sunday, May 3, 2020	
Sponsor	Shanghai Allist Pharmaceutical Technology Co., Ltd. Project Lead: Li Ling	
PI	Shi Yuankai, Professor	
The phases of clinical trial	Phase III	
Indications	Locally advanced or metastatic non-small cell lung cancer (NSCLC)	
Study Objectives and Endpoints	**Study objectives**	**Study Endpoints**
	<u>Primary Objective</u>	<u>Primary endpoints</u>
	To evaluate the efficacy of alflutinib mesylate versus gefitinib as a first-line therapy in patients with locally advanced or metastatic non-small cell lung cancer with EGFR-sensitive mutations.	Progression free survival (PFS) assessed by Independent Radiological Committee as per RECIST 1.1.
	<u>Secondary Objectives</u>	<u>Secondary endpoints</u>
	1. To further evaluate the efficacy of alflutinib mesylate versus gefitinib as first-line treatment in	Overall survival (OS); Progression free survival (PFS) assessed by the investigator as per RECIST 1.1; Objective response rate (ORR) in

	patients with locally advanced or metastatic non-small cell lung cancer with EGFR-sensitive mutations;	accordance with RECIST 1.1, duration of response (DOR), depth of response (DepOR), time to progression (TTP) and disease control rate (DCR).
	2. To assess the safety of alflutinib mesylate versus gefitinib as first-line treatment in patients with locally advanced or metastatic non-small cell lung cancer with EGFR-sensitive mutations;	Type, frequency, seriousness and severity of treatment emergent adverse event (TEAE) (CTCAE version 5.0); Clinically significant laboratory test findings; Electrocardiogram (ECG); Left ventricular ejection fraction (LVEF); Physical examination findings (including vital signs, body weight and ECOG performance status score), etc..
	3. To compare the efficacy of first-line treatment with alflutinib mesylate and gefitinib in the population with Ex19del and L858R mutations positive locally advanced or metastatic non-small cell lung cancer respectively;	Progression free survival (PFS), objective response rate (ORR) and overall survival (OS) as per RECIST 1.1.
	4. To compare the efficacy of alflutinib mesylate alone versus gefitinib as first-line treatment in the population with locally advanced or	Progression free survival (PFS), objective response rate (ORR) and overall survival (OS) as per RECIST 1.1.

	metastatic non-small cell lung cancer with or without brain metastases respectively;	
	5. To assess the improvement in disease symptoms and quality of life with alflutinib mesylate alone versus gefitinib as first-line treatment in patients with locally advanced or metastatic non-small cell lung cancer with EGFR-sensitive mutations.	EORTC QLQ-C30 and EORTC QLQ-LC13.
	6. To compare the efficacy at brain of alflutinib mesylate alone versus gefitinib as first-line treatment in the population with locally advanced or metastatic non-small cell lung cancer with brain metastases respectively;	Central nervous system progression-free survival (CNS PFS), central nervous system duration of response (CNS DoR), central nervous system objective response rate (CNS ORR), central nervous system disease control rate at 6 weeks (CNS DCR_{6W}) and 12 weeks (CNS DCR_{12W}) evaluated by independent radiological committee using RECIST 1.1, in Chinese population with treatment-naïve locally advanced or metastatic non-small cell lung cancer with brain metastasis
	Exploratory Objectives	Exploratory Endpoint
	1. To assess EGFR mutational status and possible dynamic	To compare EGFR mutation status or possible changes in drug-resistant gene at

	resistance mechanisms during treatment with alflutinib mesylate and gefitinib.	baseline, steady-state and progression of disease through the ctDNA sourced from peripheral blood.
Trial design	This is a phase III, randomized, double-blind, multicenter clinical study to compare the efficacy and safety of alflutinib mesylate and gefitinib. About 358 patients with EGFR sensitive mutant, locally advanced or metastatic non-small cell lung cancer who are naïve to systematic treatment will be 1: 1 randomized to receive alflutinib mesylate 80mg per day orally under fasted state or Gefitinib 250mg per day orally under fasted state, in one cycle of therapy of 21 days, until progression of disease (PD) or reaching the criteria on termination of study treatment. Stratification factor: 1) genotype Ex19del or L858R mutation; 2) presence of concurrent brain metastasis. One tumor response evaluation will be performed once every 2 or 4 cycles (6 weeks ± 7 days or 12 weeks ±7 days) from Day 1 of the 1st cycle of therapy. Subjects who discontinue the treatment will be followed up every 12 weeks for disease condition. In case the investigator judges the subject could still benefit from continuation of treatment clinically after progression of disease, the treatment can be continued upon discussion and agreement by the sponsor. The subject, investigator and sponsor will be blinded during the study. One independent radiological committee (IRC) will be set up. According to the protocol version 3.0, when one-third of the PFS events (approximately 64 PFS events in 192 target number of PFS events) are observed, the sponsor will consider one blinded sample size assessment, which is based on the actual observed median PFS for the overall patient population. If the median PFS is slightly low overall, the sponsor will discuss necessary addition of events and corresponding adjustment of sample size with PI and regulatory authorities. In accordance with the median PFS in the blind sample size in the protocol	

	version 3.0, the target number of events will be adjusted, and one independent data monitoring committee (IDMC) will be set up for one interim analysis, see Section sample size and interim analysis for the details. For those subjects who have progressive disease and have discontinued study drugs, once T790M mutation-positive has been confirmed via blood sample or tissue test for T790M mutation, the patient should be unblinded. For the patients confirmed with negative T790M mutation, investigators can have a medical discussion with the sponsor on whether it can be unblinded, when the next therapeutic strategy may be possibly affected. The primary analysis for the primary endpoint PFS in this trial will be performed when at least 238 PFS events are observed.The safety and effectiveness results (including OS) of the primary analysis will be submitted to regulatory authorities as report for new drug application. End of study is defined as follow-up of OS for collection of OS data following completion of 238 PFS events, until about 60% death events are observed. The database is locked for the analysis of OS after the end of follow-up for OS. The final results of OS follow-up analysis will be submitted to the CDE as supplementary materials.
Estimated Investigation Time	48 months
Number of centers	About 55
Inclusion/exclusion criteria	**Inclusion criteria (only when all the following criteria are met):** 1) Subjects voluntarily participate in the study and sign the informed consent form; 2) Male or female subjects aged 18 above (18 inclusive); 3) ECOG performance status score is 0-1; no worsening within 2 weeks prior to the scoring of ECOG performance status; subjects with life expectancy ≥ 12 weeks judged by the investigator; 4) Histopathologically diagnosed, unresectable and incurable,

treatment-naïve locally advanced or metastatic pulmonary adenocarcinoma (e.g., can be systemic recurrence after previous operation for early tumor, or newly diagnosed stage ⅢB/IIIC/Ⅳ tumor. AJCC version 8 is used as the staging system for lung cancer);

5) At least one of the following EGFR sensitive mutations confirmed through central laboratory examination for the tissue sample diagnosed as locally advanced or metastatic pulmonary adenocarcinoma: Ex19del or L858R (single or mixed mutant genotype);
6) Patients must provide adequate tumor tissue sections (can not be sourced from the tumor lesion locally treated, such as irradiation, the newly occurred lesion following local therapy is acceptable) in screening period, for detection of EGFR mutation status at central laboratory, please see Central Laboratory Manual for the details;
7) No prior systemic anti-tumor therapy for advanced/metastatic non-small cell lung cancer. Patients who have received adjuvant therapy or neoadjuvant therapy (chemotherapy, radiotherapy or other therapy) can be enrolled if there is no progression within one year after treatment; for the patients who have received local therapy (radiotherapy or perfusion therapy in pleural cavity), they can participate in the study if the lesions in the range of local therapy are non-target lesions:
8) At least one tumor lesion can meet the following requirements in accordance with the response evaluation criteria in solid tumors (RECIST 1.1): it is not irradiated previously or biopsied for the screening period (if there is only one target lesion that must receive tissue biopsy, and there is no radiological examination meeting the exempting conditions in screening period, baseline tumor evaluation needs to be performed at least 14 days after the biopsy in screening period; if there is radiological examination meeting the exempting conditions in screening period as the baseline tumor evaluation, it can be determined by investigators whether

baseline evaluation will be performed again following biopsy based on the condition of lesions), and can be accurately measured at baseline, the longest diameter will be ≥10mm at baseline (short diameter is required to be ≥15mm for lymph nodes). The measurement method selected is suitable for repeated measurement accurately, and can be computed tomography (CT) or magnetic resonance imaging (MRI). If there is only one measurable lesion, it will be required not to be irradiated previously;

9) Females of childbearing potential must have a negative serum or urine pregnancy test within 7 days prior to the first dose. Adequate contraceptive measures must be taken for male patients and female patients of childbearing potential from the signature of informed consent form to 6 months after the last dose of study drug. For details, please refer to section 3.6 contraceptive measures, definition of women of childbearing potential and contraceptive requirement.

Exclusion criteria:

The patients meeting any one of the following criteria will be excluded from this study:

1) Having received any one of the following therapies prior to randomization:

- Previously receiving systematic antitumor therapy for advanced/metastatic non-small cell lung cancer (e.g., standard chemotherapy, targeted therapy, biotherapy, immunotherapy, etc.); please refer to the inclusion criterion 7 for neoadjuvant and adjuvant therapies;
- Previously receiving other systematic anticancer therapy for advanced/metastatic non-small cell lung cancer;
- Patients who have received intrapleural perfusion therapy can be enrolled only after the hydrothorax is stable for 28 days or above;
- Prior systemic anti-tumor therapy of EGFR-TKI;
- Having received major operation within 28 days prior to the first dose of

study drug (in China, for the definition of major surgical operation, please refer to grade 3 and 4 surgery specified in the Management Method for Clinical Application of Medical Technology implemented on May 1, 2009);

- Having received radiation in an area of ≥30% bone marrow or a wide range of radiotherapy within 28 days prior to the first dose of study drug; having received local radiotherapy or palliative radiotherapy for bone metastasis within 14 days prior to the first dose of study drug;
- Having received CYP3A4 potent inhibitor or inducer within 7 days prior to the first dose, or need to continue treatment with these drugs during the study (drug list is provided in Appendix 6 in detail);
- Having received the traditional Chinese medicine and Chinese patent drug preparation indicated for tumors within 7 days prior to the first dose, or need to continue treatment with these drugs during the study;
- Currently receiving the drug therapy known to prolong QTc interval, and need to continue treatment with these drugs during the study (drug list is provided in Appendix 7 in detail);
- Discontinuation of other clinical investigational products for less than 14 days prior to the first dose;

2) The toxicity associated with previous anti-tumor treatment do not recover to ≤CTCAE grade 1, except for alopecia and ≤CTCAE grade 2 peripheral neurotoxicity caused by chemotherapy; please refer to the exclusion criteria 7 for bone marrow and hepatic and renal functions;
3) Mixed histological type, i.e., pulmonary adenocarcinoma mixed with squamous cell carcinoma;
4) Presence of spinal compression or symptomatic brain metastasis; except the patients with no symptoms, stable condition or no need to use steroids for 28 days or above prior to the start of study treatment, the patients who have received local radiotherapy for brain metastasis can be enrolled only

after the brain metastasis symptoms are stable for 28 days or above, after the end of radiotherapy;

5) Having other malignant tumor or history of other malignant tumor; except basal cell carcinoma of skin, carcinoma in situ of cervix and ductal carcinoma in situ that have been effectively controlled;
6) Clinically serious gastrointestinal dysfunction that may affect the intake, transport and absorption of study drug, for example, inability to take drugs orally, uncontrollable nausea or vomiting, history of large area gastrectomy, uncured recurrent diarrhea, atrophic gastritis (age < 60 years at the onset of disease), uncured gastric disorder requiring long-term use of PPI antacid, Crohn's disease, ulcerative colitis;
7) Inadequate bone marrow reserve and hepatic and renal functions with the following laboratory values (no transfusion of blood or blood products, no use of granulocyte colony-stimulating factor or other hematopoietic stimulating factors for correction within two weeks prior to blood collection for laboratory test for enrollment):

- Absolute neutrophil count < 1.5×10^9/L;
- Haemoglobin <90g/L;
- Platelet count < 90×10^9/L;
- Serum total bilirubin >1.5×upper limit of normal (ULN); total bilirubin >3×ULN in case of determined Gilbert syndrome (unconjugated hyperbilirubinemia) or hepatic metastasis;
- Serum ALT and/or AST >2.5 × ULN (AST and/or ALT > 5× ULN for those with metastases to liver);
- Blood creatinine >1.5×ULN, or creatinine clearance < 50 mL/min (calculated according to Cockcroft-Gault formula, see Appendix 2 for details.);
- International normalized ratio (INR) > 1.5, and activated partial prothrombin time (APTT) >1.5×ULN;

8) Having cardiovascular disease meeting any one of the following conditions:

- Mean of three QTcFs on electrocardiography (ECG) >470msec under rested state, as calculated using Fridericia formula, see Appendix 9 for the details;
- Any important abnormalities with clinical significance in cardiac rhythm, conduction or morphology of resting ECG, e.g., complete left bundle branch block, third-degree heart block, second-degree heart block, PR interval>250 msec, etc.;
- Various factors that may increase the risk of prolonged QTc or arrhythmic event, for example, heart failure, hypokalemia, congenital long QT syndrome, sudden death for unknown reason in the first-degree relative before 40 years old in the family history;
- Left ventricular ejection fraction (LVEF) < 50%;

9) HBV, HCV or HIV active infection. All the subjects will be screened for HBV, HCV or HIV infection in screening period;

- Positive HBsAg and HBV DNA ≥1000cps/ml (or 200IU/ml) or HBV DNA above the minimum lower limit of detection (if the lower limit of detection of HBV DNA is above 1000cps/ml at the study site) ;
- anti-HCV antibody positive and HCV RNA positive;
- HIV antibody positive;

10) Known previous history of interstitial lung disease, drug induced interstitial lung disease, radiation pneumonitis requiring steroid treatment; or acute attack of or ongoing pulmonary symptoms that are considered by investigators as unsuitable for enrollment, or high-risk factors that are judged as possible interstitial lung disease and unsuitable for enrollment at baseline;

11) Known or suspected allergy to the study drug and/or its excipients;

12) Female patients in pregnancy or lactation;

	13) Presence of any disease or medical condition that is unstable or may affect its safety or compliance with the study, as considered by investigators, for example, uncontrolled hypertension, uncontrolled diabetes, active bleeding diathesis.
Study Drug	Investigational drug: Alflutinib Mesylate Tablets (AST2818), tablet, 40 mg/tablet; 2 tablets once, once daily, taken orally in fasting condition. Gefitinib dummy tablets, tablet, dummy tablets strength of 250 mg, 1 tablet once, once daily, taken orally in fasting condition. Comparator: Gefitinib, tablet, 250 mg/tablet, 1 tablet once, once daily, taken orally in fasting condition. Alflutinib Mesylate Tablet (AST2818) analogue tablet, tablet, 40mg specification, two tablets, once per day, orally, under fasted state.
Study Procedures	**Visits during screening period** <u>From Day -28 to Day -1 prior to the initial administration of study drug:</u> Prior to any specific study assessment or operation, all patients must sign the informed consent. The full medical history is required to be recorded at screening: • Inclusion/exclusion criteria confirmation; • Collection of unstained sections of tumor tissues; • Demographic data: including date of birth or age, gender, race/ethnicity; • Past medical history; • Previous history of tumor and antineoplastic treatment; • Current symptoms; • Physical examination; • Vital signs; • ECOG performance status score; • Laboratory test: including complete blood cell count test, coagulation

function, serum chemistry and urinalysis;

- Serum/urine pregnancy test (if applicable);
- NYHA classification and heart echocardiogram or MUGA scan;
- 12-lead-ECG;
- HBV, HCV, and HIV tests;
- Ophthalmological examination includes intraocular pressure examination, fundi examination and slit-lamp examination;
- Baseline tumor assessment according to RECIST1.1;
- Concomitant medications/accompanied treatments
- AE/SAE collection.

Visits during treatment period:

After completion of the evaluation at screening visit and all the inclusion/exclusion criteria by investigators, patients will be randomized in the study through IWRS if they are confirmed to be qualified.

Cycle 1, day 0 (C1D0):

- Inclusion/exclusion criteria reconfirmation;
- Quality of life score (EORTC QLQ-C30 and EORTC QLQ-LC13); subjects will come to the study site and complete the questionnaire independently or under the support by their family members (for illiterate subjects), prior to communication with healthcare professionals;
- Physical examination (without body height);
- Vital signs;
- ECOG performance status score;
- 12-lead-ECG;
- Laboratory test (including complete blood cell count test, serum chemistry and urinalysis);
- Serum/urine pregnancy test (if applicable);
- IWRS randomization;
- Collection of ctDNA blood samples prior to dosing;

	• Concomitant medications/accompanied treatments • AE/SAE collection. **Cycle 1, day 1 (C1D1):** • Vital signs; • ECOG performance status score; • Dispensing study drug and diary cards; • Administration of the first dose of study drug; • Concomitant medications/accompanied treatments • AE/SAE collection. **Cycle 1, day 8 (C1D8):** • Laboratory test (including complete blood cell count test, serum chemistry and urinalysis); **Subsequent cycles, day 1 (CXD1):** CXD1±3 days, once every cycle (21 days) from Cycle 2 – 6 (C2-C6); CXD1±7 days, once every two cycles (6 weeks) from Cycle 7-18 (C7-C18); CXD1±7 days, once every 4 cycles (12 weeks), after Cycle 18 (C19-CX). • Quality of life score (EORTC QLQ-C30 and EORTC QLQ-LC13); • Physical examination (without body height); • Vital signs; • ECOG performance status score; • Tumor assessments. Since C1D1, once every 6 weeks ± 7 days for the first 18 cycles or as clinically required; once every 12 weeks ± 7 days thereafter, or as clinically required; • 12-lead-ECG; • Heart echocardiogram or MUGA scan, once every 6 weeks ± 7 days for the first 18 cycles and once every 12 weeks ± 7 days thereafter, or as clinically required; • Laboratory test (including complete blood cell count test, serum chemistry and urinalysis);

	• Ophthalmological examination, as clinically required; • Concomitant medications/accompanied treatments • Collection of ctDNA blood sample (only on C3D1); • AE/SAE collection; • Dispensing and reclaiming study drug and diary cards. **Treatment termination visit (within 7 days after last dose):** • Quality of life score (EORTC QLQ-C30 and EORTC QLQ-LC13); • Physical examination (without body height); • Vital signs; • ECOG performance status score; • If a patient does not receive a heart echocardiography or MUGA scan within 28 days prior to termination of treatment/withdrawal from study, a heart echocardiography or MUGA scan should be performed at the time of termination of treatment/withdrawal from study; • 12-lead-ECG; • Laboratory test (including complete blood cell count test, serum chemistry and urinalysis); • Coagulation function; • Ophthalmological examination, as clinically required; • If a patient does not receive a tumor evaluation within 28 days prior to termination of treatment/withdrawal from study, a tumor evaluation should be performed at the time of termination of treatment/withdrawal from study; • Serum/urine pregnancy test (if applicable); • ctDNA blood samples will be collected at the time of disease progression; the patient may voluntarily provide additional histological specimens or sections containing adequate tumor tissues (see Central Laboratory Manual for details); • Collection of blood sample or tumor tissue sample for T790M mutation

testing;

- Concomitant medications/accompanied treatments
- Collection of AE/SAE, the AE/SAE occurred after start of a new antitumor therapy will be no more collected;
- Reclaiming of study drug and diary cards;
- New antineoplastic treatment and survival status.

Visit 28 days after last dose (28 days ± 7 after last dose):

It is recommended that the patient came to the hospital outpatient for follow-up or the patient should at least be followed up by phone:

- Collection of AE/SAE, the AE/SAE occurred after start of a new antitumor therapy will be no more collected;
- New antineoplastic treatment and survival status;
- Concomitant medications/accompanied treatments
- Subjects withdrawing treatment not for progression of disease will continue to receive tumor evaluation, until progression of disease, beginning of new anti-tumor treatment, withdrawal of informed consent, loss of follow-up, death or end of the study, whichever comes first.

Disease progression follow-up

Patients withdrawing treatment not for disease progression will continue to receive tumor assessments, until disease progression, withdrawal of informed consent by patients, loss of follow-up, death or end of the study, whichever comes first.

- New antineoplastic treatment and survival status;
- Tumor assessments;
- Concomitant medications/accompanied treatments
- Collection of AE/SAE (within 28 days after termination of treatment), the AE/SAE occurred after start of a new antitumor therapy will be no more collected.

	Survival visit: Information on subsequent antineoplastic therapies and survival status of patients will be collected every 12 weeks at follow-up by phone using the date of disease progression or the start date of the new antineoplastic therapy as the starting point.
Randomization and stratification information	At the screening visit, eligible subjects who have signed the informed consent form and met all the inclusion/exclusion criteria will be randomized in accordance with the following stratification information, as to ensure balanced randomization into group A and B: 1. EGFR mutation type: (Ex19del or L858R mutation); 2. With or without brain metastasis
Study variable	**Primary variable:** progression free survival (PFS) assessed by Independent Radiological Committee; **Secondary variable:** overall survival (OS), progression-free survival (PFS) evaluated by investigators, objective response rate (ORR), duration of response (DoR), depth of response (DepOR), time to progression (TTP), disease control rate (DCR), symptom improvement and quality of life improvement variable EORTC QLQ-C30 and EORTC QLQ-LC13, central nervous system progression-free survival (CNS PFS), central nervous system duration of response (CNS DoR), central nervous system objective response rate (CNS ORR), central nervous system disease control rate at 6 weeks (DCR_{6W}) and 12 weeks (CNS DCR_{12W}), safety evaluation. **Safety evaluation:** adverse events, including abnormal manifestations in clinical symptoms after administration, and clinically significant changes in physical examination, laboratory examination and ECG.
Research Hypothesis	Trial group (Alflutinib treatment group), median PFS is 16 months; Control group (Gefitinib treatment group), median PFS is 11 months.
Sample size estimate	The primary efficacy variable is PFS. Based on the blind data on the PFS judged by investigators in 66 subjects, it is considered by the sponsor to adjust

	the hypothesis in the protocol to increase number of events. When the first 358 subjects have been 1:1 enrolled within 6.5 months, assuming the median PFS of 16 months for Alflutinib and 11 months in gefitinib control group; the hazard ratio HR is 0.688 for the trial group versus control group and α is two-sided 0.05, a total of 238 target events are needed to provide at least 80% power to detect intergroup difference. After enrollment of 358 subjects in the study, the follow-up is expected to be at least 17 months, as to acquire 238 target events.
Statistical analyses	**Analysis population** This trial will use full analysis set, per-protocol set and safety set for statistical analysis. Full analysis set (FAS): According to the intent-to-treat (ITT) rules, the FAS includes all enrolled subjects that have taken at least one dose of the study drug. The FAS is the main population for efficacy evaluation in this study. Per-protocol set (PPS): Per-protocol set is a subset of the FAS that includes all subjects as defined by FAS who have completed the protocol-specified treatment or haven't had major protocol deviations requiring exclusion from the analysis set. The exact definition of major protocol deviations and the need for exclusion from the analysis set will be determined at the time of data review. The PPS set is the secondary analysis population for effectiveness; however, if the results are inconsistent with the full analysis set, the inconsistent results shall be analyzed in detail. Safety Set (SS): The SS includes all enrolled subjects who have received the study drug. **General analysis** SAS9.2 or above software is used for the statistical analysis, the full analysis set and per protocol set will be statistically analyzed, respectively. For the statistical description and inference of the data, appropriate statistical description and hypothesis test method will be selected based on the

distribution of the data. Number (number of missing case), minimum, maximum, mean, standard deviation and median will be listed for the statistical description of quantitative data; whereas the number and percentage of the variable corresponding level will be listed for qualitative data. Survival analysis method will be used for the data involving the time to event. Unless otherwise noted, two-sided hypothesis test will be used for all the statistical analysis tests, the hypothesis test level is set atα=0.05, i.e., the null hypothesis will be rejected if *P*value is less than or equal to 0.05, and the conclusion is statistically significant.

Baseline Assessments

Demographic characteristics will be descriptively summarized, and the other baseline data will be summarized or listed as appropriate.

Effectiveness evaluation

The primary efficacy endpoint is the PFS evaluated by independent radiological committee, stratified log-rank test will be used for comparison of the PFS between the two groups, p value will be calculated, the stratification factors are the type of EGFR mutation and presence of brain metastasis, the median PFS and its two-sided 95% CI will be estimated, Kaplan-Meier survival curve will be plotted, and Cox proportional hazard model will be used to calculate the hazard ratio and its 95%CI, the subgroup analysis will be performed to explore the effect of some factors, including the stratification factors, on PFS.

Subgroup analysis

1. To compare the efficacy of alflutinib mesylate alone with gefitinib as first-line treatment in the Chinese population with treatment-naïve locally advanced or metastatic non-small cell lung cancer with genotype Ex19del or L858R mutation positive respectively;
2. To compare the efficacy of alflutinib mesylate alone with gefitinib as first-line treatment in the Chinese population with treatment-naïve locally

advanced or metastatic non-small cell lung cancer with or without brain metastases respectively;

3. Cox proportional hazards regression models are used to perform subgroup analysis by the following characteristics (including but not limited to) to compare PFS between Alflutinib Mesylate group and Gefitinib group, estimate the hazard ratio and its 95% CI of Alflutinib Mesylate versus Gefitinib: gender (male vs. female), age at screening (<65 vs. ≥ 65), brain metastasis status at study entry, smoking history, and mutation type (Ex19del vs. Ex21) and ECOG PS score (0 VS. 1).

Analysis of secondary efficacy endpoints is as follows:

OS: stratified log-rank test will be used for comparison of OS between the two groups, the stratification factors are the type of EGFR mutation and presence of brain metastasis, the median OS and its two-sided 95% CI will be estimated, and Kaplan-Meier survival curve will be plotted.

PFS evaluated by investigators: stratified log-rank test will be used for comparison of the PFS evaluated by investigators between the two groups, p value will be calculated, the stratification factors are the type of EGFR mutation and presence of brain metastasis, the median PFS and its two-sided 95% CI will be estimated, Kaplan-Meier survival curve will be plotted, and Cox proportional hazard model will be used to calculate the hazard ratio and its 95%CI.

ORR evaluated by investigators and independent radiological committee: point estimation will be performed and Clopper-Pearson precision method will be used to estimate the 95% confidential interval (CI), Cochran-Mantel-Haenszel (CMH) test, chi-square test or Fisher exact test will be used to detect the difference between the two groups, and the intergroup difference in ORR rate and its 95%CI will be estimated. Subgroup analysis of ORR will be performed by the type of EGFR mutation and presence of brain metastasis, using the same analytical method.

DCR: the number and percentage of subjects with responses (PR+CR) and SD (duration of SD ≥ 12 weeks is required) will be calculated using the same analytical method as the evaluation variable of ORR.

DOR: the median DOR and its 95% CI will be estimated for the subjects with response, and Kaplan-Meier survival curve will be plotted, stratified log-rank test will be used to detect the difference between the two groups. DOR analysis population is only limited to the subjects with response records in the full analysis set.

DepOR: depth of response refers to the absolute change and percentage change of the smallest value of the sum of the longest diameters (or the shortest diameters of the lymph nodes) of target lesions from the baseline value in the absence of progression of non-target lesions and absence of new lesions, and the optimal value of depth of response will be generated from all efficacy evaluations performed before progression or before the start of subsequent anti-tumor therapy. Analysis of variance is used to compare the depth of response, calculate the unmodified mean, least squares mean, difference between the two groups, 95% CI of the difference, and p value of the optimal value of the depth of response, and compare the depth of response classified by the best overall response (BOR) of the two treatments with a waterfall plot.

TTP: the median TTP evaluated by investigators and independent radiological committee and its two-sided 95% CI will be estimated, and Kaplan-Meier survival curve will be plotted, stratified log-rank test will be used to compare the TTP between the two groups, p value will be calculated, and Cox proportional hazard model will be used to calculate the hazard ratio and its 95%CI.

EORTC QLQ-C30 and EORTC QLQ-LC13: Mixed Model for Repeated Measurements (MMRM) or analysis of covariance will be used to compare the quality of life (QoL) standard score between the two groups by treatment

group, uncorrected mean change in the standard score from baseline, least squares mean, difference between the two groups, 95% CI of the difference and p value will be calculated at each visit.

The analysis of primary efficacy endpoint will be based on FAS and PPS, respectively, with FAS as the primary analysis set. The analysis of secondary efficacy parameters will be based on FAS.

The Independent Radiological and Review Committee (IRC) will analyze the following efficacy variables based on the assessment results of measurable and non-measurable lesions in brain:

- CNS PFS (central nervous system progression-free survival): it is defined as the time from randomization to brain disease progression or death.
- CNS DoR (central nervous system duration of response): it is defined as the time from objective response (CR or PR) of measurable or non-measurable lesion in brain to brain disease progression or death.
- CNS ORR (central nervous system objective response rate): it is defined as the proportion of subjects with objective response (CR or PR) of measurable or non-measurable lesion in brain.
- CNS DCR_{6W} (central nervous system disease control rate at 6 weeks):it is defined as the proportion of subjects with disease control (duration of CR or PR or SD ≥ 6 weeks) of measurable or non-measurable lesion in brain.
- CNS DCR_{12W} (central nervous system disease control rate at 12 weeks):it is defined as the proportion of subjects with disease control (duration of CR or PR or SD ≥ 12 weeks) of measurable or non-measurable lesion in brain.

cFAS and cEFR will be used for analysis of the above central nervous system efficacy endpoint, using the same analytical method with that for the overall efficacy endpoint (the window period will be considered for the calculation), more detailed analytical method will be described in the statistical analysis plan.

Safety Evaluation

Vital signs: in accordance with the data on vital signs in screening period and at each follow-up time point, each vital sign and their changes from baseline will be statistically summarized for each time point.

Laboratory examination: the pooled analysis of laboratory examination will be mainly performed for complete blood cell count, routine urinalysis, serum chemistry and coagulation function, results of the laboratory examination items completed at each time point and normal/abnormal change from that prior to treatment (in accordance with the normal range and investigator's judgment on clinical significance) will be statistically summarized in a form of cross table, based on the laboratory examination results at baseline and each time point, and the abnormal results of laboratory examination will be presented in a tabular form for each time point.

Adverse event: all AEs will be classified according to the latest version of the International Conference on Harmonisation (ICH) Medical Dictionary for Regulatory Activities (MedDRA) coding and graded according to CTCAE v5.0. Summary of all the AEs is based on treatment emergent adverse events (TEAE).

(1) The number and percentage of all the TEAEs, TEAEs related with the study drug, SAE, grade 3 and above TEAEs, TEAEs leading to drop-out, TEAEs leading to death will be summarized.

(2) TEAE, TEAE related with the study drug and grade 3 and above TEAE will be descriptively summarized by system organ class and preferred term.

Other safety data will be presented in the form of summary tabulation or list.

Abbreviations

Abbreviations	English	English
ADR	Adverse Drug Reaction	药品不良反应
AE	Adverse Event	不良事件
AUC_{0-t}	Area under the plasma concentration-time curve from zero to last concentration time	曲线下面积 $_{0-t}$
$AUC_{0-\infty}$	Area under the plasma concentration-time curve extrapolated to infinity	曲线下面积 $_{0-\infty}$
ALK	Anaplastic Lymphoma Kinase	间变性淋巴瘤激酶
ALT	Alanine Transaminase (same as SGPT)	谷丙转氨酶
APTT	Activated Partial Thromboplastin Time	活化部分凝血活酶时间
AST	Aspartate Transaminase (same as SGOT)	谷草转氨酶
BRAF	v-Raf Murine Sarcoma Viral Oncogene Homolog B1	鼠类肉瘤滤过性毒菌致癌基因同源体 B1
C_{max}	Maximum plasma concentrations	达峰浓度
CI	Confidience Interval	置信区间
CL	Plasma clearance	血浆清除率
CNS DoR	Central Nervous System Depth of Release	脑转缓解持续时间
CNS DCR_{6W}	6 weeks Central Nervous System Disease Control Rate	6 周脑转疾病控制率
CNS DCR_{12W}	12 weeks Central Nervous System Disease Control Rate	12 周脑转疾病控制率
CNS ORR	Central Nervous System Objective Response Rate	脑转客观缓解率
CNS PFS	Central Nervous System Progress Free Survial	脑转无进展生存期
Cr	Serum creatinine	肌酐
CR	Complete Response	完全缓解
eCRF	electronic Case Report Form	电子病例报告表
CTCAE	Common Terminology Criteria for Adverse Events	不良事件的通用术语标准
CT	Computed Tomography	电子计算机断层扫描
DCR	Disease Control Rate	疾病控制率
DepOR	Depth of Release	缓解深度
DLT	Dose Limited Toxicity	剂量限制毒性
DNA	Deoxyribonucleic Acid	脱氧核糖核酸
DOR	Duration of Response	疾病缓解时间
ECOG	Eastern Cooperative Oncology Group	东部肿瘤协作组
ECG	Electrocardiogram	心电图
cEFR	Craniocerebral Evaluable for Response Set	颅内疗效可评估分析集
EGFR	Epidermal Growth Factor Receptor	表皮生长因子受体
EML4-ALK	Echinoderm Microtubule	棘皮微管结合蛋白 4-间

Abbreviations	English	English
	Associated-protein Like 4-Anaplastic Lymphoma Kinase	变性淋巴瘤激酶
FAS	Full Analysis Set	全分析集
cFAS	Craniocerebral Full Analysis Set	颅内全分析集
GCP	Good Clinical Practice	药物临床试验质量管理规范
h	hour(s)	小时
HBsAg	Hepatitis B Surface Antigen	乙型肝炎病毒表面抗原
HBV	Hepatitis B Virus	乙型肝炎病毒
HCV	Hepatitis C Virus	丙型肝炎病毒
HER2	Human Epidermal Growth Factor Receptor-2	人表皮生长因子受体 2
HNSTD	Highest Non-Severely Toxic Dose	最高非严重毒性反应剂量
HIV	Human Immunodeficiency Virus	人类免疫缺陷病毒
HR	Hazard ratio	风险比
HRQoL	Health-Related Quality of Life	健康相关生存质量
ICF	Informed Consent Form	知情同意书
ICH	International Conference on Harmonization	国际人用药物注册技术协调会
IDMC	Independent Data Monitoring Committee	独立数据监测委员会
ITT	Intention To Treatment	意向性治疗
IME	Important Medical Events	重要医学事件
INR	International Normalized Ratio	国际标准化
IRB	Institutional Review Board	伦理委员会
IRC	Independent Review Committee	独立影像学数据审核委员会
KRAS	Kirsten Rat Sarcoma Viral Oncogene	鼠类肉瘤病毒癌基因
MedDRA	Medical Dictionary for Regulatory Activities	监管活动医学辞典
mg	Milligram	毫克
Min	Minute	分钟
ml	Milliliters	毫升
MMRM	Mixed Model for Repeated Measurements	重复测量混合模型
MRI	Magnetic Resonance Imaging	磁共振成像
MTD	Maximum Tolerated Dose	最大耐受剂量
cMTS	Craniocerebral Metastases Set	颅内脑转集
MUGA	Multiple Gated Acquisition	多门电路探测
NCI	National Cancer Institute	美国国家癌症研究所
NMPA	National Medical Products Administration	国家药品监督管理局
NSCLC	Non-Small Cell Lung Cancer	非小细胞肺癌
NYHA	New York Heart Association	美国纽约心脏病协会

Abbreviations	English	English
NOAEL	No Observed Adverse Effect Level	无毒性反应剂量
ORR	Objective Response Rate	客观缓解率
OS	Overall Survival	总生存期
PD	Progressive Disease	疾病进展
PE	Physical Examination	体格检查
PFS	Progress Free Survial	无进展生存期
PI	Principal Investigator	主要研究者
PIK3CA	Phosphatidylinositol 3-Kinase Catalytic Alpha Polypeptide Gene	磷脂酰肌醇激酶-3-催化亚单位
PK	Pharmacokinetics	药代动力学
PR	Partial Response	部分缓解
PT	ProthrombinTime	凝血酶原时间
PTT	Partial Thromboplastin Time	部分凝血时间
PPS	Per-protocol Set	符合方案分析集
RECIST	Response Evaluation Criteria In Solid Tumors	实体瘤反应评估标准
RET	Rearranged During Transfection	转染重排
RNA	Ribonucleic Acid	核糖核酸
ROS1	ROS Proto-oncogene 1 Receptor Tyrosine Kinase	c-ros 肉瘤致癌因子-受体酪氨酸激酶
RP2D	Recommended Phase Ⅱ Dose	Ⅱ期推荐剂量
SAE	Serious Adverse Event	严重不良事件
SD	Stable Disease	疾病稳定
SOP	Standard Operating Procedure	标准操作流程
SS	Safety Set	安全性分析集
$t_{1/2}$	Half-life	半衰期
TEAE	Treatment Emergent Adverse Event	治疗期间出现的不良事件
TG	Triglyceride	甘油三酯
TKIs	Tyrosine Kinase Inhibitors	酪氨酸激酶抑制剂
TTP	Time To Progression	至疾病进展时间
ULN	Upper Limits of Normal	正常上限

1. Introduction

This study will be conducted in accordance with the moral, ethical and scientific principles specified in Good Clinical Practice in China, applicable government regulations as well as research policies and procedures at relevant clinical trial institutions.

1.1 STUDY BACKGROUND

Lung cancer is the malignant tumor with the fastest increase in its morbidity and mortality all over the world, and seriously endangers human health and life. As reported in the 2012 Annual report of China cancer registry[1], lung cancer is the main cause for cancer related death in China. 45.57/100,000 people die for lung cancer, including 61.00 men and 29.77 women per 100,000 people, the mortality in men is 2.05 times of that in women. In areas where the number of male smokers is high, there is an obvious change in the relative frequency of the type of lung cancer from squamous cell carcinoma to adenocarcinoma, regardless at home or abroad[2]. One study in the patients with newly diagnosed lung cancer showed that the percentage of squamous cell carcinoma was decreased from 30.41% in 1998 to 24.6% in 2007, and the percentage of adenocarcinoma was increased from 42.83% to 46.80%, in terms of the cancer subtype, from 1998 to 2007. This trend was more obvious in women[3]. Another study also found that the main histological subtype of lung cancer was obviously changed from squamous cell carcinoma to adenocarcinoma. However, the reason for this change needs to be further evaluated. In the past few decades, many molecular mechanisms of the development, growth and metastasis of lung cancer have been elucidated in translational research. Driver mutation is seen in the gene of signaling protein that is pivotal in coding cell proliferation and survival. In lung adenocarcinoma, this mutation is seen in EGFR, EML4-ALK, KRAS, ROS1, PIK3CA, BRAF, RET and HER2. Currently, tyrosine kinase inhibitors (TKIs) have been developed for these genes, including gefitinib, erlotinib and clozatinib, which are used in IPASS, BR.21 and Profile 1007 clinical trials, respectively. [4-7]Non-smoking associated pulmonary adenocarcinoma is the main subtype of lung cancer, and considered as one unique entity for its unique biological features. In recent years, a great number of studies have shown that EGFR, EML4-ALK, HER2, KRAS and BRAF are mainly seen in non-smoking associated adenocarcinoma. [8-9]The frequency of EGFR mutation is 28.0% in the unselected Chinese patients with non-small cell lung cancer (NSCLC)

and 48.5% in the patients with pulmonary adenocarcinoma. The frequency of KRAS mutation is lower in China, as compared with western countries. The frequency of EML4-ALK fusion is 6.4%, which is commonly seen in women, patients with adenocarcinoma, non-smokers and young patients. ROS1 fusion seems to be more common in the patients with adenocarcinoma[10]. These observations have changed the therapeutic strategy for lung cancer. Now it is believed that the gene test prior to treatment is critical, as to select the optimal therapeutic regimen.

The non-small cell lung cancer (NSCLC) ranks higher in the list of various types of lung cancers, accounting for about 80% ~ 85% of all lung cancers[11]. Activation of epidermal growth factor receptor (EGFR) is one common driver in non-small cell lung cancer, the EGFR mutation rate is higher in East Asians than that in the Caucasians, and such mutation is seen in about 10% Caucasians and 30% - 40% East Asians with non-small cell lung cancer[12].

With successive determination of a series of carcinogenic driver genes of lung cancer, multiple studies in China and abroad show the targeted therapeutic drugs have greatly improved the prognosis and prolonged the survival in NSCLC patients carrying corresponding driver genes[5,13-16]. The typing of lung cancer is also further subdivided into molecular subtypes based on driver genes, from the simple histopathological classification in the past[19-21]. The relationship between the efficacy of precise targeted therapy and molecular typing has been sufficiently demonstrated for advanced epidermal growth factor receptor (EGFR) sensitive mutant, anaplasticlymphoma kinase (ALK) positive NSCLC in clinical practice[5,13-18]. Results of the pivotal study CTONG1104 published in Lancet Oncology this year and EVAN study reported in World Conference on lung cancer (WCLC) support EGFR mutation detection in the patients with non-squamous cell NSCLC with N1N2 in the early stage post operation, as the postoperative adjuvant therapy with EGFR tyrosine kinase inhibitors (EGFR-TKIs) brings benefit for this portion of patients[22-23].

Multiple randomized, controlled studies on the first-line therapy for EGFR mutation positive, advanced NSCLC [5,13-15,24-29]have shown that Gefitinib, erlotinib, icotinib and Afatinib could significantly improve PFS, and the incidence of grade 3 and above adverse reactions was significantly lower as compared with chemotherapy, which established the position of Gefitinib, erlotinib, icotinib and Afatinib in the 1st-line therapy for EGFR mutant, advanced NSCLC. All the

four drugs have been approved by NMPA for the 1st-line therapy for EGFR mutant, advanced NSCLC.

Currently, the phase III randomized controlled studies comparing the 2nd generation EGFR-TKI Afatinib with chemotherapy as the 1st-line therapy for EGFR mutant, advanced NSCLC, LUX Lung3 [28] and LUX Lung6[15], have shown a significant improvement in PFS versus chemotherapy (11.1 months vs. 6.9 months, HR=0.58, 95% CI 0.43-0.78, P=0.001 and 11.0 months vs. 5.6 months, HR=0.28, 95% CI0.20-0.39, P<0.0001). A head-to-head comparison is also performed between the 1st and 2nd generation EGFR-TKI. The phase ⅡB study on the head-to-head comparison of Afatinib to the 1st generation EGFR-TKI gefitinib in the patients with EGFR mutation, LUX Lung7 [30], showed an improvement in median PFS (11.0 months vs. 10.9 months, HR=0.73, 95% CI 0.57-0.95, P=0.017), which was significantly different. The pooled analysis of the data from LUX-Lung 3 and LUX-Lung 6[31] showed that OS was significantly prolonged in Afatinib group compared with chemotherapy group, in the patients with exon 19 deletion (31.7 months vs. 20.7 months, HR=0.59, 95% CI 0.45-0.77, P=0.0001). The OS data in the patients with exon 19 deletion in Chinese subgroup in LUX-Lung 6[32] showed that the OS was significantly prolonged by 15.35 months in Afatinib group compared with chemotherapy group (31.61 months vs. 16.26 months, HR=0.61, 95% CI 0.41-0.91, P=0.0146). LUX-Lung 2, 3, 6 study showed [33]that the ORR was 71.1% and median PFS was 10.7 months (95% CI 5.6.-14.7) for Afatinib in the patients with the rare point mutation or complex mutation at exon 18~21 (Leu861Gln, Gly719Ser, Gly719Ala, Gly719Cys, Ser768lle and other rare sites). Afatinib was approved by NMPA for the 1st-line therapy for EGFR mutant, metastatic NSCLC in February 2017, In the phase III clinical study ARCHER 1050[34], the median PFS was significantly prolonged by the 2nd generation EGFR-TKI Dacomitinib versus gefitinib in the 1st-line therapy for EGFR mutation positive, advanced NSCLC (14.7 months vs. 9.2 months, HR 0.59, P<0.0001). The subgroup analysis in Chinese patients[35] showed a median PFS of 16.0 months and 9.2 months in dacomitinib group and gefitinib group, respectively (HR0.507, P<0.0001). In terms of safety, the adverse event was controllable in dacomitinib group. The efficacy and safety of the 3rd generation EGFR-TKI Osimertinib and the 1st generation EGFR-TKI in treatment of treatment-naïve, advanced, EGFR mutation positive NSCLC were compared in the randomized, double blind, phase III clinical study FLAURA[36], the results showed that Osimertinib

could significantly prolong PFS, reduce the risk for progression of disease by 54% (18.9 months vs. 10.2 months, HR0.46, 95%CI 0.37-0.57, p<0.001), and had a good safety profile as compared with the 1st generation EGFR-TKI, the incidence of grade 3 and above adverse events was lower in Osimertinib group than that in the standard treatment group (34% vs. 45%). Based on the results in this study, it is recommended in NCCN guideline to use the 3rd generation EGFR-TKI Osimertinib for the 1st-line therapy.

In order to further bring benefits for patients based on EGFR-TKI treatment, a great number of combined therapeutic patterns have been explored, including EGFR-TKI combined with chemotherapy or Bevacizumab. EGFR-TKI combined with chemotherapy pattern includes chemotherapy alternated by or simultaneously with daily EGFR-TKI: chemotherapy alternated by erlotinib was compared with simple chemotherapy in the 1st-line therapy for advanced NSCLC in the phase Ⅲ randomized, controlled study FASTACT-2[37], the median PFS and OS were significantly superior to simple chemotherapy in combined therapy group in the patients with EGFR mutation (median PFS: 16.8 months vs. 6.9 months, P<0.001; median OS: 31.4 months vs. 20.6 months, P=0.0092), the median PFS and OS in the combined therapy group were also improved compared with the historic data on EGFR-TKI alone. The phase III randomized, controlled study CTONG1509 on Bevacizumab combined with erlotinib versus erlotinib alone in treatment of advanced, non-squamous cell NSCLC with EGFR mutation is ongoing. Gefitinib simultaneously with Pemetrexed was compared with gefitinib alone as the 1st-line therapy for East Asian patients with EGFR mutant, advanced NSCLC in the phase II randomized controlled study JMIT[38], a significantly superior PFS was shown in the combined group over gefitinib monotherapy group (median PFS: 15.8 months vs. 10.9 months, P=0.029). The phase Ⅲ randomized controlled study NEJ009 on gefitinib combined with Pemetrexed and carboplatin versus gefitinib alone in treatment of EGFR mutant, advanced NSCLC is ongoing.

After a median disease control of 8~13 months, resistance to EGFR-TKI will appear finally, selection of treatment based on the clinical progression pattern has been demonstrated to have the significance of guiding clinical practice, the patients with EGFR-TKI progression will be classified into three types in accordance with the specific clinical evaluation criteria[39]: locally progressive, slowly progressive and rapidly progressive types. For the locally progressive patients, multiple

retrospective analyses have shown that continuation of EGFR-TKI combined with local therapy could still prolong PFS or TTP by 4.0~10.9 months after single or small amount of local progression in EGFR mutant patients; the subgroup analysis has shown a better efficacy in the patients with isolated progression or simple intracranial progression, as compared with those with multiple progressions and extracranial progression[40-45]. For the slowly progressive patients, the prospective study ASPIRATION[46]has explored the efficacy of continuous use of the 1st-line erlotinib in the patients with EGFR mutant, advanced NSCLC, following slow progression; the results showed that the median PFS was prolonged from 11 months (PFS1) to 14.1 months and achieved a benefit of 3.1 months in PFS in the patients continuing the medication; similar conclusion was also made in other observational studies and retrospective analysis[47-48].

For the patients with EGFR-TKI resistance, chemotherapy is currently still the classic therapeutic option. It remains controversial whether continuation of EGFR-TKI on chemotherapy could further benefit patients. The efficacy of chemotherapy and chemotherapy combined with gefitinib was compared in EGFR mutant patients following resistance to the first-line gefitinib in IMPRESS study[49-50], and no significant difference was seen in PFS in all the groups.

With progress of detection technology, gene analysis of re-biopsy after resistance to EGFR-TKI suggested that, EGFR T790M mutation is the main cause for resistance, accounting for approximately 50% or even higher[51-53]. The results from a randomized, phase III clinical study AURA3[54] comparing Osimertinib (a third generation EGFR-TKI) with platinum-based dual chemotherapy in treatment of NSCLC with EGFR-T790M-positive after resistance to the first-line EGFR-TKI showed that, compared with the standard chemotherapy, Osimertinib prolonged significantly PFS (10.1 months vs. 4.4 months, $p<0.001$). On March 22, 2017, Osimertinib was approved by NMPA of China for treatment of patients with locally advanced or metastatic non-small-cell lung cancer (NSCLC) who develop progressive disease after prior treatment with EGFR-TKI and are confirmed with EGFR T790M mutation positive by a test. By December 2016, Osimertinib had been approved by US FDA, EU EMA and China NMPA for the patients with locally advanced or metastatic T790M positive NSCLC in 47 countries (regions). Other clinical studies on positive T790M mutation are ongoing (AURA 17, NCT02442349; FLAURA, NCT02296125; ADAURA, NCT02511106).

Alflutinib mesylate (AST2818) is one third generation human epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor independently researched and developed by Shanghai Allist Pharmaceutical Technology Co., Ltd. AST2818 is demonstrated to be one effective inhibitor for EGFR sensitive mutant and T790M resistant mutant through systematic pharmaceutical and preclinical molecular mechanism, pharmacological, pharmacodynamic, pharmacokinetic and toxicological studies on AST2818; have weak inhibition on the activity of normal wild-type EGFR; oral administration of AST2818 has higher safety and tolerability than Osimertinib in rats and Beagle dogs; in the tumor model in nude mice, the inhibition on tumor is not inferior to Osimertinib.

1.2 PRECLINICAL STUDY[55]

1.2.1 MECHANISM OF ACTION

EGFR belongs to ErbB family, is one glycoprotein receptor, located in cell membrane and one product of EGF expression, and has receptor tyrosine kinase activity. There are four members in its family: EGFR (ErbB-1/HER1), ErbB-2 (HER2/neu), ErbB-3 (HER3) and ErbB-4 (HER4). EGFR consists of an extracellular ligand-binding domain, a single transmembrane region, and an intracellular domain harboring the tyrosine kinase. After binding of EGF or TGFa to the extracellular portion of EGFR receptor, it will form a homologous or heterodimer with other members of EGFR or ErbB family, Cause conformational change, thereby inducing autophosphorylation of tyrosine residues in the intracellular portion of the receptor, activation of EGFR, downstream signal transduction, regulation of cell proliferation, apoptosis, migration, survival and a series of complicated processes. EGFR downstream signaling pathways mainly include Ras/Raf/ERK/MAPK signaling pathway, PI3K/AKT signaling pathway and STAT3/5 signaling pathway. EGFR usually stays in an overactive state in tumor cells, making the regulation of cell cycle lost and leading to unlimited growth of tumor cells. Multiple studies have demonstrated that EGFR mutation and overactivation are important factors leading to uncontrolled cell growth and malignant proliferation, therefore, EGFR tyrosine kinase inhibitor (EGFR-TKI) is one important target molecule in tumor therapy.

There are numerous types of EGFR mutation, where L858R point mutation and exon 19 deletion account for 90% of all the mutations in lung cancer. The above two mutations are the effective

sensitive mutations for the 1st generation EGFR inhibitors. However, patients with EGFR mutation will finally have resistance to the 1st generation EGFR inhibitors. About 50% mechanism of drug resistance is associated with the substitution of Thr by Met at exon 20 of EGFR (T790M), i.e., T790M mutation, which increases the affinity of ATP binding to its receptor and reduces the blocking effect of the 1st generation TKIs. EGFR gene amplification, bypass signaling pathway (e.g., MET, HER2 and PIK3CA, epithelial-to-mesenchymal) conversion and tumor histological change are also involved in the mechanism of resistance to TKIs.

AST2818 is one effective inhibitor for EGFR /T790M resistant mutant and can effectively differentiate normal EGFR with EGFR T790M variation, has a weak inhibition on normal wild-type EGFR but greatly enhanced inhibition on EGFR T790M mutation. Thus, the inhibition on EGFRT 790M mutant can be achieved, on the premise the normal activity of EGFR is not affected as much as possible.

1.2.2 MAIN PHARMACODYNAMIC STUDIES

Human tumor cell xenograft model and human patient tumor tissue are selected for the response evaluation of AST2818. Cells with different phenotypes of EGFR are selected for human tumor cell xenograft model: H1975 (EGFR L858R/T790M), HCC827 (EGFR E746_A750del), PC-9 (EGFR Ex19del) and A431(EGFR WT), which can well represent the effect of the drug on EGFR sensitive mutant, drug resistant mutant and wild type.

In consideration of the adaptation of tumor cell lines passed continuously in vitro to the culture dish environment, lack of tumor microenvironment, for example, non-tumor stromal cell, extracellular matrix and microenvironment factor, makes these cell lines lose the characteristics of primary tumor after forming xenograft, and can not objectively reflect the condition of primary tumor. Human tumor tissue xenograft (PDX) model is selected. PDX model maintains the differentiation degree, morphological characteristics, structural features and molecular properties of tumor cells. To a certain extent, the characteristics of blood supply, matrix characteristics and necrotic status in PDX xenograft are consistent with that in human tumors. This provides a more consistent in vivo model with formal human trials for pharmacodynamic evaluation of tumor drugs. LU1868 model is originated from one patient with drug-resistant mutant T790M, and its potency has been recognized

in the development of multiple 3rd generation TKI drugs as the pharmacodynamic evaluation model.

The approved 1st generation EGFR inhibitor gefitinib, the 2nd generation EGFR inhibitor Afatinib and the 3rd generation EGFR inhibitor that is recognized with significant effect under clinical development are selected for the pharmacodynamic evaluation of AST2818. Generally accepted effective model, subcutaneous xenograft models in nude mice expressing EGFR L858R/T790M human lung cancer H1975, EGFR Ex19del human lung cancer PC-9, EGFR Del E746_A750 human lung cancer HCC827, wild-type EGFR human epithelial carcinoma A431, and human tumor tissue LU1868 are selected, which represent the potential clinical indications of AST2818.

The results show that AST2818 has a good activity in H1975 and LU1868 models expressing EGFR /T790M, which very clearly demonstrates an excellent efficacy of AST2818 in gefitinib-resistant tumors induced by EGFR T790M mutation. The efficacy is weak in the subcutaneous xenograft in nude mice expressing wild-type EGFR epithelial carcinoma A431, a good selectivity is shown that may obviously reduce the cutaneous toxicity of the 1st and 2nd generation EGFR inhibitors.

1.2.3 NON-CLINICAL PHARMACOKINETIC STUDIES

AST2818 has a high clearance in rats and dogs, with CL of 88.8 and 86.0 mL/min/kg, respectively; the tissue distribution is wide in rats and dogs, and the steady-state volume of distribution Vss is 20.0 and 22.5 L/kg, respectively. After intragastric administration, the exposure of the metabolite AST5902 is 132% ~ 215% and 20% ~ 36% of AST2818 in male and female rats, respectively; the exposure of the metabolite AST5902 is about 28% of AST2818 in dogs, and the metabolite is generated mainly through first-pass metabolism. In the dose range of 5~20 mg/kg, the increase of $C_{max}$and $AUC_{0-t}$of AST2818 and AST5902 is positively proportional to dose increase in rats; in the dose range of 1.5~6 mg/kg, the increase of C_{max} and $AUC_{0-t}$of AST2818 and AST5902 is higher in proportional to dose increase in dogs. The absolute bioavailability of AST2818 is 17.6% in male rats, 39.2% in female rats and 18.1%~51.7% in dogs. The elimination half-life of AST2818 in plasma is about 4.91 h in rats and 3.62 h in dogs, respectively. After administration for consecutive 7 days, the accumulation of AST2818 and the metabolite AST5902 is not obvious in rats and dogs.

After intragastric administration of AST2818 in rats, it is widely distributed in tissues, mainly including lung, digestive tract, spleen, kidney, bladder and ovarium; AST2818 can be distributed into

blood cells and also penetrate blood brain barrier. 168 h after administration, the drug concentration is reduced to below 10% of the concentration at 4h in all the tissues, except skin, testis and whole blood.

0–168 h after intragastric administration of [14C]AST2818 in rats, the recovery rate of radioactive substance is 88.7%, including 3.24% in urine, 1.86% in the flushing fluid in metabolic cage and 83.6% in feces. 0–48 h after administration in the rats receiving bile drainage operation, the excretion of radioactive substance in bile accounts for 54.6% of the dose administered. The parent drug in urine, feces and bile accounts for less than 4% of total radioactivity in rats, which shows that AST2818 is mainly eliminated through metabolism in rats, the main metabolic pathways are monooxidation, N-dealkylation, glutathione conjugation and further hydrolysis.

AST2818 basically has no inhibitory effect on CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, the IC50 is higher than 100 μM. AST2818 has no induction on CYP1A2 and CYP2B6, potential induction on CYP3A4 in human primary hepatocytes, which will be further judged in combination with its exposure in clinical trials.

The main metabolites of AST2818 in human hepatocytes can be detected in the hepatocytes of other species, with no obvious species difference. AST2818 mainly undergoes O-dealkylation, N-demethylation, monooxidation and double oxidation for metabolism in human liver microsomes, the main metabolite is N-demethylated metabolite M6-3 that is mainly catalyzed by CYP3A4, CYP2A6, 2C9 and 1A2 are involved in the generation of other metabolites.

AST2818 has low permeability and no efflux effect on Caco-2 cells in the concentration range of 2.00~50.0 μM.

1.2.4 TOXICOLOGY STUDIES

1.2.4.1 General safety pharmacology test

1) Neuropsychiatric System

Under the conditions of experiment, the no observed adverse effect level (NOAEL) of AST2818 for the central nervous system of SD rats was 200 mg/kg.

2) Cardiovascular and respiratory systems

Conscious Beagle dogs were monitored for consecutive 24 hours after single dose of AST2818 5, 15 and 45 mg/kg orally, no obvious drug related change was seen in each parameter of ECG, blood pressure and temperature.

After administration of AST2818 5, 15 and 45 mg/kg in conscious Beagle dogs, no obvious drug related change was seen in the respiratory variables (tidal volume, minute volume and respiratory frequency) in all the groups within continuous monitoring for 24 hours.

1.2.4.2 Acute toxicity test

SD rats were given single dose of 200, 800 and 1600 mg/kg AST2818 intragastrically, the target organs were spleen and thymus, the highest non-serious toxic dose (HNSTD) was 200 mg/kg and 800 mg/kg in female and male animals, respectively.

Beagle dogs were given single dose of 50, 200 and 500 mg/kg AST2818 intragastrically, no death was seen at each dose, the main reaction was the dose-dependent vomiting at the dose ≥200 mg/kg. The maximum tolerated dose (MTD) was 500 mg/kg, the exposure of AST2818 (AST5902), AUC_{0-t}, was 10770 (1592) ng·h/mL and 54780 (6132) ng·h/mL in female and male dogs, respectively, at this dose.

1.2.4.3 Long-term toxicity test

The 28-day toxicity study in SD rats showed the main target organs of toxicity were immune tissue/organ, kidney, duodenum, skin and hair after intragastric administration of AST2818 5, 25 and 75/50 mg/kg for 28 days, all the changes could be recovered except kidney after discontinuation of the drug. The no observed adverse effect level (NOAEL) was 5 mg/kg in female and male rats, the exposure of AST2818 (AST5902) was 263 (77.9) ng·h/mL and 137 (121) ng·h/mL, respectively, at this dose. The MTD was 25 mg/kg and 75 mg/kg, respectively, in female and male rats, the exposure of AST2818 (AST5902) was 998 (199) ng·h/mL and 2101 (1359) ng·h/mL, respectively.

The 28-day toxicity study in Beagle dogs showed that AST2818 2, 6 and 20 mg/kg could be tolerated in each dose group after intragastric administration for consecutive 28 days; the toxicity was characterized by gastrointestinal symptoms and changes in skin and esophagus, all the changes could

be recovered 4 weeks after discontinuation of the drug. The no observed adverse effect level (NOAEL) was 2 mg/kg, the plasma exposure of AST2818 (AST5902), AUC0-t, was 223 (77.7) ng·h/mL and 215 (71.1) ng·h/mL, respectively, in female and male dogs.

1.2.4.4 Mutagenicity test

1) Alflutinib Mesylate bacterial reverse mutation test

AST2818 has no mutation-inducing effect on Salmonella typhimurium strain TA97, TA98, TA100, TA102 and TA1535.

2) Alflutinib Mesylate chromosome aberration test in CHL cell

Under the condition of non-metabolic activation (-S9) for 4h, AST2818 has no effect of inducing chromosomal aberration in CHL cells; under the condition of -S9 24h and metabolic activation (+S9) for 4h, AST2818 has a suspicious effect of inducing chromosomal aberration at the dose ≥0.6 and 7.0μg/mL.

3) Alflutinib Mesylate bone marrow micronucleus test in mice

AST2818 does not induce an increase in the micronucleus rate of polychromatic erythrocytes in the bone marrow of mice.

1.2.4.5 Reproductive toxicity test and literature materials

The no observed adverse effect level (NOAEL) of AST2818 for the pregnant rats and embryo-fetal development was 15 mg/kg; no malformation of appearance, viscera or skeleton was observed in fetuses.

1.2.4.6 Carcinogenicity test

AST2818 is one anticancer agent and exempted from carcinogenicity test.

1.2.4.7 Dependence test

AST2818 is one anticancer agent and exempted from dependence test.

1.3 CLINICALSTUDIES[55]

Alflutinib Mesylate has carried out three clinical studies:

1) "A open-label, single-arm, multi-center Phase I clinical trial (ALSC001AST2818 Study) to evaluate the safety, tolerability and pharmacokinetic of Alflutinib Mesylate in patients with advanced non-small cell lung cancer who had progressed following treatment with human epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI)". All subjects have been enrolled.

2) "A multi-center, single-arm Phase I/II clinical trial (ALSC002AST2818 Study) to evaluate the efficacy and safety of Alflutinib Mesylate in patients with advanced non-small cell lung cancer who had progressed following treatment with first- and second-generation human epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI) ". All subjects have been enrolled.

3) "A multi-center, single-arm Phase IIb clinical trial (ALSC0031AST2818 Study) to evaluate the efficacy and safety of Alflutinib Mesylate Tablets in treatment of localized advanced or metastatic non-small cell lung cancer with positive T790M mutation" All subjects have been enrolled.

1.3.1 SAFETY RESULTS

During its treatment at 20~240mg for a long time, DLT does not occur; Alflutinib Mesylate is better tolerated for the subjects.

As shown by the analysis of existing AEs, the following AEs of higher incidence rate occur after the long-time administration of AST2818 at 20~240 mg: neutrophil decrease, leukocyte decrease, diarrhea, proteinuria, ALT/AST increase, acne-like rash, required bone marrow transplantation, and prolonged QT interval at ECG examination.

As shown by the analysis of safety data, after the long-time administration of AST2818 at 20~240 mg, the type of AE does not go beyond the expectation and its frequency/severity is acceptable; diarrhea and skin reactions are mild; dose-related adverse reactions are temporarily not found; since liver damage and immune cell decrease may potentially be caused by AST2818, the monitoring and

risk control should be further reinforced.

1.3.2 EFFICACY

At present, the data of at least one imaging for 87 subjects receiving AST2818 (20~240 mg/d) have been obtained.

Overall response rate (ORR) is 61%. As preliminarily shown, AST2818 is of rapid effect initiation (median time of effect initiation is 42 days) and good continuity of efficacy; and it may be effective for brain metastasis.

1.3.3 HUMAN PHARMACOKINETIC PROFILE

As shown by preliminary results of pharmacokinetic analysis, when the dose of AST2818 is increased from 20 mg to 240 mg, blood medicine concentration is of obvious dose dependence; AST2818 has a longer half-life, which conforms to the design of qd administration.

1.3.4 Summary

According to the above study results, the tolerance, long-term safety and preliminary efficacy of AST2818 are analyzed and summarized.

1) As shown by existing data, AST2818 is well tolerable.

2) The type of AE for AST2818 does not go beyond the expectation.

3) A response is achieved at the dose of 20 mg, and a significant response is achieved at the dose of 40~160 mg.

1.4 Principles of study and basis for setup of the topic

1.4.1 Basis for the selected dose

In this double-blinded study, the dose of Alflutinib Mesylate Tablets is selected as 80 mg for the following reasons.

1. As shown by the results of preclinical study, the best-effect dose of Alflutinib Mesylate may be 80~160 mg/d; the low dose is designed according to the characteristics of its high concentration in pulmonary tissue.

As shown by the results of preclinical study, Alflutinib Mesylate is of high activity and high selectivity for sensitive mutation of EGFR and drug-resistant mutation of EGFR/T790M. As shown by the results of comparison study, both Alflutinib Mesylate and AZD9291 (a marketed drug) are of similar activity for sensitive mutation of EGFR and drug-resistant mutation of EGFR/T790M. Since recommended Phase II dose (RP2D) of AZD9291 is 80mg and plasma medicine exposure of Alflutinib Mesylate is lower than that of AZD9291, human best-effect dose of Alflutinib Mesylate is inferred as possibly 80~160 mg/d.

As also shown by the results of preclinical study, Alflutinib Mesylate is of very high concentration in pulmonary tissue as >70 folds of blood medicine concentration, which is far higher than the concentration ratio between lung and whole blood (i.e. 32.6) for AZD9291 (a drug of same kind); the treatment effect of Alflutinib Mesylate for lung cancer may be improved at lower concentration, and the potential safety hazard for lung will also be increased correspondingly at a higher concentration. Therefore, with the premise of same efficacy dose, higher safety is possessed at low dose.

2. Optimal dose of Alflutinib Mesylate is selected as 80 mg according to its clinical pharmacokinetic data.

As shown by the results of pharmacokinetic test at Phase I and Phase I/II clinical study, after the administration of Alflutinib Mesylate at 20~80 mg, plasma medicine exposure is increased linearly; as its dose is further increased, a saturated absorption begins to be achieved at 160~240 mg. Since plasma medicine exposure is closely related to the efficacy and safety of a drug, the dose before the achievement of saturated absorption should be a better dose; therefore, optimal dose of Alflutinib Mesylate is selected as 80 mg according to its clinical pharmacokinetic data.

3. After the administration of Alflutinib Mesylate at 80 mg and 160 mg, similar ORR is achieved.

As shown by the results of early clinical studies (i.e. Phase I and Phase I/II), after the administration of Alflutinib Mesylate at at 80 mg and 160 mg, similar ORR is achieved, which consists with the efficacy results of AZD9291 (a target drug of same kind); indicating that a phenomenon of efficacy saturation exists for such kind of target drug, i.e. after effective dose is achieved, drug effect can not be further improved with the dose.

4. As inferred, the safety of Alflutinib Mesylate at 80 mg may be superior to that at 160 mg.

As shown by the results of Phase I and Phase I/II clinical study, the following AEs of higher incidence rate occur after the long-time administration of AST2818 at 20~240 mg: neutrophil decrease, leukocyte decrease, diarrhea, proteinuria, ALT/AST increase, acne-like rash, required bone marrow transplantation, and prolonged QT interval at ECG examination; the incidence rate of leukocyte decrease, ALT increase, anemia and AST increase at 160 mg was significantly higher than at 80 mg.

As shown by the results of clinical pharmacokinetic test, a higher medicine exposure is achieved after the administration of Alflutinib Mesylate at 160 mg; as shown by the results of clinical study on AZD9291 (a drug of same kind), the incidence rate of diarrhea, skin reactions, neutrophil decrease and prolonged QTc interval is increased at a concentration dependence (obvious reinforcement occurs at 160 mg). Therefore, as inferred, a greater potential safety hazard may be caused after the administration of Alflutinib Mesylate at high dose; and its safety at 80 mg should be superior to that at 160 mg.

Based on the above results, within the dose range selected according to the results of preclinical study, optimal dose of Alflutinib Mesylate for further clinical study is determined as 80 mg/d by overall considering the characteristics of medicine absorption and the preliminary results of efficacy/safety.

1.4.2 Basis for the selected indication(s)

T790M mutation of EGFR is the most common mechanism for drug resistance; it is found in >50% of patients with a progressive disease after the treatment of Gefitinib or Nilotinib. In addition, primary T790M mutation is carried in some patients before the treatment of EGFR TKI. For advanced NSCLC with a drug-resistant mutation of either acquired or primary type, a better clinical benefit will be achieved by early application of third-generation EGFR TKI, which inhibits the drug-resistant mutation of T790M and the sensitive mutation of EGFR and postpones the time for effect initiation of drug-resistant mutation.

Third-generation EGFR TKI is not only of high selectivity for T790M mutation of EGFR, but also

reduces the toxic reactions caused by the inhibition of wild-type EGFR. In November 2015, Osimertinib (AZD9291) was approved by FDA for marketing as the first kind of approved third-generation tinibs drugs; in March 2017, it was approved for marketing in China. Both drug-resistant mutation of T790M and sensitive mutation of EGFR are inhibited by Osimertinib. In April 2018, Osimertinib was approved by FDA for first-line treatment of advanced NSCLC with a mutation of EGFR, according to the results of randomized controlled Phase III clinical study (FLAURA) on comparing Osimertinib with first-generation EGFR TKI (Gefitinib and Nilotinib).

Alflutinib Mesylate is a third-generation EGFR TKI of small molecule; it not only inhibits both sensitive mutation of EGFR (such as deletion of exon 19 and mutation of L858R) and drug-resistant mutation of T790M in an irreversible and highly-selective way, but also has a very low activity for wild-type EGFR. According to the characteristics of its target point and the results of efficacy and safety for NSCLC with T790M(+), the clinical benefit of Alflutinib Mesylate will be better than that of first-generation or second-generation tinibs drugs in the patients of first-treated localized advanced or metastatic NSCLC with positive EGFR mutation.

According to the above results, Alflutinib Mesylate is applicable for the patients of first-treated localized advanced or metastatic NSCLC with positive EGFR mutation.

1.4.3 Risk-benefit ratio of this study

Potential risks and control plans

1. For gastrointestinal adverse events

According to the results of clinical study on drugs of same kind and the findings of early clinical study on Alflutinib Mesylate, Alflutinib Mesylate may cause gastrointestinal reactions (mainly diarrhea). If gastrointestinal reactions occur (such as vomiting and diarrhea), drugs for symptomatic treatment such as Loperamide Hydrochloride Capsules (Imodium) should be given when necessary to control the illness state and recover as soon as possible. When serious diarrhea is ineffectively treated by Loperamide or a dehydration occurs, Alflutinib Mesylate should be suspended.

2. For cutaneous adverse events

According to the results of clinical study on drugs of same kind and the findings of early clinical

study on Alflutinib Mesylate, Alflutinib Mesylate may cause skin reactions (mainly rash). If skin reactions occur, drugs for symptomatic treatment should be given when necessary to control the illness state and recover as soon as possible. Subjects with severe skin reactions require temporary discontinuation of treatment. When serious bullous, vesicular or exfoliative skin disease occurs, Alflutinib Mesylate should be suspended or discontinued.

3. For ocular adverse events

Although obvious eye reactions have recently not yet been shown after the administration of Alflutinib Mesylate, few eye reactions are found at the clinical study on drugs of same kind. If cornea ulcer occurs in any subject, the study must immediately be stopped permanently, and relevant drugs should be given until this ulcer is resolved, by referring to the data of drugs of same kind. When acute or aggravating eye disease occurs, Alflutinib Mesylate should be suspended or discontinued. Subjects who wear contact lenses recommended to discontinue wearing their lenses if they have any mild to moderate eye symptoms (CTCAE grade ≤2) while receiving drug treatment until at least one week after symptoms have resolved. If eye symptoms or any serious recurrent eye reaction (Grade ≥3, CTCAE), the wearing of contact lens should be stopped for at least one week after the discontinuation of Alflutinib Mesylate. Within at least one week after the discontinuation of Alflutinib Mesylate, eyedrops or ocular ointments must not be used for treating the eye symptoms, except after the prior permission of investigators. If any problem occurs in the subjects, please immediately visit a hospital for consultation.

4. For pulmonary adverse events

As shown by clinical study on drugs of same kind, lung reactions are caused (mainly interstitial lung disease). When new acute or progressive lung symptoms occur (such as dyspnea, cough and fever), Alflutinib Mesylate should be suspended, and diagnostic assessment is made. If interstitial lung disease occurs, Alflutinib Mesylate should immediately be discontinued, relevant treatment should be given, and Alflutinib Mesylate can be withdrawn.

5. For blood adverse events

According to the results of clinical study on drugs of same kind and the findings of early clinical

study on Alflutinib Mesylate, Alflutinib Mesylate may cause blood reactions (mainly leukocyte decrease and neutrophil decrease). If blood reactions occur, G-CSF, GM-CSF or EPO can be given, according to the guideline of American Society of Clinical Oncology and relevant Chinese clinical guidelines. If AE of Grade ≥3 occurs, Alflutinib Mesylate should be suspended.

6. For hepatic and renal toxicity events

According to the results of clinical study on drugs of same kind and the findings of early clinical study on Alflutinib Mesylate, Alflutinib Mesylate may cause liver injury (mainly ALT increase and AST increase caused by liver injury) or kidney injury (creatinine increase). If liver/kidney toxic reactions occur, drugs for symptomatic treatment should be given when necessary to control the illness state and recover as soon as possible. If serious reactions (such as those of Grade ≥3) occurs, Alflutinib Mesylate should be suspended, until the conditions are restored to baseline state or such reactions are of Grade ≤1.

7. For cardiotoxic events

According to the results of clinical study on drugs of same kind and the findings of early clinical study on Alflutinib Mesylate, Alflutinib Mesylate may cause a prolonged QTc interval. If heart reactions occur, drugs for symptomatic treatment should be given when necessary to control the illness state and recover as soon as possible. Please refer to the principle of dose adjustment for details.

Known possible benefits:

After the administration of Alflutinib Mesylate for first-line treatment in the patients of advanced NSCLC with positive EGFR mutation, the following clinical benefit may be achieved:

1. the possible cloning of T790M mutation of EGFR is cleared in early period; and the progression of disease is better controlled.

As shown by the results of Phase III clinical trial on Osimertinib (a kind of third-generation EGFR TKI), median progression-free survival period (mPFS) is 18.9 and 10.2 months after the administration of Osimertinib and first -generation EGFR TKI (Gefitinib or Nilotinib) respectively; the risk for progressive disease is reduced by 54% through Osimertinib.

2. It may be effective against brain metastases

Brain metastasis is the most common reason for the first occurrence of progressive disease after the treatment of first -generation EGFR TKI. In patients with initial diagnosis of NSCLC, the incidence of brain metastases was approximately 20%~30%. During the course of progression of NSCLC, brain metastasis occurs by about 50%. A limited effect for brain metastasis is achieved by first -generation EGFR TKI. By passing through blood-brain barrier, Alflutinib Mesylate may effectively control, prevent or postpone the occurrence of brain metastasis. As shown by the results of early clinical study, Alflutinib Mesylate may be effective for brain tumor.

3. Active metabolites of Alflutinib Mesylate are highly selective, and its safety may be higher.

As shown by the results of preclinical study, the selectivity of active metabolites of Alflutinib Mesylate is higher than that of drugs of same kind; at a high dose, fewer gastrointestinal or skin reactions may be caused. Above inference has been verified by the results of current clinical studies.

As shown by the existing data of preclinical study and clinical study, a good efficacy and safety for advanced NSCLC with positive EGFR mutation will be achieved by Alflutinib Mesylate.

2. Study objectives

2.1 Primary objective

To evaluate the efficacy of alflutinib mesylate monotherapy versus gefitinib as a first-line therapy in patients with locally advanced or metastatic non-small cell lung cancer with EGFR-sensitive mutations.

2.2 SECONDARY OBJECTIVES

- To further evaluate the efficacy of alflutinib mesylate monotherapy versus gefitinib as first-line treatment in patients with locally advanced or metastatic non-small cell lung cancer with EGFR-sensitive mutations;
- To evaluate the safety of alflutinib mesylate monotherapy versus gefitinib as first-line treatment in patients with locally advanced or metastatic non-small cell lung cancer with EGFR-sensitive mutations;

- To compare the efficacy of first-line treatment with alflutinib mesylate and gefitinib in the population with Ex19del and L858R mutations positive locally advanced or metastatic non-small cell lung cancer respectively;
- To compare the efficacy of first-line treatment with alflutinib mesylate versus gefitinib in the population with locally advanced or metastatic non-small cell lung cancer with or without brain metastases respectively;
- To assess the improvement in disease symptoms and quality of life with alflutinib mesylate monotherapy versus gefitinib as first-line treatment in patients with locally advanced or metastatic non-small cell lung cancer with EGFR-sensitive mutations.
- To compare the efficacy at brain of alflutinib mesylate alone versus gefitinib as first-line treatment in the population with locally advanced or metastatic non-small cell lung cancer with brain metastases respectively;

2.3 EXPLORATORY OBJECTIVE(S)

To assess EGFR mutational status and possible dynamic resistance mechanisms during treatment with alflutinib mesylate and gefitinib.

3. Study plan

3.1 STUDY DESIGN AND PLAN

3.1.1 Experiment design

This is a phase III randomized, double-blind, double-dummy, parallel controlled, multicenter clinical study to compare the efficacy and safety of alflutinib mesylate monotherapy (80 mg po qd on an empty stomach) and gefitinib monotherapy (250 mg po qd on an empty stomach). Approximately 358 treatment-naive Chinese patients with locally advanced or metastatic lung adenocarcinoma with EGFR-sensitive mutations who met all the screening criteria are randomly assigned at the ratio of 1:1 to receive either alflutinib mesylate monotherapy (80 mg taken orally on an empty stomach daily) or gefitinib monotherapy (250 mg taken orally on an empty stomach daily), every three weeks for one cycle. Patients will continue treatment until progression of disease (PD), initiate new antitumor

therapy, death, intolerable toxicity, withdrawal of informed consent, discontinuance at the investigator's discretion, loss of follow-up or termination of the study, whichever occurrs first.

According to the mutation of Ex19del or L858R gene and the occurrence of brain metastasis or not, the enrolled patients are stratified for analysis.

From Day 1 of the first treatment cycle, the efficacy for tumor is assessed once every 2 or 4 cycles (6 weeks ± 7 days or 12 weeks ± 7 days) or according to the clinical need. According to RECIST 1.1, the efficacy for tumor is assessed through the same methods of imaging examination (CT/MRI) as those during screening period. Patients withdrawing treatment not for progression of disease will continue to receive tumor evaluation every 6 weeks ± 7 days, if possible, until progression of disease, initiate new anti-tumor therapy, withdrawal of informed consent, loss of follow-up, death or termination of the study, whichever comes first.

After the progression of disease, the conditions of tumor treatment and the data of survival are followed up once every 12 weeks, until the withdrawal of informed consent by subjects (including the follow-up), loss to follow-up, death of subjects, terminiation of study or completion of whole study. If investigators judge that clinical benefit can still be achieved by the continuation of treatment after the progression of disease, the treatment can be continued after the discussion with the sponsor, until clinical benefit can not be achieved in the viewpoints of investigators.

The subject, investigator and sponsor will be blinded during the study. Meanwhile, in order to reduce the bias at imaging assessment, Independent Review Committee for Imaging Assessment (IRC) is established to assess the images obtained from the randomized controlled study. According to RECIST 1.1, data of tumor imaging assessment (CT or MRI) are evaluated in all subjects by stage and at blind state.

According to the protocol version 3.0, when one-third of the PFS events (approximately 64 PFS events in 192 target number of PFS events) are observed, the sponsor will consider one blinded sample size assessment, which is based on the actual observed median PFS for the overall patient population. If the median PFS is slightly low overall, the sponsor will discuss necessary addition of events and corresponding adjustment of sample size with PI and regulatory authorities. According to the median value of PFS at blind-state sample size in study protocol (version 3.0), the number of

target events is adjusted; Independent Data Monitoring Committee (IDMC) is established; and one interim analysis is planned (See the chapter of sample size and interim analysis).

For those subjects who haveprogressive diseaseand have discontinued study drugs, T790M mutation was detected through blood sample or tissue test, Patients with T790M positive mutation should be unblinded. For the patients confirmed with negative T790M mutation, investigators can have a medical discussion with the sponsor on whether it can be unblinded, when the next therapeutic strategy may be possibly affected. The primary analysis for the primary endpoint PFS in this trial will be performed when at least 238 PFS events are observed.The safety and effectiveness results (including OS) of the primary analysis will be submitted to regulatory authorities as report for new drug application.

End of study is defined as follow-up of OS for collection of OS data following completion of 238 PFS events, until about 60% death events are observed. The database is locked for the analysis of OS after the end of follow-up for OS. The final results of OS follow-up analysis will be submitted to the CDE as supplementary materials.

If PFS is not achieved after the termination of study in a certain subject after the administrationo of Alflutinib Mesylate or Gefitinib, study drug can continue to be provided by the sponsor after the assessment of investigators and the permission of this subject, until the subject can not be benefited in the viewpoints of investigators or the request of subject for termination of study (whicher occurs first). At this stage, the sponsor only provide study drug (Alflutinib Mesylate) or control drug (Gefitinib), and only collect SAE for entering into additional safety database.

3.1.3 Primary endpoints

According to RECIST 1.1, Progression Free Survival (PFS) evaluated by an independent review committee: time from post-randomization to the time subjects experienced tumor disease progression or death.

3.1.4 Secondary endpoints

The secondary objectives of the study including:

- Overall survival (OS);

- Progression free survival (PFS) assessed by the investigator as per RECIST 1.1;
- Objective response rate (ORR), duration of response (DOR), depth of response (DepOR), time to progression (TTP) and disease control rate (DCR) as assessed by the investigators and IRC according to RECIST 1.1, progression-free survival (PFS) assessed by investigators according to RECIST v1.1 criteria ;
- Type, frequency, severity, and degree of treatment-emergent adverse events (TEAEs) in the course of treatment using NCI-CTCAE v 5.0 (CTCAE Version 5.0);
- Clinically significant laboratory test findings;
- Electrocardiogram (ECG);
- Left ventricular ejection fraction (LVEF);
- Physical examination findings (including vital signs, body weight and ECOG performance status), etc.
- PFS, ORR and OS as assessed according to RECIST 1.1 in Chinese patients of first-treated localized advanced or metastatic NSCLC with sensitive mutation of Ex19del and L858R;
- PFS, ORR and OS as assessed according to RECIST 1.1 in Chinese patients of first-treated localized advanced or metastatic NSCLC with or without brain metastasis;
- PFS of brain metastasis (CNS PFS), DOR of brain metastasis (CNS DoR), ORR of brain metastasis (CNS ORR), 6-week DCR of brain metastasis (CNS DCR_{6W}) and 12-week DCR of brain metastasis (CNS DCR_{12W}) as assessed by IRC according to RECIST 1.1 in Chinese patients of first-treated localized advanced or metastatic NSCLC with brain metastasis;
- EORTC QLQ-C30 and EORTC QLQ-LC13;

3.1.5 EXPLORATORY ENDPOINT

- To compare EGFR mutation status or possible changes in drug-resistant gene at baseline, steady-state and progression of disease through the ctDNA sourced from peripheral blood.

3.2 RANDOMIZATION AND BLINDING

This study is a randomized, double-blinded, double-simulated, parallel-controlled multi-center Phase III clinical trial. Through the international web randomization system (IWRS), the patients are randomly grouped by the competition of each center. All subjects who signed the informed consent form are assigned with a subject screening number and entered the screening. After screening qualified, chinese patients with treatment-naive locally advanced or metastatic lung adenocarcinoma with EGFR-sensitive mutation who meet all the screening criteria are randomly assigned to receive alflutinib mesylate monotherapy (80 mg, taken orally on an empty stomach daily) or gefitinib monotherapy (250 mg, taken orally on an empty stomach daily) every 3 weeks at the ratio of 1:1 in a stratified manner with EGFR mutation status (Ex19del VS.L858R) and brain metastasis status (with VS. without) at enrollment. Subjects who pass the screening will receive a unique randomization number on the day prior to the initial dose of the study drug (C1D0, i.e. prior to the first treatment cycle). The Investigator will assign a randomization number and medication number to all screened eligible subjects who are suitable for the study after randomization. If multiple subjects are scheduled to be randomized on the same day, randomization should occur in the order in which the subject arrived, rather than in the order of the screening number. If a subject's medication becomes damaged during the study, the investigator can obtain a new medication number through the IWRS system and proceed with the clinical trial. If the subject is not randomized, the reason for non-inclusion must be documented.

Non-blind randomization and blinding will be done by the randomization and blinding team of the statistician who are independent of this trial.

3.3 BLINDING MAINTENANCE AND UNBLINDING

This study is a double-blind trial in which the sponsor, investigators and subjects are blinded until the primary analysis ofthe primary endpoint PFS(except for those meeting requirements of the study unblinding conditions), and any of the subject information and grouping shall not be disclosed.

During this study, randomization number and medication number will be obtained from the IWRS. The blind control of the drug uses the double-dummy technique, and the alflutinib mesylate tablets and alflutinib mesylate mock tablets (as well as gefitinib tablets and gefitinib mock tablets) will use

the exact same packaging, administration method, label, appearance, taste and smell to hide the therapeutic drug. Combined package of alflutinib mesylate tablets and gefitinib mock tablets, combined package of Gefitinib Tablets and alflutinib mesylate mock tablets will be given the drug number after unified package. The blind codes are stored in the IWRS system and the randomization specialist.

Emergency Unblinding

Urgent unblinding: individual unblinding was only applicable for the need of urgent medical intervention, the detailed requirements on the unblinding process are seen in the clinical study protocol (). The investigator should note that the occurrence of SAE is not a prerequisite for routine immediate unblinding.

If emergency unblinding is required to treat the SAE for the patient, the investigator must immediately notify the sponsor's medical monitor to request unblinding (the investigator may unblind the patient before notifying the sponsor only in case of possible delay in emergency treatment of the patient). After approval, the sponsor authorizes the IWRS system so that the investigator can unblind the patient. The Sponsor will not be made aware of the patient's actual treatment through the emergency unblinding process.

Unblinding after withdrawal

For those subjects who have progressive disease and have discontinued study drugs, once T790M mutation-positive has been confirmed via blood sample or tissue test for T790M mutation, the patient should be unblinded. The sponsor authorizes the IWRS system so that the investigator can unblind the patient. When the next treatment strategy may be influenced in the patients confirmed as negative T790M mutation, the investigators can make a medical discussion with the sponsor on whether to be unblinded.

3.4 SELECTION OF STUDY POPULATION

3.4.1 Inclusion criterion of screening period

1. Only after conforming to all of following criteria, the patients can be enrolled into this study; the subjects volunteer to participate in this study, and sign the informed consent form.

2. Male or female subjects aged 18 above (18 inclusive);
3. ECOG performance status score is 0-1; no worsening within 2 weeks prior to the scoring of ECOG performance status; subjects with life expectancy ≥ 12 weeks judged by the investigator;
4. Histopathologically diagnosed, unresectable and incurable, treatment-naïve locally advanced or metastatic pulmonary adenocarcinoma (e.g., can be systemic recurrence after previous operation for early tumor, or newly diagnosed stage ⅢB/IIIC/Ⅳ tumor. AJCC version 8 is used as the staging system for lung cancer);
5. Diagnosed as localized advanced or metastatic lung adenocarcinoma through the pathological examination of tissue sample, and verifed as at least one sensitive mutation of EGFR in Ex19del or L858R gene (either single or mixed mutation gene) through the test at center laboratory;
6. Patients must provide adequate tumor tissue sections (can not be sourced from the tumor lesion locally treated, such as irradiation, the newly occurred lesion following local therapy is acceptable) in screening period, for detection of EGFR mutation status at central laboratory, please see Central Laboratory Manual for the details;
7. No prior systemic anti-tumor therapy for advanced/metastatic non-small cell lung cancer. Patients who have received adjuvant therapy or neoadjuvant therapy (chemotherapy, radiotherapy or other therapy) can be enrolled if there is no progression **within one year** after treatment; for the patients who have received local therapy (radiotherapy or perfusion therapy in pleural cavity), they can participate in the study if the lesions in the range of local therapy are non-target lesions:
8. At least one tumor lesion can meet the following requirements in accordance with the response evaluation criteria in solid tumors (RECIST 1.1): it is not irradiated previously or biopsied for the screening period (if there is only one target lesion that must receive tissue biopsy, and there is no radiological examination meeting the exempting conditions in screening period, baseline tumor evaluation needs to be performed at least 14 days after the biopsy in screening period; if there is radiological examination meeting the exempting conditions in screening period as the baseline tumor evaluation, it can be determined by investigators whether baseline evaluation will be performed again following biopsy based on the condition of lesions), and can be accurately measured at baseline, the longest diameter will be ≥10mm at baseline (short diameter is required

to be ≥15mm for lymph nodes). The measurement method selected is suitable for repeated measurement accurately, and can be computed tomography (CT) or magnetic resonance imaging (MRI). If there is only one measurable lesion, it will be required not to be irradiated previously;

9. Females of childbearing potential must have a negative serum or urine pregnancy test within 7 days prior to the first dose. Adequate contraceptive measures must be taken for male patients and female patients of childbearing potential from the signature of informed consent form to 6 months after the last dose of study drug. See 3.6 for details: Contraceptive measures, definition of Females of childbearing potential and contraceptive requirement.

3.4.2 Exclusion criteria of screening period

The patients meeting any one of the following criteria will be excluded from this study:

1. Having received any one of the following therapies prior to randomization:

- Previously receiving systematic antitumor therapy for advanced/metastatic non-small cell lung cancer (e.g., standard chemotherapy, targeted therapy, biotherapy, immunotherapy, etc.); please refer to the inclusion criterion 7 for neoadjuvant and adjuvant therapies;
- Previously receiving other systematic anticancer therapy for advanced/metastatic non-small cell lung cancer;
- Patients who have received intrapleural perfusion therapy can be enrolled only after the hydrothorax is stable for 28 days or above;
- Prior systemic anti-tumor therapy of EGFR-TKI;
- Having received major operation within 28 days prior to the first dose of study drug (in China, for the definition of major surgical operation, please refer to grade 3 and 4 surgery specified in the Management Method for Clinical Application of Medical Technology implemented on May 1, 2009);
- Having received radiation in an area of ≥30% bone marrow or a wide range of radiotherapy within 28 days prior to the first dose of study drug; having received local radiotherapy or palliative radiotherapy for bone metastasis within 14 days prior to the first dose of study drug;
- Having received CYP3A4 potent inhibitor or inducer within 7 days prior to the first dose, or need to continue treatment with these drugs during the study (drug list is provided in Appendix 6

in detail);

- Having received the traditional Chinese medicine and Chinese patent drug preparation indicated for tumors within 7 days prior to the first dose, or need to continue treatment with these drugs during the study;
- Currently receiving the drug therapy known to prolong QTc interval, and need to continue treatment with these drugs during the study (drug list is provided in Appendix 7 in detail);
- Discontinuation of other clinical investigational products for less than 14 days prior to the first dose;

2. The toxicity associated with previous anti-tumor treatment do not recover to ≤CTCAE grade 1, except for alopecia and ≤CTCAE grade 2 peripheral neurotoxicity caused by chemotherapy; please refer to the exclusion criteria 7 for bone marrow and hepatic and renal functions;
3. Mixed histological type, i.e., pulmonary adenocarcinoma mixed with squamous cell carcinoma;
4. With spinal cord compression or symptomatic brain metastasis (except symptomless state, stable disease, unnecessary for steroid treatment of ≥28 days before the starting of study drug); at symptom stabilization of ≥28 days after the completion of localized radiotherapy of brain metastasis;
5. Having other malignant tumor or history of other malignant tumor; except basal cell carcinoma of skin, carcinoma in situ of cervix and ductal carcinoma in situ that have been effectively controlled;
6. Clinically serious gastrointestinal dysfunction that may affect the intake, transport and absorption of study drug, for example, inability to take drugs orally, uncontrollable nausea or vomiting, history of large area gastrectomy, uncured recurrent diarrhea, atrophic gastritis (age < 60 years at the onset of disease), uncured gastric disorder requiring long-term use of PPI antacid, Crohn's disease, ulcerative colitis;
7. Inadequate bone marrow reserve and hepatic and renal functions with the following laboratory values (no transfusion of blood or blood products, no use of granulocyte colony-stimulating factor or other hematopoietic stimulating factors for correction within two weeks prior to blood collection for laboratory test for enrollment):

- Absolute neutrophil count < 1.5×10^9/L;
- Haemoglobin <90g/L;
- Platelet count < 90×10^9/L;
- Serum total bilirubin >1.5×upper limit of normal (ULN); total bilirubin >3×ULN in case of determined Gilbert syndrome (unconjugated hyperbilirubinemia) or hepatic metastasis;
- Serum alanine aminotransferase (ALT) and/or aspartate aminotransferase(AST) >2.5×ULN (ALT and/or AST >5×ULN for those with liver metastasis);
- Blood creatinine >1.5×ULN, or creatinine clearance < 50 mL/min (calculated according to Cockcroft-Gault formula, see Appendix 2 for details.);
- International normalized ratio (INR) > 1.5 and activated partial thromboplastin time (APTT) >1.5 × ULN.

8. Having cardiovascular disease meeting any one of the following conditions:

- Mean of three QTcFs on electrocardiography (ECG) >470msec under rested state, as calculated using Fridericia formula, see Appendix 9 for the details;
- Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG, e.g., complete left bundle branch block, Ⅲ degree conduction block, Ⅱ degree conduction block, PR interval>250 msec, etc.;
- Various factors that may increase the risk of prolonged QTc or arrhythmic event, for example, heart failure, hypokalemia, congenital long QT syndrome, sudden death for unknown reason in the first-degree relative before 40 years old in the family history;
- Left ventricular ejection fraction (LVEF) < 50%;

9. HBV, HCV or HIV active infection. All the subjects will be screened for HBV, HCV or HIV infection in screening period;

- HBsAg (+) and HBV DNA ≥1000 cps/mL (or 200 IU/mL) or HBV DNA higher than lower limit of quantification (LLQ) (if LLQ of HBV DNA is >1000 cps/mL);
- anti-HCV antibody positive and HCV RNA positive;
- HIV antibody positive;

10. Known previous history of interstitial lung disease, drug induced interstitial lung disease, radiation pneumonitis requiring steroid treatment; or acute attack of or ongoing pulmonary symptoms that are considered by investigators as unsuitable for enrollment, or high-risk factors that are judged as possible interstitial lung disease and unsuitable for enrollment at baseline;
11. Known or suspected allergy to the study drug and/or its excipients;
12. Female patients in pregnancy or lactation;
13. Presence of any disease or medical condition that is unstable or may affect its safety or compliance with the study, as considered by investigators, for example, uncontrolled hypertension, uncontrolled diabetes, active bleeding diathesis.

3.5 SCREENING OF FAILURE

Patients who signed informed consent, but withdrew from the study before randomization, were "screening failures." Unless under any of following conditions, the patients confirmed as failure in screening must not screened again. For re-screening, these patients must sign a new informed consent form again, and are assigned with new ID; these patients can only be re-screened for once.

- Due to the revision of study protocol, the patients should be evaluated again according to the inclusion/exclusion criteria;
- When the state of patients has been changed, a failure in screening is not caused again by the previous inclusion/exclusion criteria for failure in screening;
- Although the patients have completed the screening and conformed to all inclusion/exclusion criteria, they are not enrolled for some justifiable reasons (such as bad weather and illness in children of patients).

Before the re-screening of patients, the investigators should contact the medical monitor of the sponsor for joint decision. In order to ensure the accuracy of examination, re-examination should be made only for once, which is not considered as a re-screening. Before the re-examination, the medical monitor of the sponsor should be contacted for joint decision. The examinations completed within 28 days before the first administration of study drug must not be made again (such as HBV test, HCV test, HIV test and tumor assessment according to RECIST 1.1).

3.6 CONTRACEPTIVE MEASURES, DEFINITION OF WOMEN OF CHILDBEARING POTENTIAL AND CONTRACEPTIVE REQUIREMENT

Women of childbearing potential mean the women undergoing first menses, not receiving surgical sterilization operation (hysterectomy or ovariectomy at both sides) and not at menopausal state. Menopause includes:

- Spontaneous amenorrhea for at least 12 months, excluding the cause from medical field (such as anorexia nervosa), not previously receiving amenorrhea inducers during the period of amenorrhea (such as oral contraceptive drugs, hormone, gonadotropin releasing hormone, antiestrogen, selective estrogen receptor regulators or chemotherapeutics);
- Spontaneous amenorrhea for 6~12 months, with follicle-stimulating hormone (FSH) > 40 mlU/mL.

Since FSH level may be artificially inhibited after the hormone replacement therapy (HRT) in women, a washout period may be required to achieve a physiological FSH level. The duration of washout period is related to the function of HRT drugs. The following duration of washout period is suggested in the guideline; and the detection of serum FSH level should be judged by investigators. If serum FSH level is > 40 mIU/mL at any time of whole washout period, this woman is considered as menopausal.

- Vaginal hormone products (ring, cream and gel) are given for at least 1 week;
- Transdermal products are given for at least 4 weeks;
- Take the product orally for a minimum of 8 weeks.

From the signing of informed consent from to <6 months after the last administrationo of study drug, subjects of childbearing potential (including sexual partner of male subjects) should take sufficient contraceptive measures, and must not donate ova or sperm. Contraceptive methods acceptable in this study include: absolutely no sexual life; intrauterine devices (such as Copper T); contraceptive cervical cap (with addition of spermicidal cream or gel) plus male condom; contraceptive pellicle with addition of spermicidal cream or gel) plus male condom; or combination of at least two of above contraceptive methods. During the course of informed consent, the subjects are provided with

information on the acceptable contraceptive methods.

3.7 TERMINATION AND DROPOUT OF STUDY

The sponsor reserves the right to stop (to terminate or interrupt) the study at any time due to medical reasons or any other reasons. If the study is terminated prematurely or discontinued, then the sponsor should notify immediately the investigator, and explain the reasons. According to the requirements of relevant laws and regulations, the sponsor or investigator should also notify IRB/IEC that the study is terminated or discontinued and explain the reasons.

The investigators reserve the right for whether this study should be suspended or terminated by their study center. If the investigator terminates or discontinues the study without any prior approval by the sponsor, the investigator should notify immediately the sponsor and IRB/IEC, and provide a detailed written explanation for termination or discontinuation of the study to the sponsor and IRB/IEC.

If the study should be terminated in advance, the subjects are followed up as soon as possible, and are assessed according to the requirements of dropout. In order to fully protect the right of subjects, the investigators may be told of required additional measures.

3.7.1 Criteria for termination of research drug treatment

Patients will continue research drug treatment until progression of disease, initiate new antitumor therapy, development of an unacceptable toxicity, discontinuance at the investigator’s discretion or patient withdraws informed consent.

- When the efficacy of tumor is assessed as PD by investigators, study drug should be continued; whether it is discontinued can be determined only after obtaining the review results of IRB.

ICF for this study can be freely cancelled by the subjects at any time for any reason to drop out of study. After such dropout, the subjects of dropout will not be punished or replaced; and further treatment is not influenced. Under all conditions, any reason for termination of treatment should be recorded into original medical record and eCRF. If there are many reasons, the foremost reason should be indicated by investigators. If study drug is discontinued due to AE, the investigators should collect the outcome information on this AE as far as possible. Patients will be terminated from study

drug when the following conditions occur:

- Progression of disease (If the efficacy is confirmed as PD by both investigators and IRC, study drug should be discontinued in principle. However, if investigators think that the subject of PD can still be clinically benefited from the treatment of study drug, whether original study drug can be continued in this subject until a clinical progress is judged by investigators is determined after the discussion with the sponsor.
- Initiation of other anti-tumor therapy;
- Death;
- Lost to follow-up;
- Completion of whole clinical study (If PFS is not achieved in a certain subject after the administrationo of Alflutinib Mesylate or Gefitinib at the end of this study, study drug continues to be provided by the sponsor after the assessment of investigators as continuation of clinical benefit and the permission of this subject, until the subject can not be benefited in the viewpoints of investigators or the request of subject for termination of study (whicher occurs first).
- Adverse reactions are not resolved to Grade ≤1 (CTCAE) or baseline value after study drug is suspended for >14 days due to intolerable diarrhea or skin reactions (for for >21 days under other conditions) (If the investigators think through the assessment that the survival of subjects will be benefited from the resumption of study drug, whether it should be continued is determined after the discussion with the sponsor).
- Pregnancy;
- The subjects or their legal guardian ask to drop out of this study and cancel ICF (if the subjects ask to discontinue the study drug, they are inquired on whether to continue to participate in the study assessment and survival follow-up (such as via telephone); if if the subjects ask to drop out of whole study (including study assessment and survival follow-up), such request should be clearly recorded into original record and eCRF);
- According to the illness state of a subject, the investigators decide to terminate the treatment of this subject.

4. Study Drug

4.1 INVESTIGATIONAL DRUG

Table 1 Investigational drug

Drug name	Alflutinib Mesylate Tablets (AST2818)	Alflutinib Mesylate (AST2818) Analog Tablets	GEFITINIB	Gefitinib Analog Tablets
Strength	40 mg/tablet	Analog 40mg strength	250 mg/tablet	Analog 250mg strength
Dosage form	Tablets	Tablets	Tablets	Tablets
Manufacturer	Shanghai Allist Pharmaceutical Technology Co., Ltd. commissioned production	Shanghai Allist Pharmaceutical Technology Co., Ltd. commissioned production	AstraZeneca Pharmaceuticals	Shanghai Allist Pharmaceutical Technology Co., Ltd. commissioned production
Drug supply units	Shanghai Allist Pharmaceutical Technology Co., Ltd.			

4.2. DOSAGE REGIMEN

Both groups were given the drug orally once a day in the double-blind phase of the study, and the dosing regimen is performed as follows:

Table 2 Dosing regimens in double-blind study phase

Dose regimen		
	Test group (AST2818 group)	**Control group (Gefitinib group)**
Standard treatment		
Dose	80mg/day	250mg/day
Medicinal product(s)	AST2818 (40 mg/tablet), 2 tablets; Gefitinib dummy tablets, 1 tablet.	Gefitinib, 250 mg/tablet, 1 tablet; AST2818 dummy tablets, 2 tablet.
Usage	once daily, oral, on an empty stomach	once daily, oral, on an empty stomach
Reduced Dose		
Dose	40mg/day	250 mg/day (without reduction)
Drug(s)	AST2818 (40 mg/tablet), 1 tablets; Gefitinib dummy tablets, 1 tablet.	Gefitinib, 250 mg/tablet, 1 tablet; AST2818 dummy tablets, 1 tablet.
Usage	once daily, oral, on an empty stomach	once daily, oral, on an empty stomach

Subjects should take the drug orally on an empty stomach every morning. Two drugs in each group should be taken at the same time, usually with warm water.

Every effort should be made to maintain a consistent dosing interval of 24 hours every day.

If the subject fails to take the dose at the scheduled time point in the study, the subject may take another dose if the time window is less than 12 hours; if the time window is more than 12 hours, the subject may not take another dose, and the next dose should be taken at the next scheduled time.

If vomiting occurs after administration, no supplementary dose should be taken. The subject should take the next dose at the scheduled time.

Any changes related to medication should be recorded in the original case records and eCRF.

After the primary analysis of PFS (a primary endpoint) is completed, simulated tablets will not be provided any more after all blinded drugs are dispatched. The administration regimen is shown as follows.

Table 3 Dosing regimens after primary analysis

Dose regimen		
	Test group (AST2818 group)	**Control group (Gefitinib group)**
Standard treatment		
Dose	80mg/day	250mg/day
Medicinal product(s)	AST2818 (40 mg/tablet), 2 tablets;	Gefitinib, 250 mg/tablet, 1 tablet;
Usage	once daily, oral, on an empty stomach	once daily, oral, on an empty stomach
Reduced Dose		
Dose	40mg/day	NA
Drug(s)	AST2818 (40 mg/tablet), 1 tablets;	
Usage	once daily, oral, on an empty stomach	

The drugs are orally given via warm boiled water at fasting state at morning getup of every day; other precautions are same as those at double-blind administration.

4.3 MEDICATION COMPLIANCE

Subjects should take the study drug orally once a day as required by the trial. When study drug is not given according to relevant stipulations, a detailed record is kept, and the reasons are given. Remaining study drug is checked by investigators, so as to verify the treatment compliance of subjects. If any deviation in compliance occurs, correspondingly illustrated should be given.

4.4 PACKAGE AND LABELING OF DRUGS

The study drugs will be supplied to the trial centre with a uniform package number. In the label of

drugs, the information is included but not limited to: No. of study protocol, No. of study drug, production Lot No., specification, usage, storage conditions, expiry date and name of the sponsor; and the word of "only for clinical study" is indicated.

All study drugs were provided by Shanghai Allist Pharmaceutical Technology Co., Ltd.

During the period of blinded administration, the drugs are packed as follows.

Study group (AST2818 group): In each box, the quantity of drugs is sufficient for administration of 24 days (i.e. 48 tablets of AST2818 and 24 simulated tablets of Gefitinib);

Control group (Gefitinib group): In each box, the quantity of drugs is sufficient for administration of 24 days (i.e. 24 tablets of Gefitinib and 48 simulated tablets of AST2818).

After the primary analysis of PFS (a primary endpoint) is completed, the drugs are packed as follows.

Study group (AST2818 group): In each box, the quantity of drugs is sufficient for administration of 12 days in a subject (i.e. 8 tablets/board, 3 boards/box).

Control group (Gefitinib group): In each box, the quantity of drugs is sufficient for administration of 10 days in a subject (i.e. 10 tablets/board, 1 board/box (in package for market sale)).

4.5 DRUG DISTRIBUTION PROCEDURE

According to the precedence order of medical visit, screening No. is assigned to subjects. When a subject is judged as qualified through relevant examinations, a random number generated from IWRS system is obtained for the subject; this subject is randomly allocated into Alflutinib Mesylate (AST2818) group or Gefitinib group; corresponding study drug is dispatched by investigators according to the drug No. obtained from randomization through IWRS system. At each return visit of subjects, investigators log in IWRS system to the No. of drug to be dispatched at this visit. If a subject's medication becomes damaged during the study, the investigator can obtain a new medication number through the IWRS system and proceed with the clinical trial. The distribution and recovery of each drug shall be recorded on a dedicated record sheet in a timely manner. Registration form for dispatching/recovery of drugs is accurately completed by drug manager; all

drugs for clinical study are properly kept; after the termination of study, both registration form and remaining drugs are given to the sponsor.

After the primary analysis of PFS (a primary endpoint) is completed, after all blinded drugs are dispatched, the drugs will not be blinded any more, and the drug is dispatched by study center according to the type of group.

4.6 STORAGE AND MANAGEMENT OF INVESTIGATIONAL PRODUCTS

4.6.1 Storage

Drug for clinical trial supplied by sponsor According to the storage conditions indicated in the label, all drugs for clinical study are put into original container, which is kept in safe qualified place; and the record for registration/dispatching/recovery of study drug is managed by special persons.

All drugs for clinical study provided by the sponsor must be kept according to the following conditions: under room temperature (10~30℃), in dark place and at sealed state .

4.6.2 Management

(1) All study drugs are intended for use in clinical trials only.

(2) Dispatching/recovery of drugs: During study period, the information on dispatching/recovery of study drug in each subject is recorded into the table for dispatching/recovery of drugs, which is used as original document. Detailed information on any study drug lost (due to the damage or discarding), unused, dispatched by study center or returned to the sponsor or its designated person must be recorded into proper sheet. During study period, all supplied products and dispensary documents must be accessible to its designated person for review.

(3) Record of storage temperature of drugs: After the hand-over of drugs, the unused drugs are kept according to the storage requirements; storage temperature is recorded by special person; and highest/lowest storage temperature within each time section is recorded. If storage temperature exceeded the required value, project manager (or designated person) must immediately be contacted before the subsequent use of drugs. Such temperature is reported by project manager to the sponsor; direction and decision on whether drugs can continue to be used are obtained.

(4) Recovery/destroying of drugs: After the completion of study, all remaining drugs are uniformly recovered by the sponsor and then sent to its designated place for destroying; and the corresponding record of destroying is provided.

Relevant procedures and tables for drug management are described in detail in the drug management manual.

In order to ensure the correct use of study drug, the following records must be kept by investigators: transportation/inventory record for all above study drugs; record of dispatching/use of drugs in each subject; and record of drugs returned to the sponsor or designated person.

Investigators are responsible to receive, keep and dispatch the drugs during study period, including but not limited to:

- Confirm whether actual inventory consists with the recorded inventory;
- Confirm and complete the recording of drug batch;
- Confirm the accurate recording of all used and unused drugs;
- Confirm that all required contents are completed in an accurate legible way.

During study period, expiry date or retest date of study drug or materials is notified to investigators by the sponsor or its designated person. After the notice for expiry date of study drug or materials is received, all procedures stated in the notice must be completed by study center, including: the expired study drug or materials are arranged up and returned to the sponsor or its designated person for destroying.

4.7 CONCOMITANT DRUGS AND TREATMENT

All drugs or concomitant treatments (including nutrient supplements, preventive drug and reason for medication) given from 4 weeks before the study enrollment to 28 days after the last dosing of study drug must be recorded into the table for concomitant medication. Anti-tumor treatment given before the enrollment (including: drug treatment, radiotherapy and surgery) is reflected in original medical record, and separately recorded into eCRF.

During study period, combined drugs are used by investigators cautiously according to the following

guidelines to ensure the safety of subjects as far as possible.

During study period, optimal supporting treatment can be selected by investigators according to the conditions of the subject of subjects. Optimal supporting treatment means the therapy judged as optimal by investigators according the standard of each study center, including but not limited to: antidiarrheics, antiemetics, opium or non-opium analgesics, appetite promoters and granulocyte/erythrocyte growth promoters. If it is unclear whether a certain treatment should be used as supporting treatment, investigators should consult the medical monitor of the sponsor. Other drugs that may induce or exacerbate symptoms in clinical studies should not be combined and should be monitored more closely if they must be used.

All combined drugs used during study period should be recorded in original medical record and eCRF; at least following information is recorded for all combined drugs: name of drug, starting/ending time, administration route, administration dose and indications for treatment.

4.7.1 Prohibited medications during the study (i.e. during treatment and within 28 days after discontinuation)

During study period, the following drugs should be discontinued: anti-tumor drugs, immunomodulators, Chinese medicine or Chinese patent medicine approved by NMPA and immunoenhancers; unless new anti-tumor drugs are judged as necessary by investigators due to the progression of disease during study period.

Drugs known for prolonging the QTc interval (known risk of TdP [KR]);

CYP3A4 potent inhibitor and inducer.

Radiotherapy was not allowed for the target lesion. Palliative radiotherapy for alleviating the symptoms in non-target foci (only limited to bone metastasis) is acceptable. Treatments for bone metastasis are allowable (such as bisphosphates and Denosumab), which must be recorded in detail in original medical record and eCRF.

During study period, systemic corticosteroid or immunosuppressants are forbidden, unless under the following conditions:

- For localized application (such as rash), aerosol for inhalation (such as obstructive airway disease), eyedrops or localized injection (such as intraarticular injection).

The following drugs should be avoided as far as possible: sedatives/hypnotics; drugs possibly increasing the risk for thromboembolism (such as Erythropoietin and estrogen-based treatment); and drugs possibly causing a Torsade de pointes (possible risk for TdP [PR]). If Erythropoietin starts to be used before the recruitment (but it must not be used within 14 days before the blood is drawn for laboratory examination for enrollment), it can be given for maintenance therapy . If drugs possibly causing a Torsade de pointes (possible risk for TdP [PR]) has been stably used before the first administration of study drug , they can be continued during study period when there are no other contraindications for their use and if they are considered as necessary by investigators; but the subjects receiving combined drugs should be closely monitored. The requirements for time of stable application are shown in Attachment 7.

4.7.2 Drugs may be used as appropriate during the study period

(1) Anti-nausea treatment

Sufficient supporting treatment can be given, including: after the occurrence of vomiting, symptomatic treatment can be given; but antiemetics must not be given for prevention.

(2) Antidiarrheal therapy

When diarrhea is possibly related to study drug, Loperamide is recommended for antidiarrheal treatment.

If the subjects do not stay at study center after the first occurrence of diarrhea, Loperamide Hydrochloride Capsules is taken by the subjects by themselves; meanwhile, the investigators should immediately be contacted by the subjects, and relevant treatment is given in time according to the guidance of investigators.

Administration method for Loperamide Hydrochloride Capsules is suggested as follows: At an acute diarrhea, it is given initially at 2 capsules and then at 1 capsule after each occurrence of unformed stool; at a chronic diarrhea, it is given initially at 2 capsules, and then at a maintenance dose of 1~6 capsules a day to maintain a normal defecation of 1~2 times a day. The maximum dose should not

exceed 8 tablets per day. Its dose can be adjusted by investigators according to the clinical conventional practice.

(3) Liver protection therapy

Whenever patients develop liver function impairment, it should be treated with liver protection.

(4) Anti-hepatitis B drug therapy

If anti-HBV drugs have been used for prevention by the patients at screening, the same drug is suggested during the whole study period. If a poor effect is achieved by the past administration of Telbivudine, Lamivudine or Adefovir Dipivoxil or anti-HBV drugs were not ever given in the past, Entecavir or Tenofovir is suggested.

(5) Potassium supplement

In the patients with hypopotassemia, potassium supplements can be given to maintain a normal blood potassium level; during study period, blood potassium level is closely monitored, and potassium is continuously supplemented when necessary.

(6) If drugs conditionally inducing Torsade de pointes (conditional risk for TdP [CR]) should be combined, they can be prescribbed by investigators. However, patients receiving combined medication need to be closely monitored.

4.8 DOSE ADJUSTMENT DURING THE STUDY

4.8.1 GENERAL TREATMENT PRINCIPLES FOR TOXIC REACTIONS OCCURRING DURING STUDY PERIOD

If toxic reactions related to study drug occur during study period, the treatment of such toxic reactions, the suspension of study drug and dose reduction of study drug should be implemented according to the following principles:

If toxic reactions of Grade ≥3 (CTCAE) or intolerable toxic reactions of any grade occurring during study period are assessed by investigators as not caused by disease or progression of disease and then judged as caused by study drug,

- Firstly, treatment with investigational product should be interrupted;

- Relevant symptomatic supporting treatment is given (if adverse reactions are not related to study drug, whether study drug is suspended is determined by investigators), until the reactions are resolved to Grade 1 (CTACAE) or baseline state.

- At intolerable diarrhea or skin reactions occur, study drug is suspended for single time of ≤14 days;at other adverse reactions, it is suspended for single time of ≤21 days. If study drug is suspended for >14 days at intolerable diarrhea or skin reactions or for >21 days at other adverse reactions, the subject is suggested to drop out of study. If investigators think through overall assessment that the subject can still be benefited from the continuation of treatment, whether the subject drops out of study is jointly determined by investigators and the sponsor through the discussion.

- If toxic reactions of Grade ≥3 (CTCAE) or intolerable toxic reactions of any grade occur for the first time, study drug is suspended; if adverse reactions are resolved to Grade 1 (CTCAE) or baseline state after its suspension for less than 14 or 21 days, it can be resumed at original dose, or whether its dose is reduced is assessed by investigators according to the conditions of the subject.

- If toxic reactions of Grade ≥3 (CTCAE) or intolerable toxic reactions of any grade occur for the second time, study drug is suspended; if adverse reactions are resolved to Grade 1 (CTCAE) or baseline state after its suspension for less than 14 or 21 days, it is discontinued permanently; or whether it is resumed at original dose and whether its dose is reduced is assessed investigators according to the conditions of the subject (except the diarrhea of Grade 3 (CTCAE)).

- At a diarrhea of Grade 3 (CTCAE), it is suggested to be resumed at original dose; or whether its dose is reduced is assessed by investigators according to the conditions of the subject.

- After the dose is decreased, its dose can not be restored to the next higher level.

- If adverse reactions are still intolerable after the reduction of dose to minimum dose, the subject is suggested to drop out of study.

- When several AEs occur simultaneously, the dose of study dose should be adjusted according to the most serious AE while AE is treated.

- When the treatment of subjects is postponed or suspended, all examinations (including tumor imaging assessment) should be performed on schedule. Secondly, the reasons for dose

adjustment and administration postponement and the countermeasures/outcome for AE will be recorded in original medical record and eCRF.

Table 4 Treatment measures and dose adjustment for special toxic reactions

Target organ	Adverse events	Dose Titration
Lung	Acute or progressive symptoms of lung disease (such as dyspnea, cough and fever)	Study drug is suspended and diagnostic assessment is made; if interstitial pneumonia is confirmed, study drug is discontinued permanently.
	Interstitial Lung Disease/non-infectious pneumonia	Permanent drug discontinuation
Heart	Prolongation of QTcF interval (QTcF interval is ≥500 ms, or increased by 60 ms over baseline value) When a prolongation of QTcF is found at ECG examination during study period, ECG examination should be performed repeatedly for 3 times by an interval of 5~30 minutes; and then mean value of QTcF interval obtained from three ECG examinations is calculated.	Study drug is suspended until QTcF interval is ≥500 ms or restored to baseline value[1] (it is resumed at low dose or original dose) When the prolongation of QTcF interval occurs for the second time, study drug is discontinued permanently.
	Complicated with QTc interval and under any of following conditions: • Signs and symptoms of tip torsional ventricular tachycardia • Signs and symptoms of polytypic ventricular tachycardia • Signs and symptoms of severe arrhythmia	Permanent drug discontinuation
	Symptomless LVEF by a decrease of 10% over baseline value to <50%	Dose interruption; • If improved to baseline within 21 days, restart the administration • If not improved to baseline within 21 days, permanently discontinue
	Symptomatic congestive heart failure	Permanently discontinued
Others	Hepatic failure	Permanently discontinued
	Gastrointestinal perforation	Permanently discontinued
	Dehydration with a risk for renal failure	Dose interruption; • If QTcF interval is improved to baseline level after the suspension of study drug for less than 14 or 21 days, it begins to be resumed. • If not improved to baseline within 14/21 days, permanently discontinue.
	Acute or aggravating eye disease	
	Severe bullous, blistering or exfoliative skin conditions	• If improved to baseline within 14 days, restart the administration

Target organ	Adverse events	Dose Titration
	Serious diarrhea is ineffective treated by Loperamide; or dehydration occurs.	• If not improved to baseline within 14 days, permanently discontinue
1. According to the judgment criteria for its discontinuation, whether study drug is resumed is determined For example: At baseline, mean value of QTcF is 357 ms; at visit, mean value of QTcF is 420 ms, which is increased by 60 ms over baseline value and is lower than 450 ms. In this special case, study drug is resumed at low dose or original dose when QTcF interval is increased by <60 ms over baseline value.		

4.8.2 REGIMEN FOR DOSE ADJUSTMENT DURING STUDY PERIOD

Table 5 Dose adjustment regimen

	AST2818	GEFITINIB
Initial dose	80 mgAST2818/gefitinib analog tablets orally daily.	250 mggefitinib/AST2818 analog tablets orally daily.
Dose reductions	40 mgAST2818/gefitinib analog tablets orally daily.	250 mggefitinib/AST2818 analog tablets orally daily.

During study period, the dose of AST2818 can be reduced for once; but the dose of Gefitinib must not be decreased.

4.8.3 TREATMENT OF SPECIFIC TOXIC REACTIONS DURING STUDY PERIOD

4.8.3.1 SKIN REACTION

From treatment course until within 28 days after the completion of treatment, all subjects are suggested to avoid direct sunshine and take sun-screening measures (such as smearing of sun-screening cream). Skin reactions are avoided, or their incidence rate and severity are decreased.

In the patients with skin reactions, localized hormone ointment, localized or systemic antibiotics and localized or systemic anti-histaminics is selected by investigators according to the conditions of the subject; in serious case, dermatologists are invited for joint diagnosis.

4.8.3.2 GASTROINTESTINAL PERFORATION

At a diarrhea of Grade 2 or Grade ≥3, rational clinical treatment is selected by investigators. If the diarrhea is of Grade ≥3 (CTCAE) or is considered by investigators as clinically significant, study drug should be suspended; symptomatic treatment and electrolyte supplementation are implemented. The resumption of suspended study drug is shown in Clause 4.8.1. Any change in grade (CTCAE) of

diarrhea should be recorded in original medical record and eCRF.

4.8.3.3 LEUCOCYTE REDUCTION

When hematological toxicity occurs, the dose of study drug should be reduced, or its administration is postponed (See Clause 4.8.1). At a fever with leukocyte decrease or granulocyte decrease of Grade ≥3, symptomatic treatment (such as G-CSF) can be selected by investigators according to the conditions of the subject.

4.8.3.4 Prolongation of QTcF

If a prolongation of QTcF occurs during study period (QTcF is ≥500 ms, or is increased by 60 ms over baseline value), study drug should be suspended. When a prolongation of QTcF is found at ECG examination during study period, ECG examination should be performed repeatedly for 3 times by an interval of 5~30 minutes; and then mean value of QTcF interval obtained from three ECG examinations is calculated. The subsequent treatment such as resumption or dose reduction of study drug is shown in Clause 4.8.1.

4.8.3.5 INTERSTITIAL PNEUMONIA

If pulmonary symptoms (such as dyspnea) occur or are aggravated or interstitial pneumonia is suspected through the imaging examination during study period, study drug is suspended, and medical monitor of the sponsor is notified within 24 hours. Necessary diagnostic measures should immediately be taken by investigators for differential diagnosis to eliminate some diseases such as pulmonary infection, allergy, cardiogenic edema or pulmonary hemorrhage. Once interstitial pneumonia is confirmed, study drug should be discontinued permanently.

In the patients confirmed as interstitial pneumonia, study drug must not be resumed. In the patients suspected as interstitial pneumonia, the feasibility for resumption of study drug is assessed by investigators and discussed with medical monitor of the sponsor.

4.9 STUDY DRUG COMPLIANCE

At each visit of the subject, the compliance of subject is assessed by investigators and/or authorized person of study center according to the number of dispatched/returned drugs and the information

provided by the subject and/or nursing person. The use record and administration dose of study drug, the interval of follow-up and the completion conditions of study are recorded/kept in tracing table for study drug or equivalent document, and are recorded/reported in eCRF.

Subjects were required to return the remaining medication at each follow-up visit. If all packing boxes dispatched at previous visit are not returned by the subject, the investigators must ask the subject, and estimate the quantity of drugs given after the previous visit. All given drugs and their administration time in each subject should be recorded in the patient diary provided by investigators. Through above methods and the inquiry of subject, the compliance is assessed.

4.10 TREATMENT OF STUDY DRUG OVERDOSE

Drug overdose means that the administration dose of study drug exceeds the dose stipulated in the study protocol. In this study, the administration dose of AST2818 and Gefitinib is stipulated as 80 mg/d and 250 mg/d respectively; if the administration dose is higher than the dose stipulated in study protocol, a drug overdose is considered; if the administration dose is higher than the dose prescribed in medical order, a drug overdose is not considered. At any drug overdose, the sponsor or its representative should be reported immediately (within 24 hours) no matter whether relevant AE occurs or not; and the page of AE in eCRF should be recorded no matter whether AE is complicated (the drug overdose is recorded as independent name of event). Reporting process, see section 7 adverse events for details.

If study drug is given at overdose, conventional clinical treatment measures can be taken, including: potential toxic reactions and relevant complications known or unanticipated for study drug are monitored continuously; symptomatic treatment is given.

5. Study Procedures

5.1 Flow Table

Flow chart for study is shown in Table 6; the volume and time of blood sampling in each subject during study period are shown in Table 7.

Table 6 Trial flow chart

Items \ Time points	Screening Period Visit	Treatment Period Visit (every 3 weeks as a treatment cycle)						Treatment Termination Visit	28 Days after the Last Dose Visit[25]	Progression Follow-up [26]	Survival follow-up (by telephone)[27,28]
		Treatment Cycle 1 (C1)			C2-C6	C7-C18	C19-CX				
	D-28~-1	C1D0	C1D1[20]	C1D8[21] (±3 days)	CXD1[22] (±3 days)	CXD1[23] (±7 days)	CXD1[24] (±7 days)	The last dose (±7 days)	28 d after the last dose (±7 days)		Every 12 weeks (±7 days)
Signing the informed consent form (ICF)[1]	X										
Inclusion/exclusion criteria confirmation	X	X									
Collection of unstained sections of tumor tissues[2]	X										
Demographic data[3]	X										
Previous medical history[4]	X										
Previous history of tumor and antineoplastic treatment[5]	X										
Current symptoms	X										
Physical examination[6]	X	X			X	X	X	X			
Vital signs[7]	X	X	X		X	X	X	X			
ECOG Performance Status Scale	X	X	X		X	X	X	X			
Complete blood cell count[8]	X	X[29]		X	X	X	X	X			
Blood biochemical examination[9]	X	X[29]		X	X	X	X	X			
Urine analysis [10]	X	X[29]		X	X	X	X	X			
Coagulation function test[11]	X							X			
Serum/urin pregnancy test (if applicable)[12]	X	X[29]						X			
Echocardiogram or MUGA scan[13]	X			Once every 6 weeks ± 7 days for the first 18 cycles and once every 12 weeks ± 7 days thereafter, or as clinically appropriate				X			
Ophthalmic examination[14]	X	based on clinical requirement									
NYHA class	X										
12-lead ECG test[15]	X	X			X	X	X	X			
HBV, HCV and HIV tests[16]	X										
Tumor evaluation [17]	X		Once every 6 weeks ± 7 days for the first 18 cycles and once every 12 weeks ± 7 days thereafter, or as								

Items \ Time points	Screening Period Visit	Treatment Period Visit (every 3 weeks as a treatment cycle)						Treatment Termination Visit	28 Days after the Last Dose Visit[25]	Progression Follow-up [26]	Survival follow-up (by telephone)[27,28]
		Treatment Cycle 1 (C1)			C2-C6	C7-C18	C19-CX				
	D-28~-1	C1D0	C1D1[20]	C1D8[21] (±3 days)	CXD1[22] (±3 days)	CXD1[23] (±7 days)	CXD1[24] (±7 days)	The last dose (±7 days)	28 d after the last dose (±7 days)		Every 12 weeks (±7 days)
			clinically appropriate								
Concomitant medications/accompanied treatments	X										
AE/SAE collection[18]	X										
Quality of life score (EORTCEORTC QLQ-C30 and EORTC QLQ-LC13)		X			X	X	X	X			
IWRS randomization		X									
Collection of ctDNA blood samples[19]		X			X			X			
Collection of T790M mutation assay blood sample/tumor tissue sample[31]								X			
Dispensing/reclaiming study medication			X[30]		X	X	X	X			
New antineoplastic treatment and survival status								X	X	X	X

1. The informed consent includes the main informed consent, the informed consent of biomarker sample collection, and the informed consent of tumor efficacy evaluation and survival follow-up of patients who withdraw from the trial during the study;
2. Sections prepared with sufficient tumor tissues at the screening period (before C1D1 administration) should be provided, and samples of primary or metastatic tumor tissues are available;
3. including date of birth, sex, and race/ethnicity;
4. All previous medical histories started before signing the ICF and considered relevant for this study except for this indication are collected, and active smoking or smoking history ≥ 5 pack-years (product of the number of packs smoked per day and the number of years smoked) in the past 10 years is generally considered as significant smoking history;
5. The following information is included: date of tumor diagnosis, pathological type, TNM staging (including the assessment at initial diagnosis and entry into this study), time of diagnosis of the first occurrence of metastases, number and location of metastases, previous anti-tumor treatment (including the start time, end time, duration and regimen of treatment; the best response of each treatment, date of failure/disease progression, and occurrence of grade 3 and above toxicity;
6. Physical examination includes height (only at screening), body weight, head, eyes, ear, nose, throat, neck, heart, chest (including lung), abdomen, four limbs, skin, lymph nodes, nervous

system, and patient's general condition;

7. Vital signs: including blood pressure, pulse, respiratory rate and body temperature. Blood pressure should be measured after the patient sits quietly for 5 minutes. If antihypertensive treatment is provided at screening period, blood pressure should be measured at 3 hours ± 2 hours after administration of antihypertensive drugs on the day of visit;
8. Hematological examination: including red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell count with differential (neutrophils, lymphocytes, eosinophils, monocytes and basophils). If the screening examination results are obtained within 7 days prior to C1D1, these examination items can be exempted;
9. Blood biochemistry includes total protein, albumin, alkaline phosphatase, fasting blood glucose, total bilirubin, direct bilirubin/indirect bilirubin, aspartate aminotransferase, alanine aminotransferase and glutamyl transpeptidase, creatinine, urea nitrogen/urea nitrogen, creatinine clearance rate and uric acid, as well as serum amylase and electrolyte (potassium, sodium, calcium and phosphorus); CPK and LDH are only performed during the screening period or during the clinical trial (in case of cardiac event). These examination items can be exempted if the screening examination result is obtained within 7 days prior to C1D1; creatinine clearance examination is not required on C1D8;
10. Routine urine examination includes specific gravity, pH, urine glucose, protein, urine ketone body, and blood cells (white blood cells, red blood cells, etc.). If the screening examination results are obtained within 7 days prior to C1D1, these examination items can be exempted;
11. Coagulation test: including prothrombin time (PT), international normalized ratio (INR) and activated partial thromboplastin time (APTT);
12. It will be completed only within 7 days prior to the initial dose.
13. Left ventricular ejection fraction is assessed by echocardiography or multigated angiography every 6 weeks ± 7 days for the first 18 cycles from C1D1, every 12 weeks ± 7 days for sequent visits from Cycle 18, or as clinically indicated by the investigator. If the screening echocardiogram or MUGA examination results are obtained within 28 days prior to C1D1 (including before signing the informed consent form), this examination can be exempted;
14. Ophthalmological examination includes intraocular pressure examination, fundus examination and slit-lamp examination. Examined may be performed during the screening period and if clinically necessary assessed by the investigator;
15. C1D0 will be tested in triplicate with 5-30 minutes apart before the initial dose. Calculate QTc interval and calculate the mean (corrected using Fridericia's formula);
16. If the test result of HBsAg is positive, HBV DNA test should be performed, and HBV DNA should be retested every 12 weeks ±7 days starting from C1D1 during the study; if the test result of HCV antibody is positive, HCV RNA test should be performed; if the test report of HBsAg, HBV DNA, HCV antibody, HCV RNA and HIV containing the normal range issued by the regular medical institution within 28 days before C1D1 (including before the informed consent) can be provided, these tests can be exempted during screening;
17. In case tumor evaluation had been performed within 28 days prior to the initial dose, and the same method was used in the same hospital, it could be used as the baseline tumor evaluation. Imaging (CT or MRI) examination of brain, chest and abdomen as well as bone scan should be performed for all subjects (patients with bone scan performed 60 days before the initial dose can be exempted); if clinically necessary, appropriate examination (CT or MRI) can be used to examine any other known or suspected disease sites (such as neck, pelvis, etc.). During the study, the subsequent tumor measurement method must be consistent with that of the baseline. In order to ensure the consistency of reading, it is recommended to use the same reader to complete the reading of all the image results of each subject. Tumor response evaluation will be performed every 6 weeks (± 7 days) in the first 18 cycles from C1D1 and every 12 weeks (± 7 days) after Cycle 18 or as clinically indicated until disease progression, Initiate new antitumor therapy, withdrawal of informed consent, lost to follow-up, death, 28 days (± 7 days) after the final dose or study termination, whichever occurs first. Patients withdrawing treatment not for disease progression will continue to receive tumor assessments, until disease

progression, withdrawal of informed consent by patients, loss of follow-up, death or end of the study, whichever comes first. Tumor evaluation visits are calculated since Cycle 1 Day 1 (C1D1) for cycles and not affected by withdrawal. If a patient does not receive a tumor evaluation within 28 days prior to termination of study treatment/study withdrawal, a tumor evaluation should be performed at the time of termination of study treatment/study withdrawal. If a patient is withdrawn from the study due to disease progression, the repeated imaging assessment is not required at the treatment discontinuation visit. An unscheduled tumor evaluation should be performed for cases with suspected progression of disease prior to the next scheduled evaluation. Additional imaging may be ordered by the investigator as clinically appropriate for the patient. If the subject is found to have brain lesions in the screening period, the brain tumor assessment should be performed in each subsequent observation period; if the subject is found to have bone metastases in the screening period, the bone scan in the subsequent observation period should be arranged by the investigator according to the subject's conditions. Subjects who continue to receive trial drug after PD should continue to undergo CT/MRI follow-up as described above. For the specific requirements, see the Imaging Manual of Study Site (or other similar documents with other names);

18. Adverse event (AE) collection: All AEs will be recorded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 during each visit. For SAEs, the active reporting period to the sponsor or its designated representative begins when the patient signs informed consent and ends 28 days after the last dose of study drug. If a patient receives a new anticancer therapy, no new AEs/SAEs will be reported;
19. ctDNA blood samples will be collected on C1D1 before administration, C3D1 and during follow-up for disease progression or end of treatment; at the time of disease progression, if patients volunteer, histological specimens or slides containing sufficient tumor histology may also be provided;
20. The exact time of C2D1, C3D1 and CxD1 is calculated according to Cycle 1 Day 1 (i.e. dosing time of C1D1);
21. Qualified laboratory report of local qualified hospital (including normal range) is acceptable for C1D8;
22. During Cycle 2 to Cycle 6 (C2-C6), follow-up should be performed every cycle (21 Days);
23. During Cycle 7 to 18 (C7-C18), follow-up should be performed every two cycles (6 weeks);
24. After Cycle 18 (C19-CX), follow-up should be performed every 3 cycles (12 weeks).
25. Discontinuation of treatment includes early termination of treatment (due to reasons other than disease progression) and end of treatment (due to disease progression). If the results of hematology, blood biochemistry and urinalysis within 7 days before discontinuation are normal or abnormal without clinical significance as assessed by the investigator, these tests may be exempted at discontinuation visit;
26. The follow-up for disease progression is mainly aimed at the patients who discontinued the treatment for reasons other than disease progression (e.g., AE). These patients will continue to receive tumor assessment as originally planned until disease progression, initiate new anti-tumor therapy, withdrawal of informed consent, lost to follow-up, death or study termination, whichever occurs first;
27. If the patient started receiving new anti-tumor treatment after treatment but before the end of treatment visit, the patient directly entered the survival visit and no longer needed to receive the end of treatment visit. If the patient terminated the treatment before disease progression, the patient should also participate in the survival follow-up to collect the information of subsequent anti-tumor treatment and survival of the patient;
28. Survival follow-up started with disease progression or initiation of a new antitumor therapy as the starting point, telephone follow-up was conducted every 12 weeks to collect subsequent antitumor treatment information and survival status of patients.

29. If the screening examination results are obtained within 7 days prior to C1D1, hematology, blood biochemistry, urinalysis and serum/urine pregnancy test may be exempted;
30. The initial dose is on C1D1;
31. Patients will be required to provide tumor tissues, blood samples or fresh biopsy samples with sufficient tumor tissue volume after disease progression and discontinuation of the study medication for determination of T790M mutation.

Table 7 Volume (mL) and time of blood sampling in each subject during study period

	Screened	Cycle 1		Cycle 2 and beyond	Termination of treatment[5]
		C1D0	C1D8	CXD1[4] (±3 days)	The last dose (+7 days)
	Safety assessment (volume: mL4)				
Complete blood cell count test	3	3[3]	3[6]	3	3
Blood biochemistry	5	5[3]	5[6]	5	5
Coagulation function	3				3
HBV/HCV/HIV	3				
Blood pregnancy test (if required)[1]	3				3
	Biomarker assessment (volume unit: mL)				
ctDNA blood samples[2]		10		10	10
T790M mutation assay blood sample[7]					10
	Total blood volume (ml)				
Based on visits	14 (or 17)	18 (or 10)	8	8; C3D1 18	11 or 14 (the tissue is provided for test on ctDNA and T790M) 31 or 34 (the blood is provided for test on ctDNA and T790M)

1. Females of childbearing potential may undergo blood or urine pregnancy tests;
2. At C1D0, C3D1 and progression of disease or follow-up after the termination of treatment, blood sample for ctDNA test is collected.
3. If ctDNA test and T790M test at C1D0 are made within 7 days of examnation during screening period, they can be exempted.
4. From Cycle 2 to Cycle 6 (C2~C6), blood sample is collected once a cycle (21 days); from Cycle 7 to Cycle 18 (C7~C18), blood sample is collected once every two cycles (6 weeks); after Cycle 18 (C19~CX), blood sample is collected once every four cycles (12 weeks).
5. If the results of hematology, blood biochemistry and urinalysis within 7 days before discontinuation are normal or abnormal without clinical significance as assessed by the investigator, these tests may be exempted at discontinuation visit;
6. Examinations at C1D8 can be made in local qualified hospital.
7. Mutation conditions of T790M can be tested through blood sample or tissue.

5.2 SCREENING PERIOD VISIT

From Day -28 to Day -1 prior to the initial administration of study drug:

Prior to any specific study assessment or operation, all patients must sign the informed consent. Through the assessment according to screening plan, whether the subject is suitable to enter this study is determined.

The full medical history is required to be recorded at screening:

- Inclusion/exclusion criteria confirmation;
- Collection of unstained sections of tumor tissues;
- Demographic data: including date of birth, gender, ethnic group / race;
- Previous medical history (all previous medical histories started before signing the ICF and considered relevant for this study except for this indication are collected, and active smoking or smoking history ≥ 5 pack-years (product of the number of packs smoked per day and the number of years smoked) in the past 10 years is generally considered as significant smoking history.) ;
- Previous medical history of tumor and anti-tumor treatment history, including date of tumor diagnosis, pathological type, TNM staging (including the assessment at initial diagnosis and entry into this study), time of diagnosis of the first occurrence of metastases, number and location of metastases, previous anti-tumor treatment (including the start time, end time, duration and regimen of treatment; the best response of each treatment, date of failure/disease progression, and occurrence of grade 3 and above toxicity;
- Current symptoms;
- Physical examination: including height, body weight, head, eyes, ear, nose, throat, neck, heart, chest (including lung), abdomen, four limbs, skin, lymph nodes, nervous system, and patient's general condition;
- Vital signs: including blood pressure, pulse, respiratory rate and body temperature. Blood pressure of patients should be taken after 5 minutes of sitting;

- ECOG performance status score: it is advisable to evaluate ECOG score by the same investigator throughout the study;
- Laboratory test: including complete blood cell count test, coagulation function, serum chemistry and urinalysis;
- Serum/urine pregnancy test (if applicable);
- Grading according to NYHA, UCG or MUGA examination, particularly assessment of LVEF; If the report of UCG or MUGA examination made by formal medical institutions within first 28 days of C1D1 (including the time before the informed consent can be provided, these examinations can be exempted during screening period.
- 12-lead-ECG;
- HBV, HCV and HIV tests: if the test result of HBsAg is positive, HBV DNA test should be performed, and HBV DNA should be retested every 12 weeks ± 7days from C1D1; if the test result of HCV antibody is positive, HCV RNA test should be performed; if the test report of HBsAg, HBsAb, HBeAg, HBeAb, HBcAb, HBV DNA, HCV antibody, HCV RNA and HIV containing the normal range issued by the regular medical institution within 28 days before C1D1 (including before the informed consent) can be provided, these tests can be exempted during screening;
- Ophthalmological examination includes intraocular pressure examination, fundi examination and slit-lamp examination;
- Tumors assessments: tumors are evaluated in accordance with RECIST-1.1. In case tumor evaluation had been performed within 28 days prior to the first dose, and the same method and equipment were used in the same hospital, it could be used as the baseline tumor evaluation. At baseline, tumor assessment is made through the imaging examination (CT or MRI) on chest, abdomen and brain and the bone scanning (in the patients receiving bone scanning within 60 days before the first administration of study drug, it can be exempted). According to the clinical need, target foci at any other site known or suspected as the foci of tumor should also be assessed and recorded, including: number of foci, site, description, maximum diameter of each

foci, minimum diameter of lymph node, and sum of diameter of all target foci. Concrete requirements are shown in Imaging Manual of Study Center (or other stipulated documents of same kind)

- Concomitant medication/concurrent therapy: all the drug therapies and significant non-drug therapies from 4 weeks before study enrollment must be recorded in eCRF, including the generic name and usage, name of non-drug therapies, reason for treatment, start and end date of treatment, or if it is used continuously at present;
- AE/SAE collection.

5.3 TREATMENT PERIOD VISITS

After completion of the evaluation at screening visit and all the inclusion/exclusion criteria by investigators, patients will be randomized in the study through IWRS if they are confirmed to be qualified.

5.3.1 Cycle 1, Day 0 (C1D0)

1

1.1

1.1.1

1.1.2

- Inclusion/exclusion criteria reconfirmation;
- Quality of life score (EORTC QLQ-C30 and EORTC QLQ-LC13); subjects will come to the study site and complete the questionnaire independently or under the support by their family members (for illiterate subjects), prior to communication with healthcare professionals;
- Physical examination (without body height);
- Vital signs;
- ECOG performance status score;

- 12-Lead ECG will be tested in triplicate with 5-30 minutes apart before the initial dose, QTc interval and its mean should be calculated.
- Laboratory examination (including complete blood cell count, serum chemistry and urinalysis). If the screening examination results are obtained within 7 days prior to C1D1, these examination items can be exempted;
- Serum/urine pregnancy test (if applicable);
- IWRS randomization;
- Collection of ctDNA blood samples prior to dosing;
- Concomitant medications/accompanied treatments
- AE/SAE collection.

5.3.2 Cycle 1, Day 1 (C1D1)

- Vital signs;
- ECOG performance status score;
- Dispensing study drug and diary cards;
- First dose of study drug;
- Concomitant medications/accompanied treatments
- AE/SAE collection.

5.3.3 CYCLE 1, DAY 8 (C1D8±3)

- Laboratory examination (including complete blood cell count, serum chemistry and urinalysis); laboratory report of local qualified hospital (including normal range) is accepted.

If abnormal results are found at laboratory examination made in local hospital, investigators are contacted to assess the abnormal results and determine whether to subsequently make an unscheduled follow-up or treatment adjustment.

5.3.4 Subsequent cycles. Day 1 (CXD1)

From Cycle 2 to Cycle 6 (C2~C6), the follow-up is made once a cycle (21 days, CXD1±3 days); from Cycle 7 to Cycle 18 (C7~C18), the follow-up is made once every two cycles (6 weeks, CXD1±7 days); after Cycle 18 (C19~CX), the follow-up is made once every four cycles (12 weeks, CXD1±7 days).

- Quality of life score (EORTC QLQ-C30 and EORTC QLQ-LC13); subjects will come to the study site and complete the questionnaire independently or under the support by their family members (for illiterate subjects), prior to communication with healthcare professionals;
- Physical examination (without body height);
- Vital signs;
- ECOG performance status score;
- Tumor assessments. Since C1D1, once every 6 weeks ± 7 days for the first 18 cycles or as clinically required; once every 12 weeks ± 7 days thereafter, or as clinically required;
- 12-lead-ECG;
- Echocardiography or MUGA examination, especially the evaluation of left ventricular ejection function. Once every 6 weeks ± 7 days for the first 18 cycles from C1D1, or as clinically required; and once every 12 weeks ± 7 days thereafter, or as clinically required;
- Laboratory test (including complete blood cell count test, serum chemistry and urinalysis);
- Whether ophthalmological examination was performed is determined by investigators according to the clinical need.
- Concomitant medications/accompanied treatments
- Collection of ctDNA blood sample (only on C3D1);
- AE/SAE collection;
- Dispensation and recovery of study drug and log card.

5.4 TREATMENT DISCONTINUATION VISIT (WITHIN 7 DAYS AFTER THE LAST DOSE)

- Life of quality scale (EORTC QLQ-C30 and EORTC QLQ-LC13); After the subject reaches study center, the questionnaire is completed by the subject independently or under the aid of relatives (for the illiterate subject) before the communication with medical health professional persons.
- Physical examination (without body height);
- Vital signs;
- ECOG performance status score;
- If a patient does not receive echocardiography or MUGA examination within 28 days prior to termination of study treatment/study withdrawal, especially the evaluation of left ventricular ejection function, then chocardiography or MUGA examination should be performed at the time of termination of study treatment/study withdrawal;
- 12-lead-ECG;
- Laboratory examination (including complete blood cell count, serum chemistry and urinalysis); if the results of these examinations are available within 7 days prior to this visit and are normal or abnormal but without clinical significance as assessed by the investigator, then these tests may be exempted;
- Coagulation function;
- Whether ophthalmological examination was performed is determined by investigators according to the clinical need.
- If a patient does not receive a tumor evaluation within 28 days prior to termination of treatment/withdrawal from study, a tumor evaluation should be performed at the time of termination of treatment/withdrawal from study;
- Serum/urine pregnancy test (if applicable);

- ctDNA blood samples will be collected at the time of disease progression; the patient may voluntarily provide additional histological specimens or sections containing adequate tumor tissues (see Central Laboratory Manual for details);
- Collection of blood sample or tumor tissue sample for T790M mutation testing;
- Concomitant medications/accompanied treatments
- Collection of AE/SAE, the AE/SAE occurred after start of a new antitumor therapy will be no more collected;
- Recovery of study drug and log card
- New antineoplastic treatment and survival status.

5.5 Visits 28 days after the last dose (28±7 days after the last dose)

It is recommended that patients come to the hospital for outpatient follow-up, at least telephone follow-up.

- Collection of AE/SAE, the AE/SAE occurred after start of a new antitumor therapy will be no more collected;
- New antineoplastic treatment and survival status;
- Concomitant medications/accompanied treatments
- Subjects withdrawing treatment not for progression of disease will continue to receive tumor evaluation, until progression of disease, beginning of new anti-tumor treatment, withdrawal of informed consent, loss of follow-up, death or end of the study, whichever comes first.

5.6 Progression follow-up

Subjects withdrawing treatment not for progression of disease will continue to receive tumor evaluation, until progression of disease, beginning of new anti-tumor treatment, withdrawal of informed consent, loss of follow-up, death or end of the study, whichever comes first.

- New antineoplastic treatment and survival status;
- Ophthalmological examination, as clinically required;

- Tumor assessments. Since C1D1, once every 6 weeks ± 7 days for the first 18 cycles or as clinically required; once every 12 weeks ± 7 days thereafter, or as clinically required;
- Concomitant medications/accompanied treatments
- Collection of AE/SAE (within 28 days after termination of treatment), the AE/SAE occurred after start of a new antitumor therapy will be no more collected.

5.7 Survival follow-up

Information on subsequent antineoplastic therapies and survival status of patients will be collected every 12 weeks at follow-up by phone using the date of disease progression or the start date of the new antineoplastic therapy as the starting point. If the patient started receiving new anti-tumor treatment after treatment but before the end of treatment visit, the patient directly entered the survival visit and no longer needed to receive the end of treatment visit.

If the patient terminated the treatment before disease progression, the patient should also participate in the survival follow-up to collect the information of subsequent anti-tumor treatment and survival of the patient.

6. Efficacy and safety evaluation

6.1 Anti-tumor response evaluation

In case tumor evaluation had been performed within 28 days prior to the initial dose, and the same method was used in the same hospital, it could be used as the baseline tumor evaluation. Imaging (CT or MRI) examination of brain, chest and abdomen as well as bone scan should be performed for all subjects (patients with bone scan performed 60 days before the initial dose can be exempted); if clinically necessary, appropriate examination (CT or MRI) can be used to examine any other known or suspected disease sites (such as neck, pelvis, etc.). During the study, the subsequent tumor measurement method must be consistent with that of the baseline. In order to ensure the consistency of reading, it is recommended to use the same reader to complete the reading of all the image results of each subject. Tumor response evaluation will be performed every 6 weeks (± 7 days) in the first 18 cycles from C1D1 and every 12 weeks (± 7 days) in the sequent visits from Cycle 18 or as clinically indicated until disease progression, start of a new antitumor treatment withdrawal of

informed consent, lost to follow-up, death, 28 days (± 7 days) after the final dose or study termination, whichever occurs first. Patients withdrawing treatment not for disease progression will continue to receive tumor assessments, until disease progression, withdrawal of informed consent by patients, loss of follow-up, death or end of the study, whichever comes first. Tumor evaluation visits are calculated since Cycle 1 Day 1 (C1D1) for cycles and not affected by withdrawal. If a patient does not receive a tumor evaluation within 28 days prior to termination of study treatment/study withdrawal, a tumor evaluation should be performed at the time of termination of study treatment/study withdrawal. If a patient is withdrawn from the study due to disease progression, the repeated imaging assessment is not required at the treatment discontinuation visit. An unscheduled tumor evaluation should be performed for cases with suspected progression of disease prior to the next scheduled evaluation.

Tumor response evaluation will be performed every 6 weeks (± 7 days) in the first 18 cycles after start of treatment from C1D1 and every 12 weeks (± 7 days) in the sequent visits from Cycle 18 until disease progression, start of a new anti-tumor therapy, withdrawal of informed consent, lost to follow-up, death study termination, whichever occurs first. If the tumor assessment is progressive disease by investigator, IRC confirmation is required. If disease progression is not confirmed by the IRC, tumor imaging continues as described above until disease progression is confirmed by the IRC, or the start of new antineoplastic therapy, withdrawal of patient consent, lost to follow-up, death, or study termination, whichever occurs first. If the subject is found to have brain lesions in the screening period, the brain tumor assessment should be performed in each subsequent observation period; if the subject is found to have bone metastases in the screening period, the bone scan in the subsequent observation period should be arranged by the investigator according to the subject's conditions. Subjects who continue to receive trial drug after PD should continue to undergo CT/MRI follow-up as described above. For the specific requirements, see the Imaging Manual of Study Site (or other similar documents with other names).

Record of target lesions: number, site, description, maximum diameter measurement of each lesion (except lymph node) and minimum diameter measurement of lymph node, including sum of the diameters of all the target lesions.

In this study, besides the tumor assessment made by local investigators, all data of imaging

examination (CT/MRI) for efficacy assessment are also collected, so that the efficacy assessment is further regularly verified by IRC (see the Manual of IRC).

6.2 SAFETY EVALUATION

Safety observation indices include: adverse events, indices of clinical laboratory examination (such as blood routine examination, urine routine examination, blood biochemistry and coagulation examination), vital signs, ECG examination, physical examination (including: weight) and ECOG scale. Safety will be evaluated comprehensively by the type, frequency and severity of adverse events. To evaluate the clinical safety using NCI CTCAE version 5.0 thoughout the study. At each clinical visit, the AE should evaluated for the patient. The start and end time of AEs, highest severity, correlation with the study drug, effect on study drug treatment, presence of combined therapy and outcome conditions should be recorded on the eCRF.

During screening period and at each visit, vital signs, physical examination (including: height and weight) and ECOG scale should be assessed; or during study period, the frequency of physical examination is increased according to the clinical signs. It is advisable to evaluate ECOG performance status score by the same investigator throughout the study.

12-lead ECG examination: heart rate, P-R interval, QRS interval, QT interval, QTc interval and diagnosis: At C1D0, ECG examination should be performed repeatedly for 3 times by an interval of 5~30 minutes before the first administration; and then QTc interval and its mean value obtained from three examinations is calculated, which is calibrated through Fridericia's formula. At other examination time stipulated in study protocol and by examination frequency increased by investigators according to the clinical signs during study period, ECG examination is performed. 12-lead ECGs should be performed after the patient has been rested in a supine position for at least 10 minutes in each case. Results of all 12-lead examinations at supine position should be recorded in file.

Echocardiography or MUGA: including left ventricular ejection fraction and diagnosis. During the whole study period, LVEF assessment of specific subject is suggested to be completed by same technician through same apparatus as far as possible.

Ophthalmological examination: including intraocular pressure examination, fundi examination and

slit-lamp examination. During screening period, it is completed; during study period, it is made additionally when it is judged as clinically necessary by investigators.

During screening period, treatment period and follow-up period, blood routine examination, coagulation functional examination, blood biochemistry and urine routine examination are performed through study procedures, whose examination frequency can be increased according to the clinical signs.

Specific evaluation items include:

- **Complete blood cell count:** red blood cell count, hemoglobin, hematocrit, platelet count, white blood cell count with differential (neutrophils, lymphocytes, eosinophils, monocytes and basophils);
- **Blood biochemistry**: total protein, albumin, alkaline phosphatase, fasting blood glucose, total bilirubin, direct bilirubin/indirect bilirubin, aspartate aminotransferase, alanine aminotransferase and glutamyl transpeptidase, creatinine, urea nitrogen/urea nitrogen, creatinine clearance rate and uric acid, as well as serum amylase and electrolyte (potassium, sodium, calcium and phosphorus); CPK and LDH are only performed during the screening period or during the clinical trial (in case of cardiac event);
- **Routine urine examination**: specific gravity, pH, urine glucose, protein, urine ketone body, and blood cells (white blood cells, red blood cells, etc.);
- **Coagulation function test:** thrombin time, prothrombin time, activated partial thrombin time and international normalized ratio;
- **tSerum or urin pregnancy test** (pre-menopausal females only);
- **HBV test, HCV test and HIV test:** HBsAg, HbsAb, HbeAg,HbeAb, HbcAb, HBV DNA (for the subjects with HBsAg(+)), HCV antibody, HCV RNA PCR (for the subjects with positive HCV antibody), HIV antibody.

6.3 Quality of life assessment

The EORTC QLQ-C30 was developed by EORTC Quality of Life in 1993. It consists of 30 items

that measure functioning (HRQoL) and symptoms in cancer patients of all cancer types. The questions are divided into 5 multifunctional scales (including physical, role, emotional, cognitive, and social functioning); 3 symptom scales (including fatigue, pain, and nausea/vomiting); a global HRQoL scale; 5 single items assessing other symptoms commonly experienced by cancer patients (including dyspnoea, appetite loss, insomnia, constipation and diarrhoea) and an item of financial impact of the disease. EORTC QLQ-C30 is a valid and reliable PRO method suitable for the population with this disease .

The EORTC QLQ-LC13 is a fully validated supplemental module to measure lung cancer-related symptoms and side effects of standard chemotherapy and radiotherapy. The EORTC QLQ-LC13 includes assessment of cough, haemoptysis, dyspnoea and site pain (symptom); oral pain, dysphagia, peripheral neuropathy and alopecia (treatment-related side effects) and analgesics.

Questionnaire of EORTC QLQ-C30 and EORTC QLQ-LC13 is shown in Attachment 5.

7. Adverse events

7.1 Definition

7.1.1 Definition of adverse events

An adverse event is defined as any medical adverse event occurred in the patient or subject in the drug clinical study, which is not necessarily causally related to the study drug. An adverse event can be an exacerbation of pre-existing symptoms, signs, laboratory abnormalities, or a newly diagnosed disease, laboratory abnormalities, etc.

7.1.2 Results of laboratory examination defined as AE

The following guidelines should be considered when investigators determine whether the change in laboratory values is an adverse event:

- Abnormal laboratory results leading to change in the investigational product (e.g., dose interruption);
- Concomitant and/or surgical intervention required to relieve abnormal laboratory results;
- Correlation between the abnormal laboratory results and clinical condition;

- Correlation between the abnormal laboratory results and serious adverse events.

7.1.3 Vital Signs Findings defined as AE

Not every vital sign abnormality qualifies as an AE. A vital sign result should be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g. dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific assessment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

7.1.4 Disease progression

During study period, events definitely caused by progression of disease are not treated as AE or SAE; symptoms, signs or abnormality at laboratory examination caused by progression of disease are not treated as AE or SAE; the hospitalization or death only caused by progression of disease is not reported as SAE. If the clinical symptoms can not confirmed as completely caused by progression of disease or do not conform to the anticipated manifestations of progressive disease, they can be reported as AE/SAE.

Deterioration of clinical symptoms may occur in some subjects. In this case, a progression of disease is obviously indicated by clinical symptoms of subjects but not supported by the change in size of tumor; or the progression of disease is obvious enough to make investigators possibly determine that the disease needs not be further assessed. In such cases, the determination of clinical progression is based on symptomatic deterioration. Since the deterioration of these symptoms should be a particular case, the objective progression of disease should be completely recorded by investigators as far as possible.

If whether an event is only caused by the study disease can not be determined, this event should be reported as AE or SAE.

7.1.5 Serious Adverse Events

A serious adverse event (SAE) is an medical adverse event meeting at least one of the following serious criteria:

1. Leading to death;
2. Life-threatening (Note: The term 'life-threatening' in the definition of SAE referred to an event in which the subject had been at risk of death at the time of the event, rather than an event which hypothetically could have caused death if it had been more severe.) ;
3. Requiring hospitalization or prolonged hospital stay; note: the following hospitalization does not belong to SAE in this study:

- The subject visit the emergency room or other departments of the hospital for <24 hours but not admitted (excluding important medical event or life-threatening event).
- Surgery on an elective date or scheduled operation prior to signing the informed consent form.
- Admitted for originally scheduled medical procedure/surgical operation according to the study protocol.
- Routine medical examination requiring hospitalization for evaluation of baseline/trending of health status (e.g., routine colonoscopy).
- Admission to the department of medicine/surgery that has been scheduled not for rescue or treatment of disease prior to entry in the study; however, these conditions need to be well documented.
- Hospitalization for other living conditions that is unrelated with health status and does not need pharmacological/surgical intervention (e.g., no housing, finance constraints, temporary absence of caregivers, family environment and management reasons).
- Admitted to receive anticancer therapy without any other SAEs.

4. Resulting in permanent or significant disability/incapacity;

5. Congenital anomaly/birth defect;

6. Other important medical events (IME).

In other cases, expedited reporting should be decided after medical and scientific judgment if the important medical event may not threaten life immediately or lead to death or hospitalization but may endanger patients or need interventional measures to prevent any one of the other consequences listed in the above definition. Examples of such events are allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependence or drug abuse.

7.2 ACCESS TO OBTAIN THE INFORMATION OF ADVERSE EVENTS

The investigator is to record all directly observed adverse events and all adverse events spontaneously reported by the study subject/legal delegate in the original medical record. In addition, the occurrence conditions of AE are also inquired from subjects or their legal representatives not in a guiding way.

7.3 TREATMENT OF ADVERSE EVENTS

If AE occurs during study period which is related to study drug or not, investigators should judge the severity of AE, and decide on whether to take measures, such as suspension of study, administration of combined drugs, non-drug treatment and hospitalized treatment.

7.4 CAUSALITY ASSESSMENT

Relationship between an adverse event and the study drug will be determined by the investigator based on the clinical judgment and the following definitions, including 5 grades: definitely related, probably related, possibly related, possibly unrelated, and definitely unrelated. The first three grades are adverse effects of the drug. The causal relation should be judged according to the following five principles:

1) Whether there is a reasonable precedence relationship between the start time of medication and the onset time of an adverse event.

2) Whether the suspected adverse event complies with an known adverse event type of the drug.

3) Whether the suspected adverse event may be explained with the effect of concomitant medications, the patient's clinical status or effects of other therapies.

4) Whether the adverse event disappears or abates after drug discontinuation or dose reduction.

5) Whether a same reaction occurs after reuse of the drug.

The Principal Investigator/Sub-Investigator will assess the relationship of all adverse events to the drug, using the following scale:

Table 8 Table of assessment of correlation between the adverse events and the drug

Definitely related	A clinical adverse event, including laboratory test abnormality, occurring in a plausible time relationship to study drug administration, and which cannot be explained by concurrent disease or other drugs or chemical. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The adverse event must be definitive pharmacological or phenomenological, using a satisfactory re-challenge if necessary.
Probably related	A clinical adverse event, including laboratory test abnormality, with a reasonable time relationship to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows an clinically reasonable response an withdrawal (de-challenge). Rechallenge information is not required to fulfill this definition.
Possibly related	A clinical adverse event, including laboratory test abnormality, with a reasonable time relationship to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Possibly not related	A clinical adverse event, including laboratory test abnormality, with a time relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanation.
Unrelated	When AE is obviously caused by other factors (such as clinical conditions of subjects, other treatments or combined drugs), AE is considered as unrelated to study drug.

7.5 SEVERITY(CTCAE GRADE)

Investigators or sub-investigators are responsible to assess the causal relation and severity of AE and SAE, and finally review/confirm the accuracy of event information and assessment. The severity of AE will be evaluated with reference to CTCAE version 5.0. If the adverse event occurred is not within the range of this criteria, investigators must categorize the severity of each adverse event in accordance with clinical judgment. The severity in accordance with CTCAE version 5.0 is defined as below:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Grade 2: Moderate; small, local, or noninvasive treatment is required; age-matched instrumental activities of daily living are limited[*].
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization; disabling; limiting self care ADL[**]. Note: severe case is not certainly equivalent to serious case. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

([*] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. [**] Self care ADL refer to bathing, dressing and undressing, eating food, washing hands and face, taking medications, and not bedridden.)

7.6 OUTCOME OF AE

Resolved/recovered;

Resolved/recovered with sequelae;

Not resolved/not recovered;

Persistent;

Death;

not known.

7.7 FOLLOW UP OF ADVERSE EVENTS

All AEs occurring during study period are followed up by investigators; follow-up time is determined according to the illness state; during follow-up period, necessary measures for treatment and therapy are taken to minimize the harm of subjects and fully ensure the safety of subjects. The course of follow-up and results of treatment are recorded in detail. At the termination of study or at dropout of subjects, the unresolved AE or SAE must be followed up until any of following conditions is met:

- The event is resolved; or
- The event stabilizes; or
- The event is restored to baseline level (if baseline level is available); or
- More information is unlikely to be obtained (for example: the subjects refuse to provide more information; or as proven by evidences, the subjects are still lost to follow-up despite of utmost effort); or
- The event is at a level uniformly considered as acceptable by investigators and the sponsor.

Under the following conditions, the event is considered as resolved: health state of subjects has been restored to baseline level; or investigators predict that AE will not be further improved or aggravated. AE not resolved at the last AE assessment is traced by investigators according to the medical conventional practice. During the follow-up period of long term survival, investigators are not responsible for active collection of new adverse events.

7.8 RECORDING OF ADVERSE EVENTS

All AEs occurring from the signing of ICF by subjects until 28 days after the last administration of study drug should be recorded in eCRF, no matter whether this AE is related to study drug or not. The information on all AEs should be recorded in concise, correct and standard medical terminology as far as possible, including: name of AE, starting time, ending time, outcome, grade of severity, countermeasures for study drug, seriousness and relevance.

Special instructions for recording of adverse events/serious adverse events

If the diagnosis of event is known at the time of reporting, the name of diagnosis should be recorded into eCRF (or SAE if applicable), but the event is not recorded as single symptom or sign (for example: an event is recorded as hepatitis, but not as increase of transaminase/bilirubin or jaundice). However, if a serious signs and/or symptoms can not be medically defined as single diagnosis or syndrome at the time of reporting, each sign or symptom is separately recorded as SAE or AE in eCRF (or SAE if applicable). If a diagnosis is determined subsequently, single sign and/or symptom is substituted with the diagnostic terminology of AE in eCRF (or SAE if applicable).

Although drug treatment is terminated for any reason, a certain subject can still continue to participate in the study.

- During follow-up period of survival time, continuous AE should be traced, and the information of follow-up continues to be collected.
- Before the end of follow-up period of survival time, SAE related to study drug should still continue to be collected; after the progress of follow-up is reported to the sponsor according to the standard deadline and procedures of SAE report and during follow-up period of survival time, the information on all death cases continues to be collected and recorded in eCRF.

The time section for active collection of information on AE (i.e. stage of active collection) lasts from the obtaining of ICF from subjects until at least 28 calendar days after the last administration of study drug.

For the patients within a failure in screening, the stage of active collection ends when the state of failure in screening is determined.
If new anti-cancer treatment is started, the recording period for non-serious AE ends when such new treatment is started.

Table 9 Time section for collecting the information on AE and SAE

	Treatment period	28 d after the last dose	Survival follow-up period
All new AEs are collected into eCRF	Yes	Yes	No
All ongoing AEs are collected into eCRF	Yes	Yes	Yes
All SAE related to study drug collected by eCRF	Yes	Yes	Yes
All SAE unrelated to study drug collected by eCRF	Yes	Yes	No

7.9 REPORTING OF SEVERE ADVERSE EVENTS

When SAE occurs from the signing of ICF by subjects until 28 days after the last administration of study drug (no matter whether SAE is related to study drug and study procedures or not), the written report on SAE should be completed by investigators within 24 hours after the learning of its occurrence. If a patient receives a new anticancer therapy, no SAEs will be reported.

Once SAE is learned, investigators should take the following actions:

- The timely proper treatment measures for subjects are immediately taken when necessary; SAE is reported to drug regulatory department, health administrative department, ethics committee

and the sponsor (or its representative) within 24 hours after the learning of its occurrence.

- In the serious adverse event report form, the following contents should be included as far as possible: general information of the patient, name of investigational product, name/duration/severity of the SAE, correlation with investigational product, treatment and event outcome.

- The information on follow-up is recorded in a new SAE report, and indicated as information on follow-up of SAE reported previously.

SAE (including: the suspected unanticipated SAE) is reported by the sponsor according to the applicable local regulations.

When SAE occurs after the termination of stage of active collection, SAE considered by investigators after the learning of its occurrence as at least possibly rationally related to study drug should be reported according to the above reporting procedures for SAE. At the termination of study or at dropout of subjects, the unresolved SAE is followed up 7.7 Follow Up of Adverse Events as AE.

7.10 REPORTING OF DEATHS

All deaths that occur during the study, or within the 28 day after the administration of the last dose of study treatment, must be reported as the following regulations:

- Deaths that was unequivocally due to disease progression shoud be recorded but was not reported as an SAE.

- If a death is not (or uncertainly) caused by progression of disease, AE causing such death is recorded and reported as SAE. If possible, the following contents should be stated in the report: coaction of progression of disease; main cause of death; and any concomitant reason for death.

- Deaths with an unknown cause should always be reported as an SAE. However, every effort should be made to determine the cause of death. The cause of death of subjects can better be assessed through autopsy; if autopsy is made, the duplicate of autopsy report should be submitted to the sponsor (or its representative) in urgent way within the stipulated time.

- When a death occurs after the termination of stage of active collection, the death considered by

investigators after the learning of its occurrence as at least possibly rationally related to study drug should be reported according to the following reporting procedures for SAE.

New cancers

- New cancers are SAEs. New cancer mean the cancer occuring just after the participation of this subject in this study and not as main reason for study treatment. Excludes metastases lesions of original cancer.

7.11 REPORT AND FOLLOW-UP TRACINGS OF PREGNANCY EVENT

When the investigator learns that the female subject is pregnant, the investigator must ask the patient to withdraw from the trial and follow up until the termination of the pregnancy or childbirth. Investigators should report all pregnancies to the Ethics, Sponsor or the delegate immediately in the form of pregnancy reporting within 24 hours after learning the pregnancy event. Although the pregnancy is not a AE by itself, a close observational follow-up should still be made, and the outcome of pregnant event is determined. The results of pregnant event are recorded in the follow-up report on pregnancy, which is submitted to ethics committee and the sponsor (or its representative) according to the deadline and procedures for initial report. Female companion of male subject is reported and followed up through the same procedures; but this male subject is not required to drop out of study. Other AEs conforming to conditions of SAE occurring during the pregnancy period should be reported according to the reporting procedures for SAE. Ectopic pregnancy, natural abortion, induced abortion caused by medical and health reasons, stillborn fetus and SAE of neonates (not limited to neonatal death, congenital abnormality [including congenital abnormality of aborted baby] are recorded and reported as SAE. Elective abortions without complications should not be handled as SAEs.

Neonatal death occurring within one month after the birth is reported as SAE, no matter whater is the causal relation. In addition, the death of baby at >1 month after the birth assessed by investigators as related or possibly related to exposure to study drug is reported as SAE.

8. committee

8.1 INDEPENDENT REVIEW COMMITTEE ON IMAGING (IRC)

Independent review committee on imaging (IRC) will be established. According to RECIST 1.1, data of tumor imaging assessment (CT or MRI) of all subjects are periodically evaluated by external IRC at blind state. Detailed operating procedures are shown in the Guidance Manual on Independent Imaging Assessment.

8.2 INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

An Independent Data Monitoring Committee (IDMC) will be established for this study. IDMC is an important component for ensuring the protection of subjects and the integrity of data. At the initation of IDMC and for data monitoring, a meeting is held by IDMC. IDMC mainly aims to periodically monitor the data of efficacy and safety in each treatment group of this study; meanwhile, IDMC also raises formal suggestions, such as whether study protocol needs be revised and whether the study is continued or terminated. For detailed operation process please see “Constitution of Independent Data Monitoring Committees”

9. Statistical methods

9.1 STATISTICAL AND ANALYTICAL PLANS

Methods and contents of statistical analysis adopted in this study will be shown in detail in the additional SAP. If study protocol needs be revised and such revision is judged by the sponsor and/or principal investigator as great influence on the methods and contents of statistical analysis, SAP should be revised correspondingly to consist with this protocol.

The detailed statistical analytical plan (SAP) must be finalized and approved through signature before the locking of database. When primary endpoint and main analytical methods are changed, study protocol should be revised correspondingly. However, other contents of SAP inconsistent with study protocol should be listed, described and explained in this document.

9.2 SAMPLE SIZE ESTIMATION

According to the results of blind-state data obtained from 66 cases judged as PFS events by

investigators, the hypothesis of study protocol can be adjusted by the sponsor to increase the number of events. When the first 358 subjects have been 1:1 enrolled within 6.5 months, assuming the median PFS of 16 months for Alflutinib and 11 months in gefitinib control group; the hazard ratio HR is 0.688 for the trial group versus control group and α is two-sided 0.05, a total of 238 target events are needed to provide at least 80% power to detect intergroup difference.

After 358 patients are enrolled into this study, they will be followed up for at least 17 months so as to obtain 238 cases of target events. 。

9.3 INTERIM ANALYSIS

In this study, one interim analysis will be made, which is implemented by IDMC. Through O'Brien-Fleming border concomitant in Lan-DeMets α consumption function, interim analysis is made when about 50% of PFS events (i.e. about 119 cases of PFS events) are found.

According to the number of confirmed PFS events, endopoint border of interim analysis and primary analysis is obtained.

When about 119 cases of PFS events (i.e. about 50% of target events) are found, interim analysis is made; in order to control the error of Class I in whole study as 0.05 (two-sided), α consumption of interim analysis is set as 0.00306 (two-sided) according to the Lan-DeMets method for α consumption. Actual α consumption of interim analysis is determined according to the number of events found at actual interim analysis. If P value of interim analysis is ≤0.00306 (two-sided), the efficacy of study drug is considered as significantly superior to that of control drug.

If the study is still continued after the interim analysis, there are just 238 cases of PFS events in the database locked at primary analysis of PFS. If P value of Log-rank test (two-sided) is ≤0.049 (two-sided), H0 is refused. If the number of final events exceeds the number stipulated in the study protocol, all events recorded in the database at locking are used; and the information renewed at interim analysis is not used to calculate final border again.

By overall considering the conditions of efficacy assessment at interim analysis, IDMC suggests whether the sample size is estimated by the sponsor again. 。

9.4 INDEPENDENT DATA MONITORING COMMITTEE (IDMC)

The data of efficacy and safety are periodically reviewed by IDMC, so as to protect the rights and interests of subjects for ethics and safety.

IDMC is comprised of clinical oncologists and statistician who are independent on the sponsor and have no major conflict of interest with the sponsor.

IDMC is responsible to periodically review study data, and raise the suggestions for study (such as continuation as schedule, protocol adjustment and termination). Decided by Shanghai Allist Pharmaceutical Technology Co., Ltd. finally.

Operating procedures for IDMC are shown in the contents of IDMC in this study.

9.5 ANALYSIS POPULATIONS

This trial will use full analysis set, per-protocol set and safety set for statistical analysis.

Full analysis set (FAS): According to the intent-to-treat (ITT) rules, the FAS includes all enrolled subjects that have taken at least one dose of the study drug. The FAS is the main population for efficacy evaluation in this study.

Per-protocol set (PPS): Per-protocol set is a subset of the FAS that includes all subjects meeting the definition of FAS set who have completed the protocol-specified treatment or haven’t had major protocol deviations requiring exclusion from the analysis set. The exact definition of major protocol deviations and the need for exclusion from the analysis set will be determined at the time of data review. The PPS set is the secondary analysis population for effectiveness; however, if the results are inconsistent with the full analysis set, the inconsistent results shall be analyzed in detail.

Safety Set (SS): The SS includes all enrolled subjects who have received the study drug.

9.5.1 Brain metastases analysis population

Craniocerebral Full Analysis Set (cFAS): A subset of FAS, which includes subjects who meet the definition of FAS and have measurable brain lesions and non-measurable brain lesions at screening visit assessed by the Independent Review Committee on Imaging (IRC). This analysis set is used for the subgroup analysis of the efficacy of the Independent Review Committee on Imaging (IRC)

reading assessments.

Craniocerebral Full Analysis Set (cFAS): A subset of cFAS, which includes subjects who meet the definition of FAS and have measurable brain lesions at screening visit assessed by the Independent Review Committee on Imaging (IRC). This analysis set is used for efficacy analysis based on measurable lesion reading results in subjects with brain metastases as assessed by the Independent Review Committee on Imaging(IRC).

Craniocerebral Metastases Set (cMTS): A subset of the FAS, which includes all subjects with target and non-target brain lesions assessed by the investigator during the screening period/baseline visit who meet the definition of the FAS. This analysis set will be generated by programming subjects with both target and non-target brain lesions from the screening investigator reading data. This analysis set is used for the subgroup analysis of the validity of the investigator reading assessments.

9.6 HYPOTHESIS TESTING

This study is a confirmatory trial. The alternative hypothesis is that the efficacy of alflutinib monotherapy (80 mg, daily, taken orally on an empty stomach) is superior to that of gefitinib monotherapy (250 mg, daily, taken orally on an empty stomach) in the treatment of primary locally advanced or metastatic Chinese patients with EGFR sensitive mutation.

H_0: S1 (t) = S2 (t) represents the survival rate of patients receiving the two treatments is the same

H_1: S1 (t) ≠ S2 (t) represents the survival rate of patients treated with alflutinib monotherapy is superior to that of patients treated with gefitinib monotherapy, with two-sided α at 0.05.

9.7 GENERAL ANALYSIS

SAS 9.2 or above version software will be used for statistical analysis. For the statistical description and inference of the data, appropriate statistical description and hypothesis test method will be selected based on the distribution of the data. Number (number of missing case), minimum, maximum, mean, standard deviation and median will be listed for the statistical description of quantitative data; whereas the number and percentage of the variable corresponding level will be listed for qualitative data. Survival analysis method will be used for the data involving the time to

event. Unless otherwise noted, two-sided hypothesis test will be used for all the statistical analysis tests, the hypothesis test level is set atα=0.05, i.e., the null hypothesis will be rejected if Pvalue is less than or equal to 0.05, and the conclusion is statistically significant.

9.8 BASELINE EVALUATION

Demographic data are summarized through the descriptive statistic; other baseline data are summarized or tabulated according to the actual conditions.

9.9 EFFICACY EVALUATION

According to RECIST 1.1, the efficacy is assessed. The definition of CR, PR, SD and PD is shown in Attachment 1.

9.9.1 Analysis of primary endpoint(s)

Primary efficacy endpoint is PFS assessed by IRC. PFS is compared between two groups through the stratified Log-rank test with the type of EGFR mutation and existence of brain metastasis or not as stratification factors; P value is calculated; median value and 95% CI (two-sided) of PFS are estimated; Kaplan-Meier survival curve is plotted; Hazard ratio and its 95% CI are calculated through Cox proportional hazards model; and subgroup analysis is made to explore the influence of some factors (including stratification factors) on PFS.

9.9.2 Analyses of secondary endpoints

OS: OS is compared between two groups through the stratified Log-rank test with the type of EGFR mutation and existence of brain metastasis or not as stratification factors; P value is calculated; median value and 95% CI (two-sided) of OS are estimated; and Kaplan-Meier survival curve is plotted.

PFS assessed by investigators: PFS assessed by investigators is compared between two groups through the stratified Log-rank test; P value is calculated; median value and 95% CI (two-sided) of PFS are estimated; Kaplan-Meier survival curve is plotted; and hazard ratio and its 95% CI are calculated through Cox proportional hazards model.

ORR evaluated by investigators and independent radiological committee: point estimation will be

performed and Clopper-Pearson precision method will be used to estimate the 95% confidential interval (CI), Cochran-Mantel-Haenszel (CMH) test, chi-square test or Fisher exact test will be used to detect the difference between the two groups, and the intergroup difference in ORR rate and its 95%CI will be estimated. Subgroup analysis of ORR will be performed by the type of EGFR mutation and presence of brain metastasis, using the same analytical method.

DCR: the number and percentage of subjects with responses (PR+CR) and SD (duration of SD ≥ 12 weeks is required) will be calculated using the same analytical method as the evaluation variable of ORR.

DOR: In the subjects with a response of disease, median value and 95% CI of DOR are estimated; Kaplan-Meier survival curve is plotted; and intergroup difference is tested through the stratified Log-rank test. DOR analysis population is only limited to the subjects with response records in the full analysis set.

DepOR: Depth of response refers to the percentage change of the smallest value of the sum of the longest diameters (or the shortest diameter of the lymph nodes) of target lesions (the best value for depth of response), from the baseline value in the absence of progression of non-target lesions and appearance of new lesions and the best value for depth of response will be generated from all efficacy evaluations performed before progression or before the start of subsequent anti-tumor therapy. Analysis of variance is used to compare the depth of response, calculate the unmodified mean, least squares mean, difference between the two groups, 95% CI of the difference, and p value of the optimal value of the depth of response, and compare the depth of response classified by the best overall response (BOR) of the two treatments with a waterfall plot.

TTP assessed by investigators and IRC: Median value and 95% CI (two-sided) of TTP are estimated; Kaplan-Meier survival curve is plotted; TTP is compared between two groups through the stratified Log-rank test with the type of EGFR mutation and brain metastasis or not as stratification factor; P value is calculated; and hazard ratio and its 95% CI are calculated through Cox proportional hazards model.

9.9.3 Brain Metastases Efficacy Analysis

The Independent Radiological and Review Committee (IRC) will analyze the following efficacy

variables based on the assessment results of measurable and non-measurable lesions in brain:

- CNS PFS (central nervous system progression-free survival): it is defined as the time from randomization to brain disease progression or death.
- CNS DoR (central nervous system duration of response): it is defined as the time from objective response (CR or PR) of measurable or non-measurable lesion in brain to brain disease progression or death.
- CNS ORR (central nervous system objective response rate): it is defined as the proportion of subjects with objective response (CR or PR) of measurable or non-measurable lesion in brain.
- CNS DCR_{6W} (central nervous system disease control rate at 6 weeks):it is defined as the proportion of subjects with disease control (duration of CR or PR or SD ≥ 6 weeks) of measurable or non-measurable lesion in brain.
- CNS DCR_{12W} (central nervous system disease control rate at 12 weeks):it is defined as the proportion of subjects with disease control (duration of CR or PR or SD ≥ 12 weeks) of measurable or non-measurable lesion in brain.

cFAS and cEFR will be used for analysis of the above central nervous system efficacy endpoint, using the same analytical method with that for the overall efficacy endpoint (the window period will be considered for the calculation), more detailed analytical method will be described in the statistical analysis plan.

9.9.4 Subgroup analyses

1. To compare the efficacy of first-line treatment with alflutinib mesylate and gefitinib in the initial treatment in the population with genotype Ex19del and L858R mutations positive locally advanced or metastatic Chinese non-small cell lung cancer respectively;
2. To compare the efficacy(PFS, OS, ORR) of first-line treatment with alflutinib mesylate and gefitinib in the initial treatment in the population with or without locally advanced or metastatic Chinese non-small cell lung cancer respectively;
3. Cox proportional hazards regression models are used to analyze the following characteristics

(including but not limited to) of subgroups: gender (male vs. female), age at screening (<65 vs. ≥ 65), brain metastasis status at enrollment, smoking history, and mutation type (Ex19del vs. L858R) ECOG PS score (0 VS. 1), comparison of PFS between alflutinib mesylate single agent and gefitinib in two goups, estimated hazard ratio and its 95% CI of alflutinib mesylate versus gefitinib.

9.9.5 Living quality scoring analyses

EORTC QLQ-C30 and EORTC QLQ-LC13: Mixed Model for Repeated Measurements (MMRM) or analysis of covariance will be used to compare the quality of life (QoL) standard score between the two groups by treatment group, uncorrected mean change in the standard score from baseline, least squares mean, difference between the two groups, 95% CI of the difference and p value will be calculated at each visit.

9.10 SAFETY EVALUATION

Vital signs: According to the data of vital signs during screening period and at each visit, each index of vital signs at each visit and its change value over baseline value are summarized statistically.

Laboratory examination: Among the items of laboratory examination, blood routine examination, urine routine examination, blood biochemistry and coagulation functional examination are mainly summarized. According to the results of laboratory examination at baseline and at each visit, the results of laboratory examination items completed at each visit and the value of their normal/abnormal change over that before the treatment are separately summarized in the form of cross table (according to the normal range and judgment of investigators for clinical significance); abnormal results of laboratory examination at each visit are also tabulated.

Adverse event: all AEs will be classified according to the latest version of the International Conference on Harmonisation (ICH) Medical Dictionary for Regulatory Activities (MedDRA) coding and graded according to CTCAE v5.0. All AEs will be summarized mainly as treatment-emergent adverse events (TEAEs), i.e., AEs occurring after the initial dose of study drug are defined as adverse reactions that occur after the initial dose of study drug or occur before the dose of study drug and worsen during the administration of study drug.

(1) The number and percentage of all the TEAEs, TEAEs related with the study drug, SAE, grade 3 and above TEAEs, TEAEs leading to drop-out, TEAEs leading to death will be summarized.

(2) TEAE, TEAE related with the study drug and grade 3 and above TEAE will be descriptively summarized by system organ class and preferred term.

Other safety data will be presented in the form of summary tabulation or list.

10. Quality control of trial

In order to ensure the accuracy, consistency, completeness and reliability of the trial data generated in this protocol, the study should follow the standard operating procedure (SOP) of the investigator site, GCP guideline and relevant regular requirements from CFDA.

This trial will be monitored by the clinical monitors from the sponsor or their designated unit. The on-site follow-up will be performed prior to initiation of the trial at the center and at appropriate time points during conduction of the trial. The communication record will also include teleconference and correspondence.

In accordance with the requirement in principles of GCP guideline, the trial monitor must be allowed to look up the original documentation of investigators, in order to check: consistency of the data recorded in eCRF; protection of subject's safety and rights; whether the trial is conducted in accordance with currently approved protocol and all the regulatory requirements in operation.

Investigators agree to cooperate with relevant inspections fully in accordance with the requirement in the protocol in a written form, and allow authorized personnel to look up all the documentations directly. Various materials recorded in the original medical record and regarded as the original material will be locked prior to conduction of the trial.

Each study base may be audited by the auditors sent by the sponsor or inspected by the regulatory authorities. In case of such audit/inspection, investigators should agree to allow inspectors to look up the original documents directly and schedule time to discuss various findings with relevant staff.

11. Ethical requirements

11.1 SIGNING OF INFORMED CONSENT FORM

Investigators or their designated personnel (if recognized by local law) should be responsible for acquisition of the written informed consent form from each patient participating in the this trial, after explaining the objective, method, expected benefit and potential risks of the trial sufficiently. Investigators or their designated personnel must also explain and state that the patient can refuse to participate in the trial completely freely or withdraw the informed consent form for any reason at any time. If a new safety signal is obtained whilst leading to major change in the risk/benefit evaluation, the informed consent form should be evaluated and updated. In such circumstance, all the patients (including those who are receiving the treatment) should be informed of the new safety information, provided with the modified copy of form and re-evaluated for continuation of participation in the trial. The signed informed consent form must be kept in the subject's file. The informed consent form must be expressed in a language that the subject can read and understand. The investigator must provide the subject with a copy of the informed consent form.

11.2 INFORMED CONSENT FORM REVISION

If important safety data on the study drug obtained during conduction of the trial, the informed consent form will be modified and amended correspondingly. The modified copies of ICF approved by IRB at the study base will be kept at the site of the sponsor. After approval by IRB at the study base, each patient participating in and newly recruited in the trial will be required to provide their consent for the recently approved version of informed consent form.

11.3 INDEPENDENT ETHICS COMMITTEE(IRB)

The sponsor and investigators will prepare all the relevant materials, including the protocol, informed consent form, copy of investigator’s brochure, approval letter and drug inspection report from relevant authorities and any advertisement for recruiting subjects, which will be provided to IRB by investigators. The written ethical approval letter was submitted by the investigator to the sponsor. The trial can not be initiated before acquisition of the protocol and informed consent form approved by IRB by investigators and receipt of the copy of letter of ethical approval by the sponsor. In accordance with IRB rules and regulations at the study center, all the amendments, regular

progress reports and report of serious adverse events must be submitted to IRB in real time.

11.4 PROTECTION OF SUBJECT RIGHTS

In order to ensure conduction of this clinical trial according to ethical requirement, investigators should comply with internationally recognized guideline, the study is intended to acquire the scientific knowledge derived from this trial whilst minimizing the risk of participants, and will be helpful for better investigation of the non-small cell lung cancer metastatic.

The participants will provide the written informed consent form in order to demonstrate that they were voluntary to participate in this trial. The updated safety information was provided to investigators, Independent Ethics Committee and subjects by the sponsor, so that the subjects could consider the voluntariness in continuous participation in the trial.

11.5 COMPENSATION

Except the standard health care, an agreement will be signed separately for the financial operation of additional workload at the trial base. Subjects will not receive any compensation for participation in the trial. However, various reasonable temporary advances resulted from participation in the trial (e.g., travel expenses) can be compensated by the sponsor. If any injury related with the trial occurs, the patient will be provided with corresponding compensation and/or therapeutic measures.

12. Data management

12.1. DATA CAPTURE SYSTEM

1) Electronic Data Capture System will be used in the study. Construction of electronic case report form (eCRF): eCRF is constructed by data manager according to protocol and study medical record.

2) Assignment of authority: According to different roles (such as data entry person, data administrator, investigators (principal investigator) and clinical monitor), an account is created separately, and different authority is assigned. The contents of a study center can only be viewed by this center. Data entry person can enter/modify the data and solve the query; investigators can view, enter, modify the data, solve the query, and verify the data; besides the authority of investigators, principal investigator can make an electronic signature; clinical monitor can view

the data, send/close the query and verify the raw data; and data administrator can view the data, send/close the query, and freeze, lock and verify the data.

3) Data entry: clinical investigator or data entry personnel (clinical coordinator) designated by investigator timely and accurately enter source data into eCRF.

4) Sending and solving of query: After the data are entered into the database of electronic data collection (EDC), the data are verified by the system according to the data verification plan (for the edited logical verification), and then a systemic query is sent automatically for the problematic data; the data can also be verified manually by clinical monitor and data administrator, and a manual query is sent through EDC database for the problematic data; both systemic query and manual query are confirmed and answered by data entry person or investigators, and wrong data are modified when necessary until the query is solved. While answering the unsolved query, a query can be made on this data point again by data administrator and clinical monitor; all records are kept in EDC database.

5) Modification and verification of data: After the data are verified by data entery person or investigators, the data can be modified; and the reason for modification should be indicated in eCRF. Investigators can finally verify all data.

6) Electronic signature on eCRF: After all data in database have been verified and cleared as no query by clinical monitor and data administrator, the data are frozen by data administrator by not modifying them; the truthfulness and integrity of frozen data are confirmed by principal investigator through electronic signature.

7) Locking and exporting of database: After all data pass the verification at data verification meeting, the database is locked by data administrator according to the decision on database locking. If there is any modification after lock of database, it needs to be applied and can be executed only after joint signature and confirmation by the sponsor, investigators, medical specialist, statisticians, project manager and data manager through sufficient discussion. All the data will be finally exported from EDC database by data manager and submitted to statisticians for analysis.

8) After the end of trial, eCRF were recorded in the form of PDF for disc and archival as required.

Investigators should keep the clinical trial data until 5 years after termination of the clinical trial. The sponsor should keep the clinical trial data until at least 5 years after approval of the investigational product. However, if required by current regulations or the agreement with the sponsor, these materials can also ber kept for a longer time. The Sponsor will notify the Investigator of the time when the data needn't be stored by written notice.

Detailed procedures of the data management will be described in the data management plan.

12.2 REQUIREMENTS FOR DATA COMPLETION OF THE INVESTIGATOR

1) All required pages of eCRF should be completed in Chinese by investigators in accurate, integral and logical way and by avoiding abbreviation and symbol as far as possible. All data completed in eCRF should consist with source data.

2) All the items in trial record need to be filled in, must not be blank or missed(blank without record should be filled in according to the requirement).

3) Laboratory test and the accessory test items are complete.

4) When a query is generated by database and treated by investigators, the data are first confirmed before the anwer of query; the data are renewed at the corresponding data point of eCRF when necessary; and the data can be renewed and modified only by investigators or their authorized persons passing relevant training.

5) This database can be entered only by investigators or their authorized persons passing relevant training; the authorized person should well know study protocol and grasp the principles of GCP.

6) All data are entered by investigators in the page of eCRF. After the data are verified and cleared as no query by clinical monitor and data administrator, an electronic signature is made by investigators through their own user name and password. If the data are renewed after the signature, the renewed eCRF is signed again by investigators. Electronic signature should be made by investigators in all pages of eCRF for all screened patients and all enrolled patients.

12.3 REQUIREMENTS FOR DATA MONITORING OF CLINICAL MONITOR

1) During study period, clinical monitor visits study center to inspect the conditions of informed consent, screening and enrollment of subjects.

2) Clinical monitor can discuss with working person at study center on the verification results of eCRF and source document. All errors, omissions and queries are corrected and answered by investigators in the database.

3) Investigators confirm that all AEs have been recorded in eCRF, and that SAE has been reported and recorded in file.

4) To check whether the supply, storage, dispensation, recovery of the investigational product are in accordance with relevant regulations or not, and make corresponding records;

5) During the period of monitoring visit, clinical monitor can contact the working person at relevant study center to obtain source document, and provide proper environme nt for completing the verification of study associated documents. During study period, clinical monitor periodically meets the investigators to provide the feedback information on study implementation.

6) the monitor will compare the data in the eCRFs with the hospital records (source documents). The nature and position of all source documents are specified to ensure that all sources of raw data necessary for completion of eCRF have been understood; clinical monitor can also contact study center to verify these data sources.

12.4 RECORDS AND STORAGE OF TEST DATA

1) All detailed original documents of subjects are kept by investigators to ensure that the data in database are accurate, integral and timely. Original document and medical record should be clear and detailed, and can be recognized by the personnel participating in the clinical trial easily.

2) The data in eCRF can be modified only by investigators or their authorized person.

3) After the end of trial, eCRF were printed for disc and archival as required. All trial documents

have to be retained until 5 years after the end of the study. However, if required by current regulations or the agreement with the sponsor, these materials can also ber kept for a longer time. The Sponsor will notify the Investigator of the time when the data needn't be stored by written notice.

13. Data Management

All materials provided by the sponsor to investigators (including this study protocol) can not be disclosed, and must be kept as secret.

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Proper technological and organizational measures should be taken to prevent the following conditions: without prior approval, personal data are disclosed or obtained; the data are destroyed accidentally or illegally; and the data are lost or modified accidently. According to the requirements of the duties, sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The contents of informed consent of subjects (or their legal representative) include: personal data are treated; original medical record (source data/documents) of subjects can be directly obtained by investigators or study institutions for some purposes (such as monitoring and supervision relevant to study; review of Ethics Committee; and review of supervisory institutions).

The sponsor has the right to issue or publish information or data related with the study, or submit them to the Drug Administration Department. If other individuals or units relevant to this study hope to issue or publish study results or relevant data, the permission of the sponsor should be solicited in advance. The sponsor shall seek permission of the investigator if the sponsor has the sponsor's name appeared in the issuance, publication, or advertisement content.

14. Publication policy

Objective, content and results of this clinical trial as well as all the future information must be strictly

confidential. All materials and results are copyrighted by the sponsor.

After the end of the trial or when the data have been adequate (through sponsor's rational judgment), investigators can prepare the data sourced from the trial for publication. Prior to public release, such data should be submitted to the sponsor to review and issue opinions. In order to ensure the sponsor can issue opinions and propose relevant suggestions, the materials for public communication should be submitted to the sponsor for review at least 60 days prior to submission for publication, public communication or review by the public release committee.

Investigators must agree that all the reasonable opinions issued by the sponsor and related with the article to be published by investigators will be added in the article by investigators.

During review of the article to be published, the sponsor has the right to postpone publication of the article in order for the sponsor to take measures to protect their patent information. All the materials related with the trial can not be published without the sponsor's written approval. Except legal cause, the sponsor or the principal investigator can not reveal the trial results to any third party before bilateral agreement on data analysis and interpretation is reached.

15. Amendments of and deviation from trial protocol

15.1 TRIAL PROTOCOL AMENDMENT

In case the protocol needs to be changed following approval, the written amendment signed by the same personnel needs to be provided. The amendment should be informed to the Independent Ethics Committee involved and put on record at National Medical Products Administration. Changes that have significant effect on patient's safety in the trial need to be approved by the responsible Independent Ethics Committee and put on record at National Medical Products Administration.

The amendment should be distributed to all the personnel involved in conduction of the trial. Change to all the procedures required in the amendment should be informed to all the personnel.

15.2 DEVIATION FROM TRIAL PROTOCOL

Major deviation from the protocol is defined as various events or behaviors of subjects or investigators leading to inability to evaluate the primary objective of this protocol or unreliable evaluation results.

The ethics committee should establish, record in a written form and follow up the procedures, the established procedures should include: any deviation from the protocol or any change to the protocol can not be performed prior to written approval of corresponding amendment, except the necessary deviation as to eliminate immediate risk, or changes only involving the logistics or administration of the trial.

Without the sponsor's consent and prior review and written approval of the amendment by the ethics committee, investigators can not make any deviation from the protocol or any change to the protocol, except the necessary deviation as to eliminate the immediate risk or changes only involving logistics or administration of the trial (e.g., changing monitors or telephone number). In order to eliminate the immediate risk, investigators can make any deviation from the protocol or any change to the protocol without prior approval by the ethics committee. Investigators should submit deviations or changes conducted, reasons for deviation or change, and planned amendment to the protocol where possible, if appropriate:

- Submit to ethics committee for review and approval;
- Submit to the sponsor to get their consent;
- Submit to regulatory authorities. Investigators or their designated personnel should record of and make explanations for various conditions that have deviated from the approved protocol.

16. Trial discontinuation and closure

16.1 TRIAL DISCONTINUATION REQUIRED BY THE SPONSOR

The sponsor retains the right to interrupt or permanently discontinue this trial at one study site or all study sites for various reasons at any time (including but not limited to safety or ethical issue or serious violation from relevant requirement).

In special circumstances, the trial can be terminated in one separate trial base, if the sponsor has reasonable reason, for example, trial fraud is suspected or the trial does not comply with the guideline in Good Clinical Practice.

If the sponsor makes a decision that such action is necessary, the sponsor will discuss this question with investigators (including the reason for taking such action). The sponsor will inform

investigators of interruption of this trial in advance, prior to its conduction.

If the trial is interrupted or terminated for safety reason, the sponsor will inform all the other investigators and/or institutional organizations conducting the trial immediately, and the interruption or termination of the trial as well as the reason will also be informed to the regulatory authorities. If required by corresponding regulations, investigators must inform the ethics committee immediately and provide the reason for the interruption or termination.

16.2 END OF TRIAL

Once the trial ends, the monitors will conduct the following but not limiting work together with investigators or staff at the base:

- Traceability, harmonization and disposition of unused investigational products;
- Check the integrity of the trial records in the sites;

If the trial is permanently discontinued, all the trial materials must be returned to the sponsor. In addition, all the unused investigational products will be disposed in accordance with corresponding procedure. The economic compensation for investigators and/or institutional organizations will refer to the agreement between investigators and the sponsor.

The sponsor will inform the ethics committee that the trial has ended within 90 days after end of the clinical trial. If the trial needs to be terminated prematurely, this time period will be reduced to 15 days and an unambiguous interpretation will be made for its reason. Study center is guaranteed as sufficient time and proper resources. Investigators should possess the ability to prove that they can complete the recruitment of patients at the required number within the negotiated recruitment period.

A list of their designated persons relevant to this study and relevant qualifications are provided by investigators.

Before the starting of this study, investigators should provide the sponsor (or its representative) with the latest resume of investigators and coordinating investigators.

If the subject has an attending physician, this attending physician should, after the permission of subject, be told by investigators that the subject is participating in this study.

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Annex 1 Response Evaluation Criteria in Solid Tumors (RECIST)

http://www.eortc.be/recist/documents/RECISTGuidelines.pdf

1. Definition of the Lesion

At baseline level, tumor lesions/lymph nodes can be divided as measurable and non-measurable according to the definitions below:

Measurable:

Tumor lesions: at least one diameter that could be precisely measured (recorded as maximum diameter), its minimum length is as below:

CT scan 10 mm (thickness of CT scan is no more than 5 mm)

Clinical routine instrument 10 mm (tumor lesion that could not be accurately measured by diameter-measuring instrument should be recorded as non-measurable)

Chest X-ray 20mm

Malignant lymph nodes: pathologically enlarged and measurable, short axis ≥15mm for single lymph node in CT scan (thickness of CT scan recommended no more than 5mm). Only the short axis is measured and followed up at baseline and during follow-up.

Non-measurable:

All the other lesions, including small lesions (maximum diameter＜10mm or short axis of pathological lymph node ≥10mm and ＜15mm) and non-measurable lesions. Non-measurable lesions include: meningeal disease, ascites, pleural or pericardial effusion, inflammatory breast cancer, skin/pulmonary cancerous lymphatic inflammation, abdominal mass that can not be diagnosed and followed up by radiology, as well as cystic lesion.

Special considerations on the measurement of lesions

Osseous lesion, cystic lesion and the lesion previously given topical therapy needed to be specially noted:

Osseous lesion:

Bone scan, PET scan or plain X-ray are inappropriate for measurement of osseous lesions, however, they can be used for confirmation of the presence or disappearance of osseous lesions;

If the osteolytic lesion or mixed osteolytic/osteogenic lesion with determined soft tissue component could be evaluated with tomographic imaging technique, such as CT or MRI, when the soft tissue component meets the above definition on measurability, these lesions can be regarded as measurable lesion;

Osteoblastic lesions belong to non-measurable lesions.

Cystic lesions:

The lesions meeting the definition of radiologically simple cyst should not be considered as malignant foci as they are simple cysts in terms of the definition; they are neither measurable lesions nor the non-measurable lesions.

Cystic metastatic lesions that meet the above definition on measurability can be considered as measurable lesions. However, if non-cystic lesions are present in the same patient, the non-cystic lesions should be preferably selected as the target lesion.

Lesions treated topically:

The lesions located at the site once radiated or treated with other topical therapies are generally considered as non-measurable lesions, unless clear progression occurred in these lesions. The study protocol should describe the conditions for these lesions to become measurable lesions in detail.

2. Measurement of lesions

Measurement of all the tumors is recorded in meter in the clinical evaluation. All the baseline evaluations in terms of the size of tumor foci should be completed as much as close to before the start of treatment, and must be completed within 14 days (2 weeks) prior to the start of treatment.

Methods of evaluation:

Baseline evaluation and subsequent measurements of a lesion should be carried out by the same techniques and methods. All the lesions must be radiologically evaluated except those that can not be

radiologically evaluated but only be evaluated with clinical examinations.

Clinical lesion: only the superficial clinical lesions with diameter ≥10mm measured could be considered as measurable lesions (e.g., cutaneous nodule). For patients with cutaneous lesions, it is advised to use the color image containing one ruler to measure the size of lesion for documentation. When the lesion is evaluated with radiology and clinical examination simultaneously, the radiological evaluation should be used as much as possible as it is more objective and can be reviewed repeatedly at the end of the study.

Chest X-ray: when the progression of tumor is used as the important endpoint, chest CT should be used preferably, as it is more sensitive than X-ray, in particular for new lesions. Breast X-ray are only suitable when the lesion measured has a clear border and pulmonary ventilation is patent.

CT, MRI: CT is currently the best reproducible method for evaluation of efficacy. The definition of measurability in this guideline is based on the thickness of CT scan ≤5mm. If the thickness of CT scan is more than 5mm, the measurable lesion should be at least 2 times of the thickness. MRI could also be accepted in some circumstances (e.g., systemic scan).

Ultrasound: ultrasound should not be used as one method for measurement of the size of lesion. Ultrasonography is not reproducible after the end of measurement due to its dependency on the operation, thus could not ensure the technical and measurement consistency between different measurements. If one new lesion is found in ultrasound during the trial, CT or MRI should be used for confirmation. If the exposure to the radiation from CT scan is considered, alternative MRI can be used.

Endoscopic and laparoscopic examination: these techniques are not recommended for the objective evaluation of tumors, however, these methods can be used for confirmation of CR when biopsy specimen was obtained, and for confirmation of recurrence in the trial using recurrence after CR or surgical resection as the study endpoint.

Tumor marker: tumor marker can not used independently to evaluate the objective response of tumors. However, if the marker level exceeds the upper limit of normal at baseline, it must return to the normal level when it is used to evaluate complete response. As the tumor marker varies for disease, it is needed to be considered when including this measurement criteria in the protocol. The

specific criteria on CA-125 response (recurrent ovarian cancer) and PSA response (recurrent prostate cancer) have been published. The criteria on CA-125 progression have been established by the international organization of gynecological cancers, i.e., it would be added in the evaluation criteria on the objective response of tumors in the 1st-line therapy for ovarian cancer.

Cytological /histological technology: in the specific situations specified in the protocol, these techniques can be used to differentiate PR and CR (e.g., residual benign tumor tissue is usually present in the lesions of germline cell tumors). When exudation is possibly one potential side reaction of one therapy (e.g., taxane compound or angiogenisis inhibitor), and the measurable lesion met the criteria on response or stable disease; cytological technique could be used to differentiate response (or stable disease) and progression of disease when tumor related exudation occurred or became exacerbated during the treatment.

3. Tumor Responses Criteria(Target Lesion Assessment)

Complete response (CR): all the target lesions disappear, and the short diameter of all the pathological lymph nodes must be decreased to <10 mm (including target nodes and non-target nodes).

Partial response (PR): The sum of diameter of target lesion decreases by at least 30 % from the baseline level .

Progressive disease (PD): the sum of diameter of all measurable target lesions increases by at least 20 % over the minimum value of such sum or over the baseline measured value (whichever is smaller), and besides this, the absolute value of such sum should increase by at least 5 mm. Or there are one or more new lesions.

Stable disease (SD): The target lesion does not decrease in a degree of PR or increase by an intensity of PD, but changes in the intensity between PR and PD (the minimum sum of diameter is used as reference).

Attached Table 1 Timepoint response: the patient with target lesions (including non-target lesions or not)

Target lesion	Non-target lesion	New lesions	Overall response
CR	CR	Non	CR
CR	Non CR/non PD	Non	PR
CR	Unevaluable	Non	PR
PR	Non-progress or incomplete assessment	Non	PR
SD	Non-progress or incomplete assessment	Non	SD
Incomplete assessment	Non-progress	Non	NE
PD	Any conditions	Y or N	PD
Any conditions	PD	Y or N	PD
Any conditions	Any conditions	Yes	PD
CR = complete response	PR = partial response	Stable disease (SD)	PD = progressive disease NE = Non-evaluable
Notes: For non-target lesions, "non CR/non PD" are responses better than SD. Since SD becomes more and more as endpoint index of efficacy evaluation, the efficacy of non-CR or non-PD is stipulated when the conditions of no measurable lesions are not specified.			

In case of indefinite progress finding (e.g. very small uncertain new lesions and cystic degeneration or necrotic lesion of original lesions), the treatment can continue until the next assessment of efficacy. If PD is verified at the next assessment, the date of progression should be the occurring date of previous suspicious progression.

Attached Table 2 Best overall response for which it is required to confirm CR and PR

Overall response at the first timepoint	Overall response at the subsequent time points	Best overall response
CR	CR	CR
CR	PR	SD, PD, or Pra
CR	SD	If SD lasts for a sufficient time, SD is judged; and otherwise PD is judged
CR	PD	If SD lasts for a sufficient time, SD is judged; and otherwise PD is judged
CR	NE	If SD lasts for a sufficient time, SD is judged; and otherwise NE is judged
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	If SD lasts for a sufficient time, SD is judged; and otherwise PD is judged
PR	NE	If SD lasts for a sufficient time, SD is judged; and otherwise NE is judged
NE	NE	NE
Notes: CR is complete response, PR is partial response, SD is stable disease, PD is progressive disease, and NE is non-evaluable. Superscript "a": If CR occurs actually at the first timepoint, then for any disease occurs at subsequent timepoints, its response evaluation is still PD at subsequent timepoints (as the disease will occurs again after CR), even though the response evaluation of the subject does meet the PR criteria. The best response depends on whether SD appears within the minimum treatment interval. However, although CR is judged at the first time point, a small lesion sometimes seems to still appear under the scanning at the subsequent time points; and therefore, the efficacy at the first time point is actually judged as PR but not as CR. In this case, PR (but not CR) should be judged at the first time point, and PR is considered as the best response.		

Efficacy confirmation:

In the non-randomized clinical study with tumor response as primary study endpoint, the efficacy of PR and CR should be confirmed to ensure that the efficacy is not caused by error in evaluation. However, in the studies with SD or PD as primary study endpoint, the efficacy should not be confirmed again, because it is useless for explaining the study results. In case of SD, at least one measurement complies with the SD criteria specified in the protocol at the minimum time interval (generally not less than 6-8 weeks) after start of the trial.

Duration of overall duration of response:

The overall duration of response is calculated as time duration from first conformance with the criteria of CR or PR (whichever is earlier) to first actual recording with recurrence or progression of

disease (the minimum measured value recorded in the studies will be used as reference for the calculation of PD). The overall response time is the period from the time when the measurement first meets the CR criteria to the time when disease or progressive disease is first recorded.

The duration of stable disease:

The duration of SD is calculated as time duration from stating treatment to PD (or from randomization in the randomized trial), with the minimum sum in the trial as reference value (and the sum of baseline level will be used as reference for the calculation of PD, if it is the minimum). The clinical relevance during stable disease varies in different studies and for different diseases. If, in a certain trial, the proportion of patients maintaining the minimum stable disease time is used as research endpoint, then the protocol shall describe particularly the minimum time interval between two measurements in the definition of SD.

Notes: The response period and the stable disease period are impacted by follow-up frequency after baseline evaluation. This guideline is not applicable to define the standard frequency of follow-up. The frequency of follow-up should be determined by considering various factors, including type/stage of disease, treatment cycle and standard specifications. However, if a comparison needs to be made between studies, the limitation in the accuracy of these measurement endpoints should be considered.

PFS

If all the patients are required to have measurable lesions in the protocol, evaluation of progression will be relatively simple. More and more trials allow patients with or without measurable lesions to be enrolled. In such circumstance, the clinical finding of progression of disease must be described carefully and clearly for patients without measurable lesions. As the date of progression often has a deviation in its determination, the time point for observation should be the same for each test group.

Annex 2. Creatnine clearance(Cockcroft-Gault)

Concentrations of serum creatinine (mg/dL):

$$\text{Creatinine clearance rate in males (mL/min)} = \frac{(140-\text{Age})\times(\text{Weight})a}{(72)\times(\text{Serum creatinine})}$$

$$\text{Creatinine clearance rate in females (mL/min)} = \frac{(0.85)\times(140-\text{Age})\times(\text{Weight})a}{(72)\times(\text{Serum creatinine})}$$

Concentrations of serum creatinine (μmol/L):

$$\text{Creatinine clearance rate in males (mL/min)} = \frac{(140-\text{Age})\times(\text{Weight})a}{(0.81)\times(\text{Serum creatinine})}$$

$$\text{Creatinine clearance rate in females (mL/min)} = \frac{(0.85)\times(140-\text{Age})\times(\text{Weight})a}{(0.81)\times(\text{Serum creatinine})}$$

[a] Age is expressed in year and body weight is expressed in kg.

Annexes 3 American national cancer institute common terminology criteria for adverse events Version 5.0 (NCI CTCAE V5.0)

Attached Table 3 Grade of common adverse events

Adverse reactions	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Haematological:					
Anaemia	Hemoglobin <LLN~10.0 g/dL; <LLN~10.0 g/dL; <LLN~10.0 g/dL	Hemoglobin < 10.0~8.0 g/dL; < 6.2~4.9 mmol/L; < 100～80 g/L	Hemoglobin<8.0 g/dL; < 4.9 mmol/L; < 80 g/L; Need blood transfusion for treatment	Life-threatening; emergency treatment is required	Death
WBC dec	<LLN~3000/mm^3; <LLN~3.0×10^9/L	<3000~2000 /mm^3; <3.0~2.0×10^9/L	<2000~1000 /mm^3; <2.0~1.0×10^9/L	<1000/mm^3; <1.0×10^9/L	—
Platelets decreased	<LLN~75,000/mm^3; <LLN~75.0×10^9/L	<75,000~50,000 /mm^3; <75.0~50.0× 10^9/L	<50,000~25,000 /mm^3; <50.0~25.0× 10^9/L	<25,000/mm^3; <25.0×10^9/L	—
Activated partial thromboplastin time prolonged	> 1-1.5 times of upper limit of normal	> 1.5-2.5 times of upper limit of normal	> 2.5 times of upper limit of normal; Hemorrhage	—	—

Adverse reactions	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Increased INR	> 1.2-1.5 time; > 1-1.5 of baseline level (anticoagulation); Need surveillance only	> 1.5-2.5; > 1.5-2.5 times of baseline level (anticoagulation); suggested dose modifications	> 2.5; > 2.5 times of baseline level (anticoagulation	—	—
Cardiac disorder					
Electrocardiogram QTc interval prolonged	Mean QTc 450 - 480 ms	Mean QTc 481 - 500 ms	Mean QTc ≥ 501 - 60 ms; > 60 ms compared with the baseline	Torsade de pointes ; Paroxysmal ventricular tachycardia; Vital sign/symptom of serious arrhythmia	—
Creatine kinase increased	> upper limit of normal-2.5 times of upper limit of normal	> 2.5 times of upper limit of normal-5 times of upper limit of normal	> 5 times of upper limit of normal-10 times of upper limit of normal	>10 times of upper limit of normal	—
Digestive problems					
Diarrhea	Increased times of defecation of > 4 times per day compared from baseline; mild increase of the discharge at anastomosis	Increased times of defecation of 4- 6 times per day compared from baseline, moderate increase of the discharge at anastomosis; instrumental activities of daily living are limited	Increased frequency of defecation of ≥ 7 times per day compared with baseline, requiring hospitalization, severe increase of the discharge at anastomosis; Self care activities of daily living are limited	Life-threatening; emergency treatment is required	Death

Adverse reactions	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Constipation	Occasional or intermittent occurrence, occasional use of fecal softener or laxative, adjustment of dietary habit or enema	Persistent symptoms with regular use of laxatives or enemas; instrumental activities of daily living are limited	Intractable constipation requiring manual dredging; Self care activities of daily living are limited	Life-threatening; emergency treatment is required	Death
Anorexia	Decreased appetite, without change of eating habits	Change of food intake, however, associated with no decreased weight or malnutrition; oral nutritional supplementation required	Obvious weight decrease or symptom of malnutrition (e.g., insufficient oral intake of calories and/or liquid); nasal feeding or total parenteral nutritional needed	Life-threatening; emergency treatment is required	Death
Vomiting	Unnecessary for intervention	Intravenous fluid infusion at clinic; necessary for medical intervention	Need nasal feeding, total parenteral nutrition or hospitalization	Life-threatening	Death
Stomatitis	Asymptomatic or mild, no need of treatment .	Moderate pain or ulcer, not affecting oral food intake, diet adjustment needed	Severe pain, affecting oral food intake	Life-threatening; emergency treatment is required	Death
Nausea	Decreased appetite, without change of eating habits	Decreased oral food intake without significant weight loss, dehydration or malnutrition	Insufficient oral intake of energy or water, nasal feeding, total parenteral nutrition or hospitalization required	—	—

Adverse reactions	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infection					
Upper respiratory tract infection	—	Moderate; oral drug therapy required (antibiotic, antifungal, antiviral therapy)	Intravenous antibiotic, antifungal, or antiviral drugs required; ablative therapy required	Life-threatening; emergency treatment is required	Death
Urinary tract infection	—	Limitations; Oral drug therapy required (antibiotic/antifungal or antiviral therapy)	Intravenous antibiotic, antifungal, or antiviral drugs required; ablative therapy required	Life-threatening; emergency treatment is required	Death
Disorder kidney					
Protein urine	Proteinuria (+), 24h urine protein ≥ULN ~ 1.0 g	For adults: Proteinuria (++) and (+++), 24h urine protein 1.0~3.5 g children: protein/creatinine ratio in urine 0.5-1.9	For adults: 24h urine protein ≥3.5; proteinuria (++++) children: protein/creatinine ratio in urine >1.9	—	—
Blood creatinine increased	> upper limit of normal -> 1.5 times of upper limit of normal High limit	1.5~3.0 folds of baseline value; 1.5~3.0 folds of ULN	> 3.0 times of baseline value; > 3.0-6.0 times of upper limit of normal	> 6.0 times of upper limit of normal	—
Liver disorder					
Elevated alanine transaminase (ALT)	>3 folds of ULN (for normal baseline value); 1.5~3.0 folds of baseline value (for abnormal baseline value)	3~5 folds of ULN (for normal baseline value); 3.0~5.0 folds of baseline value (for abnormal baseline value)	5~20 folds of ULN (for normal baseline value); 5~20 folds of baseline value (for abnormal baseline value)	>20 folds of ULN (for normal baseline value); >20 folds of baseline value (for abnormal baseline value)	—

Adverse reactions	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Glutamic-oxaloacetic transferase increased (AST) increased	>3 folds of ULN (for normal baseline value); 1.5~3.0 folds of baseline value (for abnormal baseline value)	> 3-5 times of upper limit of normal(baseline value normal); > baseline value 3.0~5.0 folds of baseline value (for abnormal baseline value)	5.0~20.0 folds of ULN (for normal baseline value); 5.0~20.0 folds of baseline value (for abnormal baseline value)	>20.0 folds of ULN (for normal baseline value); >20.0 folds of baseline value (for abnormal baseline value)	—
Dermatosis					
Maculo-papular rash	Rash maculo-papular area < 10% of body surface area, with or without symptom(eg. Pruritus, Burning sensation and Tension)	Maculopapule 10%~30% of body surface area, with or without symptoms (such as pruritus, burning sensation and tightening sensation), and with an influence on the instrumental activity in daily life; rash >30% of body surface area, with or without mild symptoms	Papule and/or pustule >30% of body surface area, with moderate to severe symptoms, with an influence on the self-care activity in daily life	—	—
Disorder respiratory system					
Coughing	Mild symptom, nonprescription drugs treatment needed	Moderate symptom, drug therapy required, affecting instrumental activities of daily living	Severe, affecting self care activities of daily living	—	—

Adverse reactions	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Other laboratory test abnormality					
Hyperlipaemia	Changes of dietary habits needed	Drug intervention needed	hospitalization; Pancreatitis	Life-threatening consequences	Death
Hyperuricemia	Higher than ULN, without physiological abnormality	—	Higher than ULN, with physiological abnormality	> 10 mg/dL; > 0.59 mmol/L; life- threatening	Death
Hyponatremia	lower limit of normal- 130 mmol/L	125 - 129 mmol/L without symptom	125~129 mmol/L, with symptoms; 120~124 mmol/L, with or without symptoms	<120 mmol/L; life-threatening consequences	Death

For detailed information, please refer to CTCAE 5.0.

Appendix 4.ECOG performance status score criteria

Assessment criteria for performance status

Attached Table 4 Zubrod-ECOG-WHO (ZPS, 5-score scale)

Grade	Performance Status
0	No symptom, completely active movement, ability to carry out activities before ill without restriction.
1	Having symptom, being completely able to walk, but restricted heavy physical activity, ability to engage in mild or sitting-based work, such as slight housework, office work.
2	Having symptom, being able to walk and take care of daily living, but inability to carry out any physical activity, keeping awake during about more than 50% of a day (time in bed <50% in day time).
3	Having symptom, limited ability to take care of daily living, lying on bed or sitting in chair >50% in waking time, but not bedridden.
4	Complete loss of function, complete inability to take care of daily living, completely bedridden.
5	Death.

Annexes 5. Quality of life questionnaire

Attached Table 5 EORTC QLQ-C30(version 3) quality of life questionnaire

EORTC QLQ-C30(version 3) quality of life questionnaire					
We want to know some conditons on you and your health. Please answer all following questions by yourself. The answer is not distinguished as correct or wrong. You just circle on the figure most reflecting your conditions. The information that you provide will remain strictly confidential.					
Subject code (No):					
Date of birth: MM/DD/YYYY					
Today's date: MM/DD/YYYY					
		Not at All	**Somewhat**	**Quite**	**Very**
1	Do you have any difficulty in doing strenuous activities like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2	Do you have any trouble taking a long walk?	1	2	3	4
3	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4	Do you need to stay in bed or a chair during the day?	1	2	3	4
5	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
During the past week:		**Not at All**	**Somewhat**	**Quite**	**Very**
6	Were you limited in doing either your work or other daily activities?	1	2	3	4
7	7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8	Do you have Polypnoea?	1	2	3	4
9	Have you had pain?	1	2	3	4
10	Did you need to rest?	1	2	3	4
11	Have you had trouble sleeping?	1	2	3	4
12	Have you felt weak?	1	2	3	4
13	Have you lacked appetite(loss of appetite)?	1	2	3	4
14	Have you felt Nausea?	1	2	3	4
15	Do you have Vomiting?	1	2	3	4
16	Have you been constipated?	1	2	3	4
17	Have you had diarrhea?	1	2	3	4
18	Did you feel tired?	1	2	3	4
19	Did pain interfere with your daily activities?	1	2	3	4
20	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21	Did you feel tense?	1	2	3	4
22	Did you worry?	1	2	3	4
23	Did you feel irritable?	1	2	3	4
24	Did you feel depressed(low mood)?	1	2	3	4
25	Have you had difficulty remembering things?	1	2	3	4

26	Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27	Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28	Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

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

29	How are your general health conditions in the past one week?	1	2	3	4	5	6	7
		Very poor						Very good
30	How would you rate your overall quality of life during the past week?	1	2	3	4	5	6	7
		Very poor						Very good

Attached Table 6 EORTC QLQ-HCC13 quality of life questionnaire

EORTC QLQ-HCC13 quality of life questionnaire					
The patient may have the following clinical symptoms sometimes. Please indicate the extent to which you have experienced these clinical symptoms or problems during the past week.					
Subject code (No):					
Date of birth: MM/DD/YYYY					
Today's date: MM/DD/YYYY					
During the past week:		**Not at All**	**A little**	**Quite a bit**	**Very much**
1	Do you usually have a cough?	1	2	3	4
2	Do you have coughing blood(blood streaked sputum)?	1	2	3	4
3	Were you short of breath when you rested?	1	2	3	4
4	Were you short of breath when you went for a walk?	1	2	3	4
5	Were you short of breath when you climbed stairs?	1	2	3	4
6	Have you had pain in oral cavity or tongue?	1	2	3	4
7	Have you had dysphagia?	1	2	3	4
8	Have you had numbness/stinging in hands or feet?	1	2	3	4
9	Have you had alopecia?	1	2	3	4
10	Have you had chest pain?	1	2	3	4
11	Have you had pain in arms or shoulder?	1	2	3	4
12	Have you had pain in other body sites?	1	2	3	4
	If yes, please write the site:	1	2	3	4
13	Did you take any medicine for pain?	1	2	3	4
	1. No 2. Yes				
	If Yes, is the analgesic effect strong?	1	2	3	4

Attachment 6: List of potent inhibitors and potent inducers of CYP3A4

Attached Table 7 List of potent inhibitors and potent inducers of CYP3A4

Potent inhibitors of CYP3A4	Potent inducers of CYP3A4
Clarithromycin, telithromycin, troleandomycin Conivaptan Indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir, telaprevir, boceprevir, elvitegravir Itraconazole, ketoconazole, posaconazole, voriconazole Mibefradil Nefazodone	Carbamazepine, phenobarbital, phenytoin Rifampicin, rifabutin, rifapentin St. John's Wort.

Annexes 7. Medication known to prolong QT interval and/or induce Torsades de Pointes

Attached Table 8 Drugs known as prolonging QTc interval (known risk of TdP [KR]) or possibly causing torsa desde points (possible risk of TdP [PR])

Risk Categories	Drug(s)
Known risk of TdP KR	Amiodarone, Anagrelide, Arsenic Trioxide, Azithromycin, Bepridil, Chloroquine, Chlorpromazine, Cilostazol, Ciprofloxacin, Cisapride, Citalopram, Clarithromycin, Cocaine, Disopyramide, Dofetilide, Domperidone, Donepezil, Dronedarone, Droperidol, Erythromycin, Escitalopram, Flecainide, Fluconazole, Gatifloxacin, Grepafloxacin, Halofantrine, Haloperidol, Ibutilide, Levofloxacin, Levomepromazine, Levacetylmethadol, Mesoridazine, Methadone, Moxifloxacin, Ondansetro, Oxaliplatin, Papaverine, Pentamidine, Pimozide, Probucol, Procainamide, Propofol, Quinidine, Sevoflurane, Sotalol, Sparfloxacin, Sulpiride, Terfenadine, Thioridazine, Vandetanib

	Drug(s)	Time of stable use before the starting of study drug
Possible risk of TdP PR*	Alfuzosin, dolasetron, foscarnet, gemifloxacin, isridipine, nicardipine, ofloxacin, ranolazine, telithromycin, tizanidine, vardenafil, venlafaxine	2 day
	Clozapine, Granisetron, Imipramine, lithium agents, Moexipril/Hydrochlorothiazide, Risperidone, Roxithromycin	7 day
	Nortriptyline, tacrolimus	14 day
	tamoxifen	8 weeks

* Other drugs at ossible risk of TdP not listed in above table are determined after the discussion between investigators and the sponsor.

Medication known to prolong QT interval and/or related to Torsades de Pointes please visit

http://www.crediblemeds.org/everyone/composite-list-all-qtdrugs/?rf=All

Annexes 8. Anti-tumor traditional Chinese medicine

Common Chinese medicines with the indications of anti-tumor include but are not limited to:

Kang Ai Injection, Cinobufotalin, Oleum Bruceae Soft Capsules, Huazheng Huisheng Tablets, Tuomu Syrups, Mylabris, Kanglaite, Kang Ai Ping Pills, Zhong Jie Feng Injection, Ai Di Injection, Xiao Ai Ping, Ping Xiao, Oleum Bruceae Emulsion Injection, Awei Huapi Plasters, Ci Dan Capsules, Kang Li Xin Capsules, Zedoary Turmeric Oil and Glucose for Injection, Shendan Sanjie Capsules, Fu Kang Capsules, An Kang Xin Capsules

Attachment 9: Fridericia formula for QTc

$$QT_F = \frac{QT}{\sqrt[3]{RR}}$$

$$QT_F = \frac{QT}{\sqrt[3]{RR}}$$

QT refers to the time interval between the start of the Q wave and the end of the T wave

RR mean the time interval from the occurrence of one QRS wave to the occurrence of next QRS wave.

Annexes 10. New York Heart Association (NYHA) Cardiac Functional Grading

Attached Table 9 New York Heart Association Cardiac Functional Grading

Grade	Physical Activity	Status at rest	symptom(fatigue, palpitation, asthma, or angina pectoris)
Ⅰ	No limitation	no symptoms	Can't be caused by general physical activity.
Ⅱ	Slight limitation	no symptoms	Can be caused by daily physical activity
Ⅲ	Marked limitation	no symptoms	Lower than that can be caused by daily physical activity
Ⅳ	Loss	Symptomatic	Aggravation induced by any physical activity

Attachment 11: Grade of surgery in the Regulations on Clinical Application of Medical Technology

Attached Table 10 Grade of surgery in the Regulations on Clinical Application of Medical Technology

Grade	Definitions
Surgery Grade 1	Ordinary surgery with lower risk, simple course and low technical difficulty
Surgery Grade 2	Surgery with a certain risk, course of moderate complexity and a certain technical difficulty
Surgery Grade 3	Surgery with higher risk, course of a certain complexity and moderate difficulty
Surgery Grade 4	Major surgery with high risk, complicated course and great difficulty

Annexes 12. Hy's Law Criteria

According to Hy's Law criteria, drug-induced liver injury is defined as follows: increase of ALT or AST to ≥3 folds of ULN; increase of TBIL to >2 folds of ULN; without bile stagnation (ALP <2×ULN); unexplainable by other reasons, such as viral hepatitis, progression of cancer, alcoholism, ischemia, past liver disease or other drugs (FDA, 2009).