Clinical Study Protocol

Phase II, Open-label, Single-arm, Prospective, Multi-center Study to evaluate the Efficacy and Safety of Lorlatinib as Neoadjuvant Treatment in Surgically Resectable Stage IB-IIIB ALK-rearranged Non-Small Cell Lung Cancer (NEOLORA)

Version 3.0

(Version date: 9/12/2024)

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Historical versions

Version 3.0, September 12, 2024
• **Add exploratory endpoints: the correlation between biomarkers with respond and outcomes) and revise the corresponding sections. Update sections: Study Synopsis , Section 2.1, Section 3.1, and Section 7.2.**
Version 2.0, July 19, 2024
• **Updated the time window for surgical treatment after neoadjuvant therapy and added method for ALK testing. Updated sections: Study Synopsis; Section 3.1.** • **Updated the research schedule. Updated section: Section 3.1.** • **Made additional minor changes and error corrections for clarity.**
Version 1.0, April 10, 2024
Initial version.

Study Synopsis

Protocol Title: *Phase II, Open-label, Single-arm, Prospective, Multi-center Study to evaluate the Efficacy and Safety of Lorlatinib as Neoadjuvant Treatment in Surgically Resectable Stage IB-IIIB ALK-rearranged Non-Small Cell Lung Cancer (NEOLORA)*

Study Sponsor(s):	**Compound:**
Peking University People's Hospital, Prof. Fan Yang	Lorlatinib

Background and Rationale

Lung cancer remains the foremost cause of cancer-related deaths worldwide, with non-small cell lung cancer (NSCLC) constituting approximately 80% of all lung cancer cases. [1]Despite advancements, the prognosis for NSCLC patients, particularly those ineligible for surgical resection at diagnosis, is dismal, with median 5-year overall survival (OS) rates between 36% and 60%. [2]Currently, neoadjuvant (preoperative) platinum-based doublet chemotherapy regimens represent the standard care for resectable stage II or III NSCLC with oncogenic driver mutations. However, the marginal improvement in long-term survival underscores the critical need for more effective treatment strategies.[3]

The discovery of driver mutations in NSCLC has revolutionized treatment approaches, with alterations in the anaplastic lymphoma kinase (ALK) gene being one of the significant breakthroughs. ALK rearrangements are identified in 3%-7% of NSCLC cases, guiding the development of targeted therapies. ALK inhibitors, including crizotinib, ceritinib, alectinib, brigatinib, and notably lorlatinib, have significantly impacted the treatment landscape of ALK-positive NSCLC by offering substantial improvements in survival and disease control.

Lorlatinib, a potent third-generation ALK inhibitor, is distinguished by its efficacy against a wide spectrum of ALK mutations, including those conferring resistance to earlier generations of ALK inhibitors. Its ability to cross the blood-brain barrier presents an added advantage for controlling central nervous system (CNS) metastases, a frequent challenge in NSCLC management. This profile, along with encouraging outcomes from phase I and II trials demonstrating lorlatinib's robust

antitumor activity in patients who have progressed on previous ALK TKI therapies, underscores its potential as a transformative neoadjuvant therapy option. [4-6]

The advent of targeted therapies has markedly shifted the paradigm in the treatment of non-small cell lung cancer (NSCLC), particularly for patients with specific genetic alterations such as ALK rearrangements. A small retrospective study of the first-generation ALK-TKI crizotinib in the neoadjuvant setting included 11 ALK-positive, N2 NSCLC patients who received oral crizotinib (250mg twice daily) for a median duration of 30 days (range 28-120 days). This study demonstrated a 91.0% R0 resection rate with 18.2% (2 cases) achieving pathological complete response post-treatment.[7] The SAKULA study, a phase II multicenter single-arm trial, assessed the efficacy and safety of the second-generation ALK-TKI ceritinib in resectable ALK-positive NSCLC. The study enrolled 7 cases all at stage IIIA (N2), and treated with oral ceritinib (750mg twice daily) as neoadjuvant therapy. The primary endpoint of major pathological response (MPR) was 57% (95% CI: 18-90), with 2 cases achieving complete remission (29%). [8]NAUTIKA1, a phase II trial, investigated the efficacy of alectinib as neoadjuvant therapy for 8 weeks in patients with resectable stage II, IIIA, and IIIB NSCLC, followed by surgery, 4 cycles of adjuvant chemotherapy, and 2 years of alectinib adjuvant treatment. Among 9 patients, 6 achieved a major pathological response (MPR), resulting in an MPR rate of 66.7% (95%CI, 29.9%-92.5%), with a pathological complete response (pCR) rate of 33.3%. Eight patients underwent R0 resection. [9]These results indicate the feasibility and potential efficacy of ALK-TKIs in improving surgical outcomes and reducing the tumor burden before surgery, making it a promising neoadjuvant treatment option for this patient population.

This study seeks to assess the feasibility of lorlatinib as neoadjuvant therapy for patients with resectable, stage IB-IIIB ALK+ lung adenocarcinoma. Given lorlatinib's advanced efficacy in targeting ALK-positive tumors, including its activity against resistant mutations and its proficiency in managing CNS metastases,This study aims to evaluate the efficacy and safety of lorlatinib as neoadjuvant therapy in patients, focusing on improvements in pathological response, surgical outcomes, prolonged survival, and safety/tolerability.

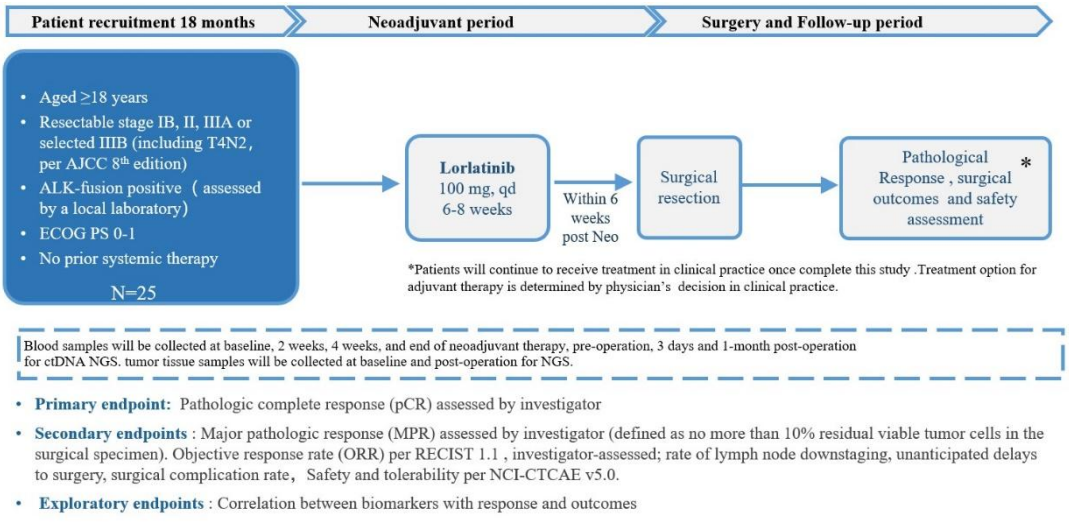
	Phase: Phase II

Study Design

Phase II, open-label, single-arm, prospective, multi-center Study

Methods

Twenty-five patients with surgically resectable stage IB-IIIB ALK-rearranged NSCLC patients will be enrolled. These patients will receive lorlatinib neoadjuvant therapy for 6-8 weeks (determined by clinicians' decision based on clinical practice) and then underwent surgery. Eligible patients will be registered to receive oral lorlatinib 100mg qd for 6-8 weeks each during the neoadjuvant therapy phase. Neoadjuvant treatment response that will be assessed by the investigator using RECIST v1.1. If no progressive disease will be documented, candidates will undergo surgery with radical intent within 6weeks after the completion of lorlatinib neoadjuvant therapy. Once patient complete surgery and pathological evaluation, she/he will remove form this study (within 1 month after surgery) and continue to receive treatment according to clinicians' decision based on clinical practice. All patients signed an informed consent prior to enrolment. Data will not be collected once patient withdrawal from this study.



Primary Objectives

To explore the pathological complete response (pCR) of lorlatinib as neoadjuvant treatment

Secondary Objectives To explore the major pathologic response (MPR) assessed by investigator ; objective response rate (ORR) per RECIST 1.1 , investigator-assessed ; surgical outcomes ; Safety and tolerability.
Exploratory Objectives: Correlation between biomarkers with response and outcomes
Study Population Patients with ALK-rearranged, resectable stage IB-IIIB non-small cell lung cancer

Number of Subjects 25 patients	**Number of Sites:** 6 site in China
Dose Level(s): Lorlatinib, 100mg, qd	**Route of Administration:** Lorlatinib, oral
Duration of Treatment 100mg, qd , 6-8 weeks	**Period of Evaluation** 1 months

Main Criteria for Inclusion

- Aged ≥18 years
- Imaging confirmed, resectable stage IB, II, IIIA or selected IIIB (including T4N2, per AJCC 8th edition)
- Histologically/cytologically confirmed lung adenocarcinoma
- Documented ALK-rearrangement mutation positive (assessed by a local laboratory)
- ECOG PS 0-1
- Patients must be treatment-naive for NSCLC and eligible to receive treatment with Lorlatinb.
- Measurable disease, as defined by RECIST v1.1
- Hematology, liver and kidney function are adequate for neoadjuvant therapy.
- Cardiopulmonary function suitable for surgical treatment (ECG, echocardiography, pulmonary function or blood gas analysis).
- Male participants must be willing to use acceptable methods of contraception.
- Female participants of childbearing potential must agree to use acceptable methods of contraception.
- Ability to provide written informed consent.

Main Criteria for Exclusion

- Mixed squamous cell carcinoma, large cell carcinoma, small cell lung cancer.
- Prior treatment with any systemic anti-cancer therapy for locally advanced NSCLC
- Non-resectable stage IB, II, IIIA or selected IIIB NSCLC evaluated by thoracic surgeons.
- Unable to tolerate curative surgery per anaesthesiologist evaluation.History of organ transplant.
- Pregnant or lactating, or intending to become pregnant during the study
- Evidence of any severe or uncontrolled systemic disease, including uncontrolled hypertension and active bleeding, that the investigator considers to be detrimental to patient participation in the study or to adherence to the protocol.
- Past medical history of Interstitial lung disease (ILD), drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD.
- A clear past history of neurological or psychiatric disorders, including epilepsy or dementia;
- Judgement by investigator that the subject should not participate in the study if the subject is unlikely to comply with the study procedures, restrictions and requirements.

Main Criteria for Evaluation and Analyses

Primary endpoint: Pathologic complete response (pCR) assessed by investigator.

Secondary endpoints:

- Major pathologic response (MPR) assessed by investigator (defined as no more than 10% residual viable tumor cells in the surgical specimen).
- Objective response rate (ORR) per RECIST 1.1, investigator-assessed;
- Surgical outcomes and intraoperative events
- Rate of lymph node downstaging;
- Unanticipated delays to surgery;
- Surgical complication rate;
- Safety and tolerability per NCI-CTCAE v5.0.

Exploratory endpoints: Correlation between biomarkers with response and outcomes

Efficacy analysis set include all patients who received at least one dose of lorlatinib.

Safety analysis set include all patients who received at least one dose of lorlatinib and had the post-treatment safety assessment.

Statistical Considerations

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP).

Sample Size Determination

According to the Simon's 2-stage mini-max design, the null hypothesis that the PCR rate is ≤ 10% will be tested against a 1-sided alternative. In the first stage, 15 patients will be accrued. If there are 1 or fewer PCR in these 15 patients, the study will be stopped early for futility. Otherwise, 10 additional patients will be accrued for a total of 25. The null hypothesis will be rejected if 6 or more PCR are observed in 25 patients. This design yields a type I error rate of 0.05 and power of 0.80 when the true PCR rate is 30%.

Statistical Analyses-Preliminary Descriptive Analysis

Descriptive data analyses will be conducted for both primary and secondary objectives. Categorical variables will be summarized including the number of non-missing observations, the frequency of the observed endpoint as well as the observed proportion. Continuous variables will be summarized including the number of non-missing observations, mean (Standard Deviation [SD]), median, Q1, Q3, and the minimum/maximum.

- PCR, MPR, and ORR will be summarized using frequency counts and percentages with 95% CIs.
- Continuous variables in surgical outcomes will be summarized using median and range.
- Categorical variables in surgical outcomes, safety and tolerability will be summarized using frequency counts and percentages.

Collection of Biological Specimens

Collection of tissue samples in this study:

For patients meeting the inclusion criteria, tissue samples will be collected at baseline and post-operation. This includes tissue specimens in paraffin blocks or formalin-fixed samples, or fresh tissue.

Collection of blood samples in this study:

For patients meeting the inclusion criteria, blood samples will be collected at baseline, 2 weeks, 4 weeks, and end of neoadjuvant therapy, pre-operation, 3 days and 1-month post-operation, with each collection involving 20 mL of blood.
Sample Size Justification Twenty-five patients will be involved in this study. Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP).

Reference

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Clinical Study Protocol

Contents

1. INTRODUCTION

Lung cancer is the most fatal malignancy in China, as estimated by National Cancer Center of China, [1]accounting for 1,060,600 new cases, and 733,300 deaths in 2022. Non-small cell lung cancer (NSCLC), constituting 80%-85% of lung cancer, is most often diagnosed in advanced stages, where surgery and local radiotherapy are no longer curative or indicated. [2] A critical molecular subset characterized by rearrangements in the anaplastic lymphoma kinase (ALK) gene represents a distinct clinical and pathological entity. These ALK rearrangements are identified in 3-7% of NSCLC patients, often manifesting in younger individuals, non-smokers or light smokers, and predominantly in those with adenocarcinoma histology.[3] The management of early-stage NSCLC, particularly stages I to IIIA, primarily involves surgical resection with curative intent, frequently complemented by adjuvant therapy to diminish the risk of disease recurrence.

Despite the availability of surgery and perioperative therapy, the recurrence rates in early-stage NSCLC remain significant, underscoring a considerable unmet clinical need for more effective and targeted therapeutic strategies. The five-year survival rates for patients with resected NSCLC are approximately 36%-60%[4], highlighting the imperative for innovative treatment approaches that can improve these outcomes. Currently, platinum-based doublet chemotherapy regimens represent the standard care for driver gene positivity resectable stage II or IIIA NSCLC, however, the marginal improvement in long-term survival underscores the critical need for more effective treatment strategies.[5.]

The discovery of ALK rearrangements in NSCLC has ushered in an era of targeted therapy, with ALK tyrosine kinase inhibitors (TKIs) significantly altering the

treatment landscape. ALK TKIs, including crizotinib, ceritinib, alectinib, brigatinib, and notably lorlatinib, have significantly impacted the treatment landscape of ALK-positive NSCLC by offering substantial improvements in survival and disease control. These agents have demonstrated remarkable efficacy in the advanced disease setting, leading to interest in their potential application earlier in the disease course, including the neoadjuvant setting. Neoadjuvant therapy with ALK-TKIs presents an opportunity to reduce tumor size and possibly improve surgical outcomes, while simultaneously addressing micrometastatic disease.

A small retrospective study of the first-generation ALK-TKI crizotinib in the neoadjuvant setting included 11 ALK-positive, N2 NSCLC patients who received oral crizotinib (250mg twice daily) for a median duration of 30 days (range 28-120 days). This study demonstrated a 91.0% R0 resection rate with 18.2% (2 cases) achieving pathological complete response post-treatment. [6] The SAKULA study, a phase II multicenter single-arm trial, assessed the efficacy and safety of the second-generation ALK-TKI ceritinib in resectable ALK-positive NSCLC. The study enrolled 7 cases all at stage IIIA (N2), and treated with oral ceritinib (750mg twice daily) as neoadjuvant therapy. The primary endpoint of major pathological response (MPR) was 57% (95% CI: 18-90), with 2 cases achieving complete remission (29%).[7] NAUTIKA1, a phase II trial, investigated the efficacy of alectinib as neoadjuvant therapy for 8 weeks in patients with resectable stage II, IIIA, and IIIB NSCLC, followed by surgery, 4 cycles of adjuvant chemotherapy, and 2 years of alectinib adjuvant treatment. Among 9 patients, 6 achieved a major pathological response (MPR), resulting in an MPR rate of 66.7% (95%CI, 29.9%-92.5%), with a pathological complete response (pCR) rate of 33.3%. Eight patients underwent R0 resection. [8] These results indicate the feasibility and potential efficacy of ALK-TKIs in improving surgical outcomes and reducing the tumor burden before surgery, making it a promising neoadjuvant treatment option for this patient population.

Lorlatinib, a potent third-generation ALK inhibitor, is distinguished by its efficacy against a wide spectrum of ALK mutations, including those conferring resistance to

earlier generations of ALK inhibitors. Clinical trials evaluating lorlatinib in ALK-positive advanced NSCLC patients, including first-line patients, those with CNS metastases and who have developed resistance to earlier-generation ALK-TKIs, have showcased its considerable efficacy and manageable safety profile. [9-11] Lorlatinib's broad activity spectrum and CNS penetration capabilities uniquely position it as a promising candidate for exploration in the neoadjuvant setting.

Building upon the therapeutic successes of ALK-TKIs in the metastatic and adjuvant settings, the potential application of lorlatinib as a neoadjuvant therapy warrants thorough investigation. The neoadjuvant approach with lorlatinib aims to exploit its potent antitumor activity against ALK-driven NSCLC to achieve significant tumor shrinkage, potentially facilitating more effective surgical resections and improving postoperative outcomes. Moreover, this strategy offers the opportunity to address micrometastatic disease early in the treatment continuum, which could translate into prolonged disease-free and overall survival rates for patients. Drawing parallels from the clinical outcomes associated with these agents, lorlatinib's superior pharmacological profile suggests that it could offer enhanced efficacy in reducing primary tumor size, achieving higher rates of complete pathological response, and potentially extending survival in patients with early-stage, resectable NSCLC harboring ALK rearrangements.

2. STUDY OBJECTIVES

2.1. Objectives

Primary Objective:

To explore the pathological complete response (pCR) of lorlatinib as neoadjuvant treatment.

Secondary Objectives:

To explore the major pathologic response (MPR) assessed by investigator ; objective response rate (ORR) per RECIST 1.1 , investigator-assessed ; surgical outcomes ; Safety and tolerability.

Exploratory Objectives:

Correlation between biomarkers with response and outcomes

2.2. Endpoints

Primary Endpoint:

- Pathological complete response (pCR), INV;

Secondary Efficacy Endpoints:

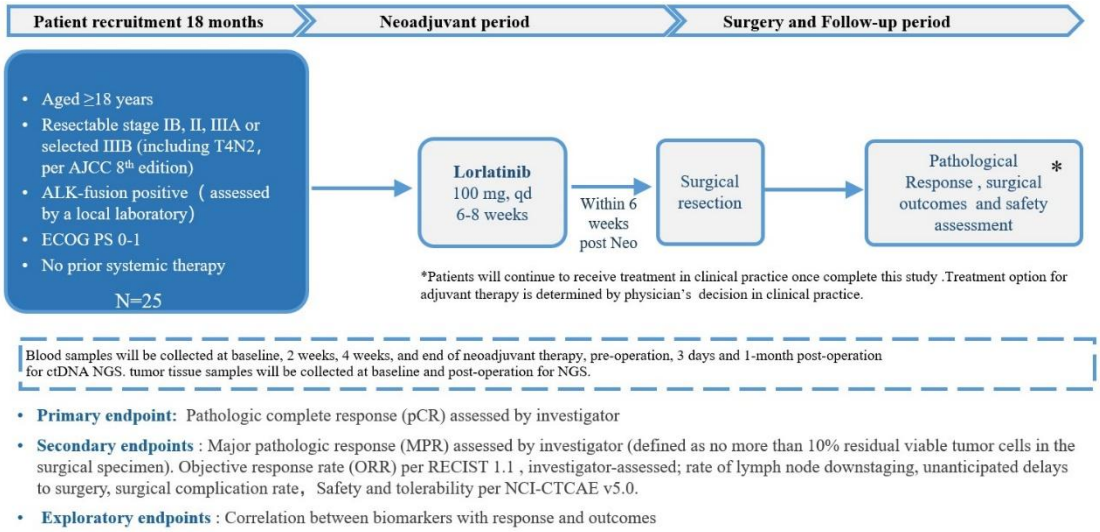
- Major pathologic response (MPR) assessed by investigator (defined as no more than 10% residual viable tumor cells in the surgical specimen).
- Objective response rate (ORR) per RECIST 1.1 , investigator-assessed;
- Surgical outcomes and intraoperative events
- Rate of lymph node downstaging;
- Unanticipated delays to surgery;
- Surgical complication rate;
- Safety and tolerability per NCI-CTCAE v5.0.

Exploratory endpoints :

- Correlation between biomarkers with response and outcomes

3. STUDY DESIGN

Figure 1. Study Design



3.1 Study design

This protocol delineates a Phase II, open-label, single-arm, prospective, multi-center study designed to evaluate the efficacy and safety of lorlatinib as a neoadjuvant therapy in patients with resectable ALK-positive non-small cell lung cancer (NSCLC). **[Figure 1]**

Eligible participants include male and female subjects aged ≥18 years, diagnosed with clinical stage IB, II, IIIA, or selected IIIB (including T4N2, as per the American Joint Committee on Cancer [AJCC] 8th edition) NSCLC, as assessed by positron emission tomography/computed tomography (PET/CT), or through computed tomography (CT), abdominal ultrasound, cranial MRI/CT, and bone scintigraphy. Enrollment criteria mandate that all tumors must test positive for ALK rearrangement, verified through Ventana ALK (D5F3), next-generation sequencing (NGS), etc. testing methods. All tumors will be of histo- and/or cytopathology consistent with NSCLC. Performance status (ECOG) 0-1 at enrolment, with no deterioration over the previous 2 weeks prior to baseline or day of first dosing of lorlatinib.

Upon meeting eligibility criteria, patients will be registered to receive oral lorlatinib at a dose of 100mg once daily (qd) for a period of 6-8 weeks, assessment will be conducted after 4 weeks, as determined by the attending clinicians based on the best clinical

practice. The duration of neoadjuvant therapy has been designed to optimize treatment efficacy while ensuring the feasibility of subsequent surgical resection.

Lorlatinib will be administered orally QD at approximately the same time of the day on a continuous daily dosing schedule, ie, without a break in dosing in the absence of drug-related toxicity. Patients must swallow the study medication whole and must not manipulate or chew the medication prior to swallowing. Patients should be instructed to take their medication at approximately the same time every day. A dosing card will be provided to the patients to provide guidance for the correct use of lorlatinib. Patients must be instructed that should they miss a dose or vomit any time after taking a dose, they must not "make it up" with an extra dose. Instead, resume the subsequent doses as originally prescribed. Any missed dose may be taken up to 6 hours prior to the next scheduled dose, otherwise it should be skipped and dosing resumed with subsequent doses as prescribed. The patient must be instructed to record all doses (including missed or vomited) in a dosing diary supplied by the site. If doses are missed or vomited, this must be indicated in the source documents and Case Record Forms (CRFs).

The response to neoadjuvant therapy will be evaluated by the investigators utilizing RECIST 1.1 criteria. Patients demonstrating no progressive disease as per these criteria will proceed to surgical resection with radical intent, scheduled within 6 weeks following the conclusion of lorlatinib neoadjuvant therapy. Patients completing the surgical intervention and pathological evaluation will conclude their participation in this study within 1-month post-surgery and may continue to receive subsequent treatment as deemed appropriate by their healthcare providers, based on prevailing clinical practice.

This study will intermittently collect blood specimens from patients at baseline, during neoadjuvant therapy, and perioperatively to explore changes in tumor biomarkers. Baseline and postoperative tissue specimens will be obtained, and Whole Exome Sequencing (WES) will be performed to investigate the correlation between neoadjuvant therapy efficacy and tissue mutation changes. Additionally, tissue

mutation results will be used to customize a blood testing panel to enhance detection rates.

Informed consent will be obtained from all participants prior to study enrollment. The consent process will ensure that patients are fully aware of the study's nature, its objectives, the investigational therapy involved, and the potential risks and benefits of participation. The study emphasizes rigorous adherence to ethical standards and patient safety, with a comprehensive plan in place for monitoring adverse events and implementing dose adjustments as necessary to manage toxicity.

Subjects will be on therapy until complete surgery and pathological evaluation, withdrawal of consent, death, or investigator decision dictated by protocol compliance, whichever occurs first. At the time of termination of study treatment, the patients could continue to receive treatment according to clinicians' decision in their clinical practice.

This study will take 18 months to enroll subjects, and each subject will be followed up for efficacy and safety during neoadjuvant process and 1-month post-surgery. Dose reduction information for management of AEs is included in Section 5.

Safety and efficacy assessments were performed throughout the treatment period and at the end-of-study visit. Routine safety assessments included the collection and evaluation of AEs, concomitant medications, vital signs, and body weight. Particular attention was given to AEs consistent with the lorlatinib toxicity profile (including lipid elevation, cognitive and mood disorder, etc.). Additional safety assessments performed at selected visits included ECOG PS, clinical laboratory tests, ECGs.

Safety assessments and efficacy assessments will be performed throughout the study as described in the Schedule of Activities (Table 1).

Study Activity	**Screening & baseline** ≤28 days of start of treatment	**Cycle 1 Week 1-4**	**Cycle 2 Week 5-8**	**End of neoadjuvant (pre-surgery assessment)**	**End of treatment visit（Surgery complete）**	**Final follow-up visit (1 month after surgery)**
Visits		**Day 1**	**Day -4±2 day**			
Informed consent[1]	X					
Medical history and demographics[2]	X					
ALK+ status	X					
Physical examination	X					
ECOG PS[3]	X	X	X	X	X	X
Brain scan MRI or CT [4]	X					
Vital signs[5], Body weight, Height[5]	X	X	X	X	X	X
ECG[6]	X	X	X	X		X
Laboratory[7]						
Hematology[8]	X	X	X	X	X	X
Blood chemistry[9]	X	X	X	X	X	X
Urinalysis[10]	X	X	X	X	X	X
Pregnancy test[11]	X				(X)	
HBV, HCV, and HIV testing	X					
Prior/Concomitant medications[12]	X	X	X	X	X	X
Adverse events[13]	X	X	X	X	X	X
Tumor imaging assessments[14]	X	X		X	X[14]	X[14]
Subject status follow-up[15]	X	X	X	X	X	X
Lorlatinib dosing[16]		X----------X				
Tumor tissue sample[17]	X				X	
Blood sample[18]	X	X (2 weeks, 4 weeks,)	X (End of treatment)	X	X (3 days after surgery)	X

Abbreviations: CT, Computed Tomography; ECG, Electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; MRI, magnetic resonance imaging; NGS, next-generation sequencing; PS, Performance Status.

1. Written informed consent is required within 28 days of start of treatment, and prior to any study specific screening procedures.

2. Medical History and demographics: General medical history including details of any concurrent illness, oncology history (including smoking status and history of weight loss in last 6 months) to be done at baseline.

3. Performance status will be assessed by the ECOG scale.

4. MRI is recommended as the preferred option.. Central nervous system (CNS) masses or meningeal involvement must be asymptomatic .and without the need for increasing doses of corticosteroids to manage CNS symptoms within two weeks of starting lorlatinib.

5. Vital signs include pulse rate, sitting or supine blood pressure, respiratory rate and body temperature. The information will be recorded in the subject's medical records and if clinically significant, data will be recorded as an adverse event (AE) in the case report form (CRF). Height will be measured at screening only.

6. ECG: A 12-lead ECG will be performed at screening and baseline for all subjects. If any subject experiences a cardiac or neurologic AE (e.g., syncope, dizziness, seizures, or stroke), unplanned ECG should be obtained at the time of the event. The ECG should be repeated if there is a clinical finding that indicates a need for a repeat ECG or if there is a finding of QTc >500 msec, and abnormal QTc findings confirmed by a manual reading by investigator or designee.

7. Laboratory studies will be performed locally (described as follows in footnotes 8-11) and may be performed up to 72 hours prior to scheduled visits to allow for availability of results at time of subject's scheduled clinic visit.

8. Hematology includes: hemoglobin, platelet count, white blood cell count, absolute neutrophil count, absolute lymphocyte count and absolute monocyte count.

9. Blood chemistry includes at screening: creatinine (and creatinine clearance to be determined by Cockcroft-Gault formula or standard formula for site), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, serum total amylase and serum total lipase. Blood chemistry at subsequent visits includes: blood urea nitrogen or urea, sodium, potassium, magnesium, calcium, alkaline phosphatase, albumin, AST, ALT, total bilirubin, and creatinine, serum total amylase and serum total lipase should be assessed if deemed necessary by the investigator.

10. Urinalysis includes: protein, glucose, blood, urinary sediment. A dipstick urinalysis may be used; however if any abnormal findings are noted then a microscopic examination must be performed. If urine protein by dipstick is ≥3+, then a urine protein/creatinine ratio (UPC) should be obtained. The patient may enter only if UPC is <2.0.

11. A pregnancy test for women of child-bearing potential should be done at screening and baseline. Pregnancy test result need to be known to be negative prior to study treatment. For baseline, in case of serum sample, pregnancy test needs to be conducted within 72 hours prior to Cycle 1 Day 1. In case of urine sample, pregnancy test needs to be conducted on Cycle 1 Day 1 before study treatment is started. It should be repeated at end of treatment visit, and as often as necessary, if mandated by institutional policy or at the discretion of the investigator.

12. Subjects will be enrolled only if they are able to stop (by discontinuation, substitution, or modification) medications that are prohibited, or if the metabolism is highly CYP2D6 dependent. Prior/concomitant medications shall be recorded at screening, and continuously throughout the study period up to the Post-Treatment Follow-Up Visit or until the subject begins a new anticancer therapy, whichever occurs first.

13. Adverse event assessment includes tumor-related, treatment-related and unrelated signs and symptoms. The reporting period for non-serious AEs starts from the time the subject has taken the first dose of study treatment and ends at last subject visit or upon initiation of a subsequent anticancer treatment, whichever occurs first. The reporting period for serious AEs starts once a subject provides informed consent and ends 28 days after the last dose of study treatment irrespective of the start of

any subsequent anticancer treatment. Subjects must be followed for AEs at Post-Treatment Follow-up Visit at least 28 (and no more than 35) days after the end of treatment, or until all drug-related toxicities have resolved or are deemed irreversible, whichever is later. The National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (CTCAE v5.0) will be used to grade AE severity.

14. Tumor assessments will include: PET/CT, or through computed tomography (CT), abdominal ultrasound, cranial MRI/CT, and bone scintigraphy at screening, in order to determine the accurate TNM staging. Physical examination for peripheral adenopathy or skin/subcutaneous nodules representing target measurable (by caliper) disease, if any are present.. Imaging serves also as safety assessment to monitor/exclude pulmonary toxicity. Chest X-ray will be performed on the first postoperative day to assess the surgical outcome and any procedural events. A chest X-ray will be conducted one month postoperatively to evaluate postoperative pulmonary recovery, including the presence of pleural effusion.

15. Subject Status Follow-up for Survival: Repeat tumor assessments are suggested to be done approximately every 4 weeks from the date of CT/MRI at the end of study treatment. Telephone contact approximately every cycle from post treatment follow-up visit to obtain regular follow-up is recommended. The information collected for subsequent therapies should include enumeration of the post-study treatment, including drugs administered, and date of initiation and discontinuation of each drug; and will be recorded in the CRF.

16. Lorlatinib 100 mg, once daily, will be administered to subjects starting on Cycle 1, Day 1. Subjects should be instructed to take their medication at approximately the same time every day. The tablets will be taken with at least 6 ounces (180 ml) of water with or without food. Treatment compliance check: The site must follow up with each subject on the day of each cycle's visit to confirm that the subject understands and complies with the dosing instructions for lorlatinib.

17. For patients meeting the inclusion criteria, tissue samples will be collected in the form of formalin-fixed paraffin-embedded blocks, formalin-fixed tissue, or fresh tissue at baseline and postoperatively. Details regarding specimen handling, storage, and residual sample management can be found in the laboratory manual.

18. For patients meeting the inclusion criteria, blood samples (20 mL each) will be collected at baseline, 2 weeks, 4 weeks, completion of neoadjuvant therapy, preoperatively, 3 days postoperatively, and 1 month postoperatively. Details regarding specimen handling, storage, and residual sample management can be found in the laboratory manual.

3.2 Safety Plan

The overall safety profile and toleration of neoadjuvant lorlatinib therapy will be based on AEs and laboratory abnormalities with regard to frequency, severity (in accordance with CTCAE v5.0), timing and relationship with study drug.

4. SUBJECT SELECTION

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before patients are included in the study.

4.1 Inclusion Criteria

Subjects must meet all the following inclusion criteria to be eligible for enrollment into the study:

- Male or female subjects who are ≥18 years of age
- Histologically or cytologically documented non-squamous surgically resectable stage IB, II, IIIA or selected IIIB NSCLC (including T4N2，per AJCC 8th edition)
- Clinical stage IB, II, IIIA or selected IIIB assessed PET/CT that can be resected
- Documented ALK-rearrangement positive (assessed by a local laboratory）
- Performance status (ECOG) 0-1 at enrolment, with no deterioration over the previous 2 weeks prior to baseline or day of first dosing of lorlatinib
- Hematology, liver and kidney function are adequate for induction therapy.
    - Adequate Bone Marrow Function, including:

    a. Absolute Neutrophil Count (ANC) ≥ 1,500/mm3 or ≥1.5 x 109/L;

    b. Platelets ≥100,000/mm3 or ≥100 x 109/L;

    c. Hemoglobin ≥9 g/dL.

    - Adequate Pancreatic Function, including:

    a. Serum total amylase ≤1.5 x upper limit of normal (ULN)*;

b. Serum lipase ≤1.5 x ULN.

*if total amylase >1.5 x ULN, but pancreatic amylase is within the ULN, then patient may be enrolled.

- Adequate Renal Function, including:

a. Serum creatinine ≤1.5 x ULN or estimated creatinine clearance ≥60 mL/min as calculated using the method standard for the institution.

- Adequate Liver Function, including:

a. Total serum bilirubin ≤1.5 x ULN;

b. Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) ≤2.5 x ULN (≤5.0 x ULN in case of liver metastases).

- Cardiopulmonary function suitable for surgical treatment (ECG, echocardiography, pulmonary function or blood gas analysis).

- Be willing and able to provide written informed consent for the trial prior to any study specific procedures. The subject must also provide consent for correlative translational study.

- Female participants of childbearing potential must agree to use acceptable methods of contraception

- Male patients must be willing to use barrier contraception.

- Serum pregnancy test (for females of childbearing potential) negative at screening. Female patients of non-childbearing potential must meet at least 1 of the following criteria:

a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or

physiological cause (which may be confirmed with a serum follicle-stimulating hormone [FSH] level confirming the postmenopausal state if appropriate);

b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

c. Have medically confirmed ovarian failure.

All other female patients (including female patients with tubal ligations) are considered to be of childbearing potential.

- Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.
- Willing and able to comply with scheduled visits, treatment plans, laboratory tests and other procedures.

4.2 Exclusion Criteria

Subjects presenting with any of the following characteristics/conditions will not be included in this clinical study:

- Mixed squamous cell carcinoma, large cell carcinoma, small cell lung cancer.
- Prior treatment with any systemic anti-cancer therapy for NSCLC including chemotherapy, biologic therapy, immunotherapy, or any investigational drug.
- Pregnant female patients; breastfeeding female patients.
- Malignancies other than the disease under study within 3 years prior to Cycle 1, Day 1, with the exception of patients with a negligible risk of metastasis or death and with expected curative outcome
- Severe infection within 4 weeks prior to initiation of study treatment, including but

not limited to hospitalization for complications of infections, or any active infection that, in the opinion of the investigator, could impact participant safety

- Pregnant or lactating, or intending to become pregnant during the study
- Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study.
- Active and clinically significant bacterial, fungal, or viral infection including hepatitis B virus (HBV) or hepatitis C virus (HCV) (e.g., in case of known HBsAg or HCV antibody positivity), known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS)-related illness.
- Clinically significant vascular (both arterial and venous) and non-vascular cardiac conditions, (active or within 3 months prior to enrollment), which may include, but are not limited to:

  a. Arterial disease such as cerebral vascular accident/stroke (including Transient Ischemic Attack -TIA), myocardial infarction, unstable angina;

  b. Venous diseases such as cerebral venous thrombosis, symptomatic pulmonary embolism;

  c. Non-vascular cardiac disease such as congestive heart failure (New York Heart Association Classification Class ≥ II), second-degree or third-degree AV block (unless paced) or any AV block with PR >220 msec; or ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, uncontrolled atrial fibrillation of any grade, bradycardia defined as <50 bpm (unless patient is otherwise healthy such as long-distance runners, etc.), machine-read Electrocardiogram (ECG) with QTc >470 msec, or congenital long QT syndrome.
- Patients with predisposing characteristics for acute pancreatitis according to investigator judgment (e.g., uncontrolled hyperglycemia, current gallstone disease) in the last month prior to randomization.

- History of extensive, disseminated, bilateral or presence of Grade 3 or 4 interstitial fibrosis or interstitial lung disease including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, and pulmonary fibrosis.

- Evidence of active malignancy (other than NSCLC, non-melanoma skin cancer, or localized prostate cancer or any in situ cancer which does not currently require treatment) within the last 3 years prior to randomization.

- Concurrent use of any of the following food or drugs (consult the sponsor if in doubt whether a food or a drug falls into any of the following categories) within 12 days prior to the first dose of lorlatinib.

  a. Known strong CYP3A inhibitors (e.g., strong CYP3A inhibitors: grapefruit juice or grapefruit/grapefruit related citrus fruits [eg, Seville oranges, pomelos], boceprevir, cobicistat, conivaptan, itraconazole, ketoconazole, posaconazole, ritonavir alone and with danoprevir or elvitegravir or indinavir or lopinavir or paritaprevir or ombitasvir or dasabuvir or saquinavir or tipranavir, telaprevir, troleandomycin, and voriconazole. The topical use of these medications (if applicable), such as 2% ketoconazole cream, is allowed.

  b. Known CYP3A substrates with narrow therapeutic index, such as astemizole*, terfenadine*, cisapride*, pimozide, quinidine, tacrolimus, cyclosporine, sirolimus, alfentanil, fentanyl (including transdermal patch) or ergot alkaloids (ergotamine, dihydroergotamine) (*withdrawn from US market).

  c. Known strong CYP3A inducers (e.g., carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's Wort). d. Known P-gp substrates with a narrow therapeutic index (e.g., digoxin).

- Other severe acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or

investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

- Patients who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the Investigator, including their family members, directly involved in the conduct of the study.
- Pregnant female patients; breastfeeding female patients; fertile male patients and female patients of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 97 days, if male or 35 days if female, after the last dose of investigational product under lorlatinib.

5. TREATMENT

5.1 Treatment Administered

A patient must sign an informed consent form (ICF) before being evaluated for study entry. Once a patient who has met inclusion and exclusion criteria has provided a signed ICF.

Patients will receive lorlatinib orally 100 mg QD, administered as 4 x 25 mg oral tablets, at approximately the same time of the day on a continuous daily dosing schedule, ie, without a break in dosing in the absence of drug-related toxicity.

Patients must swallow the study medication whole and must not manipulate or chew the medication prior to swallowing. A dosing card will be provided to the patients to provide guidance for the correct use of lorlatinib. Patients must be instructed that should they miss a dose or vomit any time after taking a dose, they must not “make it up” with an extra dose. Instead, resume the subsequent doses as originally prescribed. Any

missed dose may be taken up to 6 hours prior to the next scheduled dose, otherwise it should be skipped and dosing resumed with subsequent doses as prescribed. The patient must be instructed to record all doses (including missed or vomited) in a dosing diary supplied by the site. If doses are missed or vomited, this must be indicated in the source documents and Case Record Forms (CRFs). Lorlatinib will be administered from the date of first dosing (Cycle 1 Day 1 [C1D1]) or until 1 of the following criteria was met (whichever occurred first): complete 6-8 weeks of neoadjuvant therapy; unacceptable toxicities; global deterioration of health-related symptoms; pregnancy; withdrawal of consent; loss to follow-up; death; investigator decision dictated by protocol compliance; study termination by the investigator.

Since no clinically meaningful effect of food on the PK of lorlatinib has been observed, lorlatinib can be administered with or without food.

5.2 Lorlatinib Dose Modification

In case of adverse events, investigators are encouraged to employ best supportive care according to local institutional clinical practices or follow the guidance for selected adverse events provided as below.

Table 2. Lorlatinib Dose Modification

Dose Levels	Lorlatinib Dose
0	100 mg QD
-1	75 mg QD
-2	50 mg QD
Dose reductions below dose level -2 are not allowed.	

Patients will be monitored closely for toxicity, and the dose of lorlatinib may be adjusted as indicated in Table 2. Dose reduction by 1 and, if needed, 2 dose levels will be allowed depending on the type and severity of toxicity encountered.

If a patient has a significant toxicity from lorlatinib treatment which fails to recover within 42 days (6 weeks) or, in the opinion of the investigator, requires permanent

discontinuation of the treatment based on the severity of the adverse event, then this patient should not be further treated with lorlatinib but should remain in the trial with ongoing tumor assessments until the end of study

Recommendations for lorlatinib dose modification for treatment-related non-hematological and hematological toxicity, as well as for treatment-related toxicity of special interest, are provided in Table 3 below.

Re-escalation is not allowed except if discussed with and approved by the sponsor's medical contact.

Table 3. Lorlatinib Dose Modifications for Lorlatinib-Related Toxicities Non-Hematologic Toxicities

Toxicity	Grade** 1	Grade 2**	Grade 3	Grade 4
Pancreatitis	NA	If elevated enzymes (both amylase and lipase are Grade ≤2) are observed in the absence of radiological findings of pancreatitis: continue lorlatinib at the same dose level without dose hold. Repeat lipase and amylase and obtain pancreatic isoenzyme if possible. If radiologically confirmed pancreatitis: withhold lorlatinib dose. Repeat radiology and lipase and amylase weekly and obtain pancreatic isoenzyme. If appropriate, resume lorlatinib treatment at one dose level lower if radiology has returned to baseline and lipase and amylase are Grade ≤2.	Permanently discontinue lorlatinib.	Permanently discontinue lorlatinib.
Pneumonitis (in the absence of disease progression, pulmonary embolism, positive cultures or radiation effect)§.	Asymptomatic, radiographic findings only: No need for lorlatinib dose adjustment. Initiate appropriate monitoring.	Withhold current lorlatinib dose until toxicity has returned to baseline. Rule out infection and consider initiating treatment with corticosteroids. Then resume lorlatinib treatment at one dose level lower. Discontinue lorlatinib permanently if pneumonitis recurs or if failure to recover after 6 weeks of study treatment hold and steroid treatment.	Permanently discontinue lorlatinib.	Permanently discontinue lorlatinib.
Electrocardiogram QTc prolongation .	Assess electrolytes and concomitant medications. Correct any electrolyte abnormalities, or hypoxia. Continue lorlatinib at the same dose level.	Assess electrolytes and concomitant medications. Correct any electrolyte abnormalities, or hypoxia. Continue lorlatinib at the same dose level.	Withhold lorlatinib dose. Assess electrolytes and concomitant medications. Correct any electrolyte abnormalities, or hypoxia. Upon recovery to Grade £1 resume lorlatinib treatment at one dose level lower.	Permanently discontinue lorlatinib.
LV Dysfunction	CTCAE v5.0 does not report Grade 1.	CTCAE v 5.0 does not report Grade 2.	Permanently discontinue lorlatinib.	Permanently discontinue lorlatinib.
Non-Hematologic General	Continue lorlatinib at the same dose level.	Continue lorlatinib at the same dose level.	Withhold lorlatinib dose until toxicity is Grade £1(or has returned to baseline) then reduce the dose by 1 level or rechallenge at the same dose.*	Withhold dose until toxicity is Grade £1 (or has returned to baseline), then reduce the dose by 1 level* or

				discontinue at the discretion of the investigator.

* Patients who develop asymptomatic Grade 4 hyperuricemia or Grade 3 hypophosphatemia may continue lorlatinib without dose modification at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy to require lorlatinib dose modification .

** In cases where no specific dose adjustments for Grade 1 or Grade 2 treatment-related toxicity are provided, investigators should always manage their patients according to their medical judgment which may include dose reduction or interruption based on the particular clinical circumstances.

§ If a patient has a potential diagnosis of pneumonitis or drug-related lung injury the same evaluations/procedures provided should be considered to assist or exclude the diagnosis of pneumonitis during this period.

Hematologic Toxicities				
Toxicity	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hematologic General	Continue lorlatinib at the same dose level.	Continue lorlatinib at the same dose level.	Withhold lorlatinib dose until toxicity is Grade £1 (or has returned to baseline), then rechallenge at the same dose or reduce the dose by 1 dose level.	Withhold lorlatinib dose until toxicity is Grade £1 (or has returned to baseline) then rechallenge at the same dose or reduce the dose by 1 dose level.
Lymphopenia	Continue lorlatinib at the same dose level.	Continue lorlatinib at the same dose level.	If no evidence of infection or other clinically significant toxicity, continue lorlatinib at the same dose; otherwise, withhold dose until toxicity is Grade £1 (or baseline) then rechallenge at the same dose or reduce by 1 level.	If no evidence of infection or other clinically significant toxicity, continue lorlatinib at same dose; otherwise, withhold dose until toxicity is Grade £1 (or baseline), then rechallenge at the same dose or reduce the dose by 1 dose level.
Lipid Elevation Toxicities				
Cholesterol	Continue lorlatinib at the same dose. Consider introducing use of a statin or other lipid lowering agent as	Introduce the use of a statin or other lipid lowering agent as appropriate, and continue lorlatinib at the same dose.	Introduce the use of a statin or other lipid-lowering agent as appropriate, or increase the dose of the statin/lipid lowering agent	Increase the dose of the statin or other lipid-lowering agents, or change to a new statin/lipid lowering agent. Withhold lorlatinib dose until toxicity is

	appropriate based on investigator's medical judgment.		or change to a new agent. Either continue lorlatinib at the same dose without interruption or withhold dose until toxicity is	Grade ≤2 and then reduce the dose by 1 dose level or rechallenge at the same dose.
Triglycerides	Continue lorlatinib at the same dose. Consider introducing use of a statin or other lipid-lowering agent as appropriate based on investigator's medical judgment.	Introduce the use of a statin or other lipid-lowering agent as appropriate, and continue lorlatinib at the same dose.	Introduce the use of a statin or other lipid-lowering agent as appropriate, or increase the dose of the statin/lipid-lowering agent or change to a new agent. Either continue lorlatinib at the same dose without	Increase the dose of the statin or other lipid-lowering agents, or change to a new statin/lipid-lowering agents. Withhold lorlatinib dose until toxicity is Grade ≤2 and then reduce the dose by 1 dose level or rechallenge at the same dose.

CNS Toxicities				
Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
CNS effectsβ	Continue lorlatinib at the same dose or withhold dose until recovery to baseline.	Continue lorlatinib at same dose or withhold dose until recovery to Grade ≤1. Consider dose reduction or rechallenge at the same dose.	Withhold lorlatinib dose until toxicity is Grade ≤1. Reduce dose to the next lower dose.	Permanently discontinue lorlatinib.

[β] Examples of CNS effects could include changes in speech, memory, sleep, cognition, or vision.

5.3 Hyperlipidemia

In the lorlatinib phase 3 study B7461006, hypercholesterolemia was the most common AE reported. Elevations in lipids usually begin in the first few cycles and, if statins are not introduced, can rise to Grade 3 levels by the next treatment cycle. Therefore, the suggested management is to begin a statin for Grade 1 elevations in either cholesterol or triglycerides and to increase the statin dose if adequate control is not obtained, as outlined in Table 3.

Members of the statin class of agents are differentially sensitive to CYP3A4, and caution should be exercised when selecting statin for management of elevated lipid levels.

Pitavastatin and rosuvastatin can be used during lorlatinib treatment without dose adjustment since there is no CYP3A4 involvement in their elimination. Pravastatin, fluvastatin and atorvastatin should be used with caution during lorlatinib treatment, and a dose adjustment of these statins may be necessary (increasing dose may be considered). Lovastatin and simvastatin are not recommended for use during lorlatinib treatment.

5.4 PR Interval Prolongation

Analysis of ECG data from ongoing and completed human studies with lorlatinib has identified a subset of patients who exhibited ECG evidence of PR interval prolongation. The ECG changes appear limited to the PR interval with no impact on QRS or QT intervals.

Guidance for management of PR interval prolongation is provided in Table 4 below and examples of drug with potential PR interval prolongation effect can be found in Appendix

Table 4.PR Interval Prolongation Management

Toxicity	Not Symptomatic	Symptomatic
1st-Degree Heart Block (PR interval >200 msec)	**No dose hold or reduction needed.** Assess concomitant medications. Monitor closely by obtaining pre-dose ECG at next visit, even if unscheduled. Instruct patient to call if	**Withhold dose.** Assess concomitant medications. Obtain ECG in approximately 48 hours and re-assess symptoms and PR-interval. Restart at
2nd-Degree Heart Block	**Withhold dose.** Assess concomitant medications. Repeat ECG in approximately 48 hours. Instruct patient to call if symptoms develop that may be related to heart block. Restart at same dose or consider dose reduction if subsequent ECG does not show	**Withhold dose.** Refer for cardiac observation and monitoring. Consider pacemaker placement if symptomatic heart block persists. Resume at reduced dose only when symptoms resolve AND 2nd degree
Complete Heart Block	**Withhold dose.** Refer for cardiac observation and monitoring. Temporary pacemaker placement may be indicated for severe symptoms associated with heart block. If heart block does not resolve, placement of a permanent pacemaker may be considered. If pacemaker placed, may resume at full dose.	

Study treatment could be interrupted for Grade 3, Grade 4, or intolerable Grade 2 toxicity (using NCI CTCAE v5.0). Upon recovery to Grade 2 or baseline, and in the clinical judgment of the investigator with the agreement of the patient, the treatment could be resumed as follows:

- For interruption due to Grade 3 or intolerable Grade 2 toxicity, treatment could be resumed at the same dose level or reduced per protocol.
- For episodes of Grade 4 toxicity, reduction to the next dose level was highly recommended.

For patients whose study treatment had been interrupted due to treatment related toxicity as described above, treatment was permanently discontinued if they failed to recover within 2 weeks of dose interruption, unless there was discussion of the clinical circumstance with the Sponsor and agreement that the patient could resume treatment after a lapse of >2 weeks.

5.5 Pulmonary Toxicity

In the event of a new onset of dyspnea, persistent cough, or other pulmonary symptoms while on study treatment, and there is a concern for drug-induced interstitial lung disease, study treatment should be stopped until the subject can be adequately evaluated;

dose modification is not appropriate in this setting. Subjects should be counseled throughout study treatment to alert the investigator or designated team member immediately if they develop new or worsening respiratory symptoms.

For subjects with any new or worsening cough or dyspnea of unknown etiology (with or without fever), or unexplained symptoms or radiological findings suggestive of interstitial lung disease, testing should minimally include: measurement of oxygen saturation by pulse oximetry and chest CT. Drug-induced pneumonitis is a diagnosis of exclusion, therefore investigators must thoroughly evaluate subjects who demonstrate potential signs/symptoms of pneumonitis/pneumonia. If a subject has a potential diagnosis of pneumonitis or drug-related lung injury the following evaluations/procedures should be considered to assist or exclude the diagnosis of pneumonitis during this period:

- A sputum gram stain and culture (induced sputum if needed) bacterial, viral, fungal, protozoal, and mycobacteria;
- Human immunodeficiency virus testing;
- Blood culture if the subject is febrile;
- Thoracentesis if pleural fluid is present (examined for same pathogens as sputum);
- Bronchoscopy with bronchoalveolar lavage if appropriate. The bronchoalveolar lavage fluid should be sent for culture and cytology (same pathogens as above);
- Lung biopsy (e.g., open or thorascopic if preferable, bronchoscopy with transbronchial biopsy) if appropriate based on the subject's clinical status. Video-assisted thoracoscopy may be considered to acquire tissue via a minimally-invasive procedure;
- A plasma sample for B-type natriuretic peptide (BNP) to check for any evidence of chronic heart failure;
- If clinically appropriate, high dose corticosteroid treatment should be initiated.

Should the event be fatal, an autopsy is highly recommended to confirm/exclude the

diagnosis. For any case of suspected pneumonitis, it is concluded that a thorough investigation has excluded treatment-induced pulmonary toxicity, study treatment may resume.

5.6 Drug supplies and storage

Lorlatinib will be supplied as 100mg and 25 mg tablets for oral administration. Lorlatinib will be dispensed at the beginning of each treatment cycle (or as otherwise indicated). Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other container.

The investigator, or an approved designee (e.g., pharmacist), will ensure that all study drug is stored in a secured area, under recommended storage conditions (lorlatinib: controlled room temperature) and in accordance with applicable regulatory requirements. Under no circumstances should the investigator or other site personnel supply study drug to other investigators, subjects, or clinics, or allow supplies to be used other than directed by this study. Adequate records documenting receipt, use, return, loss, or other disposition of tablets must be kept. The drug provider may supply drug accountability forms that will be used, or may approve use of standard institution forms. The forms must identify the investigational product, including batch numbers, and account for its disposition on a subject by subject basis, including specific dates and quantities. The forms must be signed by the individual who dispensed the drug, and copies must be provided to CRO Medical upon request.

Tablets must be administered according to the study directions. The reason for missed doses should be entered on the CRF to ensure adequate records. All study drugs will be accounted for in the CRF and drug accountability inventory forms as instructed by the Sponsor. All bottles or blister cards (either used or unused) must be returned to the investigator by the subject. Unless otherwise authorized at the end of the study, all drug supplies unallocated or unused by the subjects must be returned to the provider or its appointed agent.

5.7 Selection and Timing of Dose for Each Patient

Patients were instructed to take their study treatment at approximately the same time every day, or as close as possible to the same time every day, with the following exception: for protocol-required delays (such as on specified study visit days), patients were instructed not to take their medication until after they had undergone any scheduled pre-dose assessments in the clinic and had been evaluated by the investigator for continuation of therapy.

Patients were instructed not to make up missed doses of study treatment, but rather to simply resume the regular dosing schedule on the day following a missed dose. Likewise, patients were instructed not to make up for a vomited dose by taking an extra dose the same day, but rather to resume the regular dosing schedule the next day as prescribed. Any missed or vomited doses were recorded in the source documents and eCRFs, just as all administered doses were documented.

Medication errors including those that involved patient exposure to the study product and potential medication errors or uses outside of what was foreseen in the study protocol that did or did not involve the participating patient, were reported on the AE eCRFs irrespective of the presence of an associated AE or SAE.

5.8 Prior/Concomitant Medications and Treatments

All concomitant medications should be recorded in the CRF including supportive care drugs (e.g., antiemetic treatment and prophylaxis), and the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (e.g., transfusions).

Medications intended solely for supportive care (e.g., antiemetics, analgesics, megestrol acetate for anorexia, bisphosphonates or RANK-ligands for metastatic bone disease or osteoporosis) are allowed. In case the patient is already on treatment with RANK-ligands (like denosumab) before study entry, the therapy should be at a stable dose prior to randomization.

5.8.1. Inhibitors and Inducers of CYP Enzymes

The in vitro studies have demonstrated that CYP3A, and UGT1A4 are primarily involved in the metabolism of lorlatinib, with additional minor contributions from CYP2C19 and CYP2C8. Inhibition or induction of the above enzymes may result in potential alteration of lorlatinib systemic exposure.

Initial in vitro assessment for inhibition and induction drug-drug interaction potential indicated that lorlatinib is a time-dependent inhibitor of CYP3A and also an inducer of CYP3A and CYP2B6. At substantially higher concentrations than those observed clinically, lorlatinib also inhibited CYP2C9 in in vitro studies.

To protect patient safety, the following cautions are provided:

- Lorlatinib metabolism may be inhibited by strong CYP3A inhibitors leading to a potential increase in lorlatinib toxicities. Coadministration of strong CYP3A inhibitors (e.g., boceprevir, cobicistat, conivaptan, itraconazole, ketoconazole, and posaconazole, ritonavir alone and with danoprevir or elvitegravir or indinavir or lopinavir or paritaprevir or ombitasvir or dasabuvir or saquinavir or tipranavir, telaprevir, troleandomycin, and voriconazole, grapefruit juice or grapefruit/grapefruit-related citrus fruits [e.g., Seville oranges, pomelos]) is not recommended and alternate medications should be considered. If the concomitant use of the strong CYP3A inhibitor cannot be avoided, reduce the starting dose of lorlatinib from 100 mg orally once daily to 75 mg orally once daily. In patients who have had a dose reduction to 75 mg orally once daily due to adverse reactions and who initiate a strong CYP3A inhibitor, reduce the lorlatinib dose to 50 mg orally once daily. The patient should be closely monitored for safety and reduction of the lorlatinib dose if necessary. If concomitant use of a strong CYP3A inhibitor is discontinued, increase the

lorlatinib dose (after 3 plasma half-lives of the strong CYP3A inhibitor) to the dose that was used before starting the strong inhibitor.

- Use of strong CYP3A inducers with lorlatinib is contraindicated. Lorlatinib metabolism may be induced when taking strong CYP3A inducers (e.g., carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's Wort) resulting in reduced plasma concentrations. Furthermore, when lorlatinib was coadministered with rifampin, increases in AST and ALT were noted. Discontinue strong CYP3A inducers for 3 plasma half-lives of the strong CYP3A inducer prior to initiating lorlatinib and until study treatment discontinuation. In addition, use with moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil) should be avoided due to the potential reduction in lorlatinib exposure.

- Lorlatinib induces CYP2B6 (in vitro) so concurrent use of drugs that are CYP2B6 substrates, such as bupropion and efavirenz, may have less effect. Concomitant CYP2B6 substrates should be used with caution, as the net clinical effect of lorlatinib on CYP2B6 is currently being investigated.

- Lorlatinib induces CYP3A (in vivo) which may lead to a decreased effect of concurrently used CYP3A substrates (e.g., hormonal contraceptives etc.).
  Coadministration of lorlatinib with CYP3A substrates with a narrow therapeutic index (NTI) such as alfentanil, fentanyl (including transdermal patch), astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, pimozide, quinidine, sirolimus, tacrolimus, terfenadine is not permitted at study entry. However if it is absolutely necessary to use, sponsor approval is required and the dose of the CYP3A substrate may need to be increased. The NTI CYP3A substrate should be started only

after at least 14 days of continuous lorlatinib dosing. If there is a change in the lorlatinib dosing regimen such as a dosing interruption or dose reduction, the administration of the NTI CYP3A substrate should be stopped and resumed at a readjusted dose only after at least 14 days of resumed lorlatinib dosing.

- Lorlatinib inhibits P-glycoprotein (P-gp) (in vitro) so concurrent use of drugs which are P-gp substrates with a narrow therapeutic index may have increased effect. The concurrent use of drugs which are P-gp substrates with narrow therapeutic index, such as digoxin is not permitted at study entry. The use of these drugs during the study is not recommended and alternate medications should be considered. If absolutely necessary to use during the study, it should be initiated following sponsor approval, and be used then with caution. The net clinical effect of lorlatinib on P-gp is currently being investigated.

Any questions regarding the use of alternative medications should be directed to the Investigator for guidance.

5.9 Other Anti-Tumor/Anti-Cancer or Experimental Drugs

The concurrent use of select vitamins or herbal supplements is not permitted.

5.10 Other Prohibited Concomitant Medications and Therapies

Patients are prohibited from receiving the following therapies during the treatment phase of this trial:

1. Investigational agents other than lorlatinib.

2. Other experimental pharmaceutical products.

3. Herbal remedies with anticancer properties or known to potentially interfere with major organ function or study drug metabolism (e.g., hypericin).

5.11 Hematopoietic Growth Factors

Use of granulocyte colony stimulating factors should follow the current American Society of Clinical Oncology (ASCO) guidelines. Patients who enter the study on stable doses of erythropoietin or darbepoetin may continue this treatment, and patients may start either drug during the study at the discretion of the investigator.

5.12 Supportive Care

Subjects who are receiving bone modifying agents to control pain/bone metastases as recommended in current guidelines for bone-targeted therapy (e.g. bisphosphonates or denosumab) may continue while on therapy but initiation of such a therapy after enrolment will be considered progression of disease unless otherwise agreed by the investigator in consultation with the Sponsor.

Palliative radiotherapy for painful bony lesions is permitted providing the lesions were known to be present at the time of study entry and the investigator clearly indicates the need for palliative radiotherapy is for better palliation than alternative analgesic options, and is not due to disease progression.

6. STUDY PROCEDURES

All assessments and procedures during the study are detailed in the Schedule of Activities (**Table 1**).

To allow for subject and investigator schedules, holidays, and weather or other emergencies requiring clinical facilities to be closed, all subject visits can be performed within -4/+2 days of the scheduled visit date. To allow for additional flexibility in scheduling subject visits and procedures, screening and baseline procedures may be completed on the same day. In that case, treatment must start one day after screening/baseline procedures but within three days. Baseline and Cycle 1 Day 1 procedures may be completed on the same day. However, screening assessments for *eligibility* MUST have already been completed by the preceding day. Screening, baseline, and Cycle 1 Day 1 cannot be completed all together on the same day.

6.1 Pre-screening and Informed Consent

Patients with the following will be pre-identified:

- Subjects who have newly diagnosed stage IB, II, IIIA or selected IIIB (including T4N2，per AJCC 8th edition) resectable non-squamous NSCLC;
- Subjects with an ALK-rearrangement mutation based on assessment as part of the standard of care for this disease;
- Subjects who have adenocarcinoma or its pathologically accepted variants.

Subjects meeting the above criteria must provide written informed consent prior to any study-specific procedures being performed.

6.2 Screening

All screening assessments are to be performed within 28 days prior to first study drug administration of lorlatinib. Assessment conducted prior to informed consent and within 28 days of first dose (Cycle 1 Day 1) can be used as data for screening. To establish subject eligibility for subsequent treatment, the following assessments will be completed:

- Confirm evidence of newly diagnosed stage IB, II, IIIA or selected IIIB (including T4N2， per AJCC 8th edition) resectable non-squamous NSCLC, allowable methods of disease measurement is PET/CT. The decision on which area of the body to be imaged is as determined by investigator judgment.
- Confirmation of ALK rearrangement via Ventana D5F3, NGS, etc. testing methods by local laboratory. Ventana D5F3 is recommended for reconfirmation in NGS and other testing methods;
- Vital signs, body weight and height will be measured (see Section 7.3.3);
- ECOG PS (see **Appendix 1**);
- Blood and urine samples will be collected (hematology, blood chemistry, coagulation, pregnancy test (female subjects with reproductive potential), urinalysis; see Section 7.3.2);
- A 12-Lead ECG reading will be performed with attention to QTc interval, with Fridericia's or Bazett's correction for abnormal heart rate as applicable (see Section 7.3.1);
- Prior/concomitant medication and SAE data will be collected. This would include the drug name, start/stop dates and indication.

6.3 Baseline

The following text outlines baseline assessments and procedures to be performed (see Schedule of Activities **Table 1**).

Within 2 weeks prior to Cycle 1 Day 1, the following assessments will be performed. It is unnecessary to repeat assessment at baseline if screening assessment and all laboratory evaluation items for baseline were performed at screening and within 2 weeks prior to Cycle 1 Day 1 (Pregnancy test result need to be known to be negative prior to study treatment: In case of serum sample, pregnancy test needs to be conducted within 72 hours prior to Cycle 1 Day 1. In case of urine sample, pregnancy test needs to be conducted on Cycle 1 Day 1 before study treatment is started.) and there is no clinical reason to believe the baseline has significantly changed:

- Vital signs and body weight will be measured (see Section 7.3.3);
- Demographics and medical history (relevant clinical events and conditions including tumor-related signs and symptoms); collection of subject reported weight loss over the past 6 months; history of smoking;
- Physical examination will be performed;
- A 12-Lead ECG reading will be done. QTc must be less than CTCAE v5.0 Grade 2 (≤480 msec) using Fridericia's or Bazett's correction formula with a manual reading by the investigator if required. The ECG may be repeated for evaluation of eligibility after management of correctable causes for observed QTc prolongation (see Section 7.3.1). Subject whose heart rate <45 beats per minute in the presence of clinical symptoms (e.g., hypotension, evidence of hypoperfusion) will not start study treatment;
- Blood samples will be collected (hematology, blood chemistry, coagulation and pregnancy test; see Section 7.3.2;
    a. Estimated creatinine clearance ≥30 mL/min (as determined by Cockcroft-Gault formula or the study site's standard formula);
    b. Absolute neutrophil count (ANC) ≥1500 cells/mm^3;
    c. Platelets ≥100,000 cells/mm^3;
    d. Hemoglobin ≥9.0 g/dL;
    e. Bilirubin ≤ 1.5 x ULN;
    f. AST (also known as SGOT) and ALT (also known as SGPT) ≤2.5 x ULN (≤ 5.0 x ULN if hepatic metastases);
- Prior/concomitant medication and SAE data will be collected and reviewed;

Subjects who sign the informed consent, and successfully completed screening and baseline assessments will subsequently be assigned open label lorlatinib. Treatment must start within 3 days.

6.4 Study Period

6.4.1 Cycle 1 Day 1

Cycle 1 Day 1 procedures may be completed on the same day as Baseline procedures (see the Schedule of Activities, **Table 1**). The following assessments and procedures will be performed:

- Vital signs and body weight will be measured (see Section 7.3.3);
- ECOG PS (see **Appendix 1**);
- Concomitant medication and AE data will be collected and reviewed.

Subjects will be given a diary to record study medication compliance details. Subjects will be asked to bring back all used packs of study medication and the diary when they return for the next visit.

Subjects will be instructed to avoid extended unprotected exposure to sunlight (e.g., sunbathing) or tanning for the duration of the study period and end of treatment visit (approximately 4 weeks after completion of study drug).

6.4.2 Cycle 1 Day 15 (±2 days)

Subjects will attend the clinic on Cycle 1 Day 15 (±2 days) for the following assessments:

- Vital signs and body weight will be measured (see Section 7.3.3);
- Concomitant medication and AE data will be collected and reviewed.

6.4.3 Day 1 of Subsequent Cycles (-4/+2 days)

Subjects will visit the investigator site on Day 1 (-4/+2 days) of each subsequent cycle for the following assessments:

- Vital signs and body weight will be measured (see Section 7.3.3);
- ECOG PS (see **Appendix 1**);
- Blood samples will be collected (hematology, blood chemistry, see Section 7.3.3). Safety laboratory tests may be done up to 72 hours prior to the visit;
- Concomitant medication and AE data will be collected and reviewed;

After the end of Cycle 1, follow the study schedule as outlined in Table 1:

- Tumor assessments will occur after the end of Cycle 1 then follow the study schedule as outlined in Table 1. The assessment may be performed up to 7 days prior to the visit to facilitate availability of results to the investigator at the time of the clinic visit.

6.4.4 Imaging

A CT scan of the tumor area will be conducted at the end of Cycle 1 (within 7 days of the start of subsequent cycle including Day 1 of subsequent cycle). The scan is to include the chest and other applicable sites of disease, determined by the investigator.

6.4.5 End of Treatment Visit

If a subject comes off treatment for complete surgical treatment, intolerance to study treatment, or subject withdrawal, etc., they should return to the study site as soon as possible for assessments of efficacy and safety as follows (see Schedule of Activities Table 1).

- Vital signs and body weight will be measured (see Section 7.3.3);
- ECOG PS (see Appendix 1);

- Blood and urine samples will be collected (hematology, blood chemistry, coagulation, pregnancy test [if required], urinalysis; see Section 7.3.2). Safety laboratory tests may be done up to 72 hours prior to the visit;
- Concomitant medications and AE data collection and review;
- If tumor assessments have not been done within the last 4 weeks for patients who discontinue treatment for reasons other than disease progression, these will be obtained as soon as feasible;

6.4.6 Post Treatment Follow-up Visit

At least 28 days, and no more than 35 days, after discontinuation of treatment, subjects will return to the study site and the following assessments will be performed (see Schedule of Activities Table 1).

In case subjects continue on therapy after complete surgical treatment, assessments of safety and survival status at post treatment follow-up visit should be performed at least 28 days, and no more than 35 days after end of treatment visit assessments.

- Vital signs and body weight will be measured (see **Section 7.3.4**);
- Subsequent cancer therapy;
- Concomitant medications and AE data collection and review.

Subjects continuing to experience treatment-related toxicity at this point after discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.

6.4.7 Follow-up

Subjects should be followed up until 1 month after surgical treatment. Telephone contact or other means to obtain timely regular follow-up is recommended. The

information for subsequent therapies collected and recorded on the CRF should include drugs administered, date of initiation and discontinuation of each medication.

6.4.8 Subject Withdrawal

A subject may withdraw from treatment at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or administrative reasons. Reasons for withdrawal include, but are not limited to the following:

- Progressive disease as defined by RECIST version 1.1 (as determined by investigator assessment) and judged by investigator that the patient no longer derives clinical benefit from study treatment;
- New systemic anticancer therapy instituted;
- Unacceptable toxicity;
- Global deterioration of health-related symptoms;
- Study non-compliance;
- Subject becomes pregnant;
- Subject withdraws from treatment;
- Lost to follow-up;
- Die;
- Study termination by investigator.

If subjects require more than 2 consecutive weeks of dose interruption, a discussion should be made with the investigator.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. The investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request the subject returns for a final visit if applicable, and follow up with the subject regarding any unresolved AEs.

If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The investigator may retain and continue to use any data collected before withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that the study required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a study required test cannot be performed, the investigator will document the reason and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible.

7.1 Timing of Assessments

All subjects being considered for the study must sign an informed consent within 28 days of start of treatment, and prior to any study specific screening procedures. Baseline assessments must be performed within 14 days prior to commencing study treatment, except pregnancy test (if applicable). Pregnancy test result needs to be known to be negative prior to study treatment. In case of serum sample, pregnancy test needs to be conducted within 72 hours prior to Cycle 1 Day 1. In case of urine sample, pregnancy test needs to be conducted on Cycle 1 Day 1 before study treatment is started.

On visits after Cycle 1 Day 1, laboratory assessments may be performed up to 72 hours and tumor/imaging assessments up to 7 days prior to Day 1 of any cycle in order for results to be available for investigator review at time of subject visit.

7.2 Efficacy Assessments

7.2.1 Tumor Response Assessment

Objective tumor response will be measured using RECIST v1.1 (see Appendix 3) and assessed by the investigator (INV).

Imaging tumor assessments at screening are to be performed within 28 days prior to commencing study treatment. All measurements should be recorded in metric notation using a ruler or calipers.

Investigators are encouraged to select greater than one lesion, representative and reproducible and to include the largest lesion, when identifying target lesions to be followed.

The same method and technique should be used to characterize each lesion identified and reported at Baseline, during the study treatment period, and during follow up.

7.2.2 Tumor Tissue

Informed consent will be obtained prior to tissue acquisition and testing for each patient. After the last cycle of induction therapy, the tumor tissues will be collected immediately by surgical resection. Tumor and lymph node collection from definitive surgical resection and sampling of fresh tumor sample (as applicable dependent on the size of residual tumor) is mandatory on the day of surgery. Processing of the remainder of the specimens for histopathologic analysis should be performed within 72 hours of the procedure. Sections will be used for local pathology review assessing pCR and MPR.

Tumor tissue samples collected during the screening period and post-operation will be used for Whole Exome Sequencing (WES) to investigate the correlation between changes in tissue clonality and neoadjuvant therapy efficacy. Additionally, based on

tissue mutation results, a customized blood testing gene panel (PANEL) will be designed to enhance detection rates in blood samples. Residual specimens should be processed for histopathological analysis within 72 hours of collection. Sections will be reviewed by the local laboratory for pathological assessment to evaluate pCR and MPR.

7.2.3 Blood Sample Analysis for ctDNA (circulating tumor DNA)

For patients meeting the inclusion criteria, blood samples (20 mL each) will be collected at baseline, 2 weeks, 4 weeks, and end of neoadjuvant therapy, pre-operation, 3 days and 1-month post-operation to provide specimens for biomarker analysis. These samples will be used for ctDNA analysis based on NGS platforms to evaluate the correlation between biomarkers with respond and outcomes.

7.3 Safety Assessments

The following parameters will be assessed at time points detailed in **Table 1** Schedule of Activities:

- ECG;
- Safety laboratory data;
- ECOG PS (ref to **Appendix 1** is needed);
- Vital signs;
- AEs.

7.3.1 12 Lead ECG

A 12-Lead ECG will be performed at screening and baseline with a 10 second rhythm strip. If the subject experiences signs or symptoms of a cardiac or neurologic

disorder (specifically syncope, dizziness, seizures, or stroke), ECG should be obtained at the time of the event.

To ensure safety, if there is finding of QTc >500 msec, the ECG must be repeated. If there is finding of QTc >500 msec again (i.e., ≥CTCAE Grade 3), the ECG must be reviewed by qualified personnel at the site as soon as the finding is made, including verifying that the machine reading is accurate and that the Fridericia's or Bazett's correction formula is applied.

An electronic reading of prolonged QTc must be confirmed by a manual reading. Before concluding that an episode of QTc prolongation is due to study drug, thorough consideration should be given to potential precipitating factors (e.g., a change in the subject's clinical condition, the effect of concurrent medication, electrolyte disturbance) and a possible evaluation by a specialist. If the QTc reverts to ≤500 msec, and it is the opinion of the investigator that the prolongation was not due to the study drug, treatment may be continued with regular ECG monitoring.

7.3.2 Safety Laboratory Data

Safety laboratory studies may be done up to 72 hours prior to the point indicated on the Schedule of Activities (Table 1) on any cycle, to facilitate availability of results to the investigator at the time of the clinic visit.

Table 5: Laboratory Evaluations

Screening for Eligibility		
Hematology	Blood Chemistry	Other
Hemoglobin Platelet count WBC count Absolute neutrophil count Absolute lymphocyte count Absolute monocyte count	AST (SGOT) ALT (SGPT) Creatinine Total bilirubin	Urinalysis (blood, protein, glucose, by dipstick; microscopic examination of sediment if abnormalities on urine dipstick) Calculation of the creatinine clearance determined by the Cockcroft-Gault formula or site's standard formula. Pregnancy Test (urine or serum)
Baseline and during the Treatment Period		
Hematology	Blood Chemistry	Other
Hemoglobin Platelet count WBC count Absolute neutrophil count Absolute lymphocyte count Absolute monocyte count	Alkaline phosphatase AST, ALT Total bilirubin Calcium (total or ionized) Magnesium Potassium Sodium BUN or urea Albumin	Pregnancy test (urine or serum) at baseline. In case of serum sample, pregnancy test needs to be conducted within 72 hours prior to Cycle 1 Day 1. In case of urine sample, pregnancy test needs to be conducted on Cycle 1 Day 1 before study treatment is started. Pregnancy test (urine or serum) at end of treatment if mandated by institutional policy or at the discretion of the investigator.

7.3.3 Vital Signs

Vital signs include pulse rate, sitting or supine blood pressure, respiratory rate and body temperature.

The information will be recorded in the subject's medical records and if clinically significant, data will be recorded as an AE in the CRF.

8. ADVERS`E EVENT REPORTING

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain adequate information both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE requiring immediate notification by drug label. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator.

As part of ongoing safety reviews conducted by the investigator any non-serious AE that is determined by the investigator to be serious will be reported as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1 Reporting Period

For SAEs, the active reporting period to the investigator or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, i.e., prior to undergoing any study-related procedures and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product regardless of the start of any subsequent cancer therapy. SAE should be reported via the CRF in the active reporting period. Following the active safety reporting period, other SAEs of which the investigator becomes aware should be reported to drug provider, unless the SAE is attributed by the investigator to complications of either the underlying malignancy or any subsequent anti-cancer therapy or to the patient's participation in a subsequent clinical study.

Non-serious adverse events should be recorded on the CRF from the time the subject has taken at least one dose of study treatment through last subject visit.

If a subject begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started.

8.2 Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation during which a subject is administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Exposure during pregnancy;
- Exposure via breast-feeding;
- Medication error.

Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as an AE.

8.3 Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered an AE by the investigator.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.4 Serious Adverse Events

A SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as a SAE unless the outcome is fatal within the safety-reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as a SAE. If the malignancy has a fatal outcome during the study or within the safety-reporting period, then the event leading to death must be recorded as an AE and as a SAE with CTCAE Grade 5 (see Section 8.6).

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.4.1 Potential Cases of Drug Induced Liver Injury

Abnormal values in AST and/or ALT concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT ≥3 times ULN concurrent with a total bilirubin ≥2 times ULN with no evidence of hemolysis and an alkaline phosphatase ≤2 times ULN or not available.

- For subjects with pre-existing AST or ALT or total bilirubin values above ULN, the following threshold values should be used in the definition mentioned above:

- For subjects with pre-existing AST or ALT baseline values above the normal range: AST or ALT ≥2 times the baseline values and ≥3 times ULN, or ≥ 8 times ULN (whichever is smaller).

concurrent with

- For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin of ≥2 times ULN and increased by >1 time the ULN or ≥3 times ULN (whichever is smaller) with no evidence of hemolysis and an alkaline phosphatase ≤ 2 times ULN or not available.

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment and the possibility of hepatic neoplasia (primary or secondary) should be considered. In addition to repeating AST and ALT, laboratory tests should include albumin, creatinine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time, international normalized ratio, and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced patient, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (e.g., biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal liver function tests.

Such potential Hy's Law cases should be reported as SAEs.

8.5 Hospitalization

Adverse events reported from studies associated with hospitalization or prolongations of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (e.g., caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself a SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (e.g., for work-up of persistent pre-treatment laboratory abnormality);
- Social admission (e.g., subject has no place to sleep);
- Administrative admission (e.g., for yearly physical examination);
- Study-specified admission during a study (e.g., for a procedure required by the study protocol);
- Hospitalization for observation without a medical AE;
- Optional admission not associated with a precipitating clinical AE (e.g., for

elective cosmetic surgery);

- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire study and/or for the individual subject;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs; however, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.6 Severity Assessment

All AEs must be graded according to CTCAE v5.0 (http://ctep.cancer.gov/reporting/ctc.html).

GRADE	Clinical Description of Severity
0	No Change from Normal or Reference Range
1	MILD Adverse Event
2	MODERATE Adverse Event
3	SEVERE Adverse Event
4	LIFE-THREATENING OR DISABLING Adverse Event
5	DEATH RELATED TO Adverse Event

A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.7 Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the Sponsor (see Section 8.11). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines a SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.8 Exposure During Pregnancy

For investigational products, an exposure during pregnancy (also referred to as exposure in-utero [EIU]) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been directly exposed to (e.g., environmental exposure) the investigational product, or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to the investigational product (maternal exposure);
- A male has been exposed, either due to treatment or environmental, to the

investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy (paternal exposure).

If any study subject or study subject's partner becomes, or is found to be, pregnant while receiving the investigational product or within 28 days of the last treatment on study, the investigator must submit this information to drug provider on an Exposure-in-Utero Form. In addition, the investigator must submit information regarding environmental exposure to lorlatinib in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the Exposure-in-Utero Form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery (see below for information related to induce termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information on all EIU reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination (i.e., induced or spontaneous abortion) and then notify drug provider of the outcome. The investigator will provide this information as a follow up to the initial Exposure-in-Utero Form. The reason(s) for an induced abortion should be specified. An EIU report is not created when an ectopic pregnancy report is received since this pregnancy is not usually viable. Rather, a SAE case is created with the event of ectopic pregnancy.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth or neonatal death]), the investigator should follow the procedures for reporting SAEs.

In the case of a live birth, the "normality" of the newborn can be assessed at the time of birth (i.e., no minimum follow-up period of a presumably normal infant is required before an Exposure-in-Utero Form can be completed). The "normality" of an aborted

fetus can be assessed by gross visual inspection, unless pre-abortion test findings are suggestive of a congenital anomaly.

Additional information about pregnancy outcomes that are classified as SAEs follows:

- "Spontaneous abortion" includes miscarriage and missed abortion;
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 1 month that the investigator assesses as possibly related to the exposure during pregnancy to the investigational medication should be reported.

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Exposure-in-Utero Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document on the Exposure-in-Utero Form that the subject was given this letter to provide to their partner.

8.9 Withdrawal Due to Adverse Events

Withdrawal due to an AE should be distinguished from withdrawal due to insufficient response, according to the definition of an AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws due to a SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.10 Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

8.11 Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If a SAE occurs, expedited reporting will follow local and international regulations, as appropriate. Adverse events should be reported using concise medical terminology on the CRF.

8.11.1 Serious Adverse Event Reporting Requirements

For all SAEs, the investigator is obligated to pursue and provide information to drug provider in accordance with the timeframes for reporting. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to the drug provider or its designated representative.

8.11.2 Non-Serious Adverse Event Reporting Requirements

Non-serious adverse events should be recorded on the CRF from the time the subject has taken at least one dose of study treatment through last subject visit.

8.11.3 Reporting Requirements to Regulatory Authorities

Adverse event reporting, including suspected serious unexpected adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated and maintained by the investigator. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint and/or its analysis will also be reflected in a protocol amendment.

9.1 Sample Size Determination

According to the Simon's 2-stage mini-max design, the null hypothesis that the PCR rate is ≤ 10% will be tested against a 1-sided alternative. In the first stage, 15 patients will be accrued. If there are 1 or fewer pCR in these 15 patients, the study will be stopped early for futility. Otherwise, 10 additional patients will be accrued for a total of 25. The null hypothesis will be rejected if 6 or more PCR are observed in 25 patients. This design yields a type I error rate of 0.05 and power of 0.80 when the true PCR rate is 30%.

9.2 Efficacy Analysis

9.2.1 Analysis Populations

The following subject populations will be assessed:

Full-Analysis-Set (FAS) Population

The FAS will include all participants who are enrolled. The FAS will be the primary population for evaluating all efficacy endpoints and participant characteristics.

Safety-Analysis-Set (SAT) Population

The SAT Population will include all subjects who receive at least 1 dose of study medication. The SAT Population will be the primary population for evaluating

treatment administration/compliance and safety. Efficacy endpoints may be assessed in this population as well.

9.2.2 Definition of Primary Endpoint

Pathological complete remission (pCR): It is defined as absence of any residual cancer cell in both the primary tumor lesion and lymph node specimens assessed post-surgery.

9.2.3 Analysis of Primary Endpoint

Pathological complete response (pCR): It refers to absence of any residual cancer cell in both the primary tumor lesion and lymph node specimens assessed post-surgery.

Descriptive data analyses will be conducted for both primary and secondary objectives. Categorical variables will be summarized including the number of non-missing observations, the frequency of the observed endpoint as well as the observed proportion. Continuous variables will be summarized including the number of non-missing observations, mean (Standard Deviation [SD]), median, Q1, Q3, and the minimum/maximum.

- pCR will be summarized using frequency counts and percentages with 95% CIs.
- Continuous variables in surgical outcomes will be summarized using median and range.

Categorical variables in surgical outcomes, safety and tolerability will be summarized using frequency counts and percentages.

9.2.4 Definitions of Secondary Efficacy Endpoints

Major pathologic response (MPR): defined as ≤10% residual viable tumor cells histologically detected in the resected primary tumor and all resected lymph nodes after surgery.

Objective response rate (ORR): defined as a complete response or a partial response at the presurgical radiologic evaluation, based on the investigator's assessment according to RECIST v1.1;

Surgical outcomes and intraoperative events:

Rate of lymph node downstaging: It is defined as the proportion of patients who have completed the neoadjuvant lorlatinib treatment before surgery and have achieved a N stage downing of the tumor as confirmed by CT evaluation after 6 weeks in all patients who have completed the treatment.

Unanticipated delays to surgery: It is defined as the proportion of patients who have unanticipated delays to surgery > 6 weeks after completion of neoadjuvant treatment.

Surgical complication rate: It is defined as the proportion of patients who have completed the surgery after neoadjuvant lorlatinib treatment.

Safety and tolerability per NCI-CTCAE v5.0.

9.2.5 Analysis of Secondary Endpoints

All analyses will be performed using the FAS.

Objective Response on each treatment arm will be summarized based on the investigator's assessment. The number and percent of subjects achieving objective response (CR or PR) will be summarized along with corresponding 2-sided 95% CI using the binomial distribution.

MPR rate refers to the proportion of patients ≤10% residual viable tumor cells histologically detected in the resected primary tumor and all resected lymph nodes after surgery assessed by the investigator.

Descriptive data analyses will be conducted for both primary and secondary objectives. Categorical variables will be summarized including the number of non-missing observations, the frequency of the observed endpoint as well as the observed proportion. Continuous variables will be summarized including the number of non-missing observations, mean (Standard Deviation [SD]), median, Q1, Q3, and the minimum/maximum.

- MPR, and ORR will be summarized using frequency counts and percentages with 95% CIs.

- Continuous variables in surgical outcomes will be summarized using median and range.

Categorical variables in surgical outcomes, safety and tolerability will be summarized using frequency counts and percentages.

Descriptive statistics will be used to summarize subject characteristics, study conduct, subject disposition, treatment administration/compliance, and safety parameters.
Data will also be displayed graphically, where appropriate.

9.3 Safety Analysis

The SAT Population will be the primary population for evaluating safety.

All subjects who receive at least one dose of study medication will be included in the summaries and listings of safety data. The overall safety profile and toleration of lorlatinib will be characterized by type, frequency, severity (as graded by CTCAE v5.0), timing and relationship of study treatment of AEs and laboratory abnormalities, by

treatment arm, as appropriate.

10. STUDY ORGANISATION AND COMMITTEES

10.1 Study Coordination

The study is an investigator-initiated trial conducted by Peking University People's Hospital.

10.2 Trial Management Committee

The Trial Management Committee will oversee study planning, monitoring, progress, review of information from related research, and implementation of recommendations from other study committees and external bodies (e.g. ethics committees).

11. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, the investigator will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practice (GCP) are being followed. The investigator will review source documents to confirm that the data recorded on CRFs are accurate. The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections, and that sufficient time is devoted to the process.

12. DATA HANDLING AND RECORD KEEPING

12.1 Case Report Forms/Electronic Data Record

As used in this study, the term CRF should be understood to refer to an electronic data record. Some of the sourced documents may be in paper format but whenever possible these should be transferred to an electron format.

A CRF is required to be completed for each subject who provides informed consent. The completed original CRFs are the sole property of investigator and should not be made available in any form to third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator’s site and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

12.2 Record Retention

The investigator will keep records, including the identity of all participating subjects (i.e., sufficient information to link records such as CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), local regulations, or as specified in the Clinical Study Agreement, whichever dictates a longer period. The study records must be transferred to a designee, such as another investigator, another institution, or to an independent third party.

13. ETHICS

13.1 Institutional Review Board /Independent Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, study amendments, informed consent forms, and other relevant documents (e.g., recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC in writing immediately after the implementation.

13.2 Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), and the Declaration of Helsinki (World Medical Association 1996 and 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

13.3 Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any forms, reports, publications, or in any other disclosures, except where required by law.

The informed consent form must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC before use.

The investigator must ensure that each study subject, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent form.

13.4 Subject Recruitment

Advertisements approved by IRB/IEC and investigator databases may be used as recruitment procedures.

14. PUBLICATION OF STUDY RESULTS

The investigator will, on request, remove any previously undisclosed confidential information (other than the study results themselves) before disclosure.

The first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - “Ethical Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is defined in the Clinical Study Agreement between the Sponsor and the institution. In this section, entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

16. REFERENCES

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APPENDIX 1 ECOG Performance Status

12.

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

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APPENDIX 2 Medications with Potential PR Interval Prolongation Effect

24. Note that the drugs listed below are examples and this is not intended to be an all-inclusive listing

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Electrophysiologic Effects of Select Drugs on PR Interval Based on Product Labeling		
Drug	**Action**	**Indications**
Affecting AV nodal conduction (PR interval		
Adenosine	Adenosine receptor	PSVT
Amiodarone	Cardiac ion channels	Antiarrhythmics
Disopyarmide		
Encainide		
Flecainide		
Moricizine		
Propafenone		
Verapamil		
Arsenic trioxide	Multiple actions	Acute promyelocytic Leukemia
Atazanavir	HIV-protease inhibitors	Antiretroviral inhibitor
Lopinavir/Ritonavir		

Saquinavir		
Digoxin	Multiple actions	Congestive heart failure
Dolasetron	5HT3 receptor antagonist	Antiemetic
Fingolimod	S1P receptor modulator	Multiple sclerosis
Lacosamide	Not fully characterized	Partial-onset seizures
Pregabalin	Not fully characterized	Neuropathic pain
Mefloquine	Plasmodicidal effects	Antimalarial
Drugs were initially screened using the PDR3D database for PR interval prolongation using terms "PR interval prolongation", "AV block", "AV conduction delay", or "heart block". Drugs were subsequently selected for inclusion on the basis on descriptions of PR interval prolongation/AVB contained with Warning or Precautions sections of drug labels. PSVT, Paroxysmal supraventricular tachycardia.		

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APPENDIX 3 RECIST Version 1.1

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33. Adapted from E.A. Eisenhauer, et al: New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247.

34. CATEGORIZING LESIONS AT BASELINE

35. Measurable Lesions

36. Lesions that can be accurately measured in at least one dimension.

37. Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm)

38. Lesions with longest diameter at least 20 mm when assessed by Chest X-ray

39. Superficial lesions with longest diameter 10 mm or greater when assessed by caliper

40. Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

41. NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for

all other measurable lesions.

42. Non-measurable disease

43. Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

44. Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.

45. Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

46. Normal sites

47. Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.

48. Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

49. RECORDING TUMOR ASSESSMENTS

50. All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

51. Target lesions

52. All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

53. If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

54. Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

55. Non-target disease

56. All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

57. OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

58. Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

59. Target disease

60. Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis < 10 mm). All target lesions must be assessed.

61. Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.

62. Stable Disease (SD): Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.

63. Progression Disease (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.

64. Indeterminate: Progression has not been documented, and

65. one or more target measurable lesions have not been assessed

66. or assessment methods used were inconsistent with those used at baseline

67. or one or more target lesions cannot be measured accurately (e.g., poorly visible unless due to being too small to measure)

68. or one or more target lesions were excised or irradiated and have not reappeared or increased.

69. Non-target disease

70. CR: Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be 'normal' in size (<10 mm short axis).

71. Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.

72. PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

73. Indeterminate: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

74. New Lesions

75. The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is

equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

76. Supplemental Investigations

77. If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy. If no disease is identified, objective status is CR.

78. If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy to clarify status.

79. Subjective Progression

80. Subjects requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as discontinuation due to Global Deterioration of Health Status. Every effort should be made to document objective progression even after discontinuation of treatment.

81. Table 1. Objective Response Status at Each Evaluation

Target Lesions	Non-target Disease	New Lesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate, or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate, or Missing	No	Stable
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

82. If the protocol allows enrollment of patients with only non-target disease, the following table will be used:

83. Table 2. Objective Response Status at each Evaluation for Patients with Non-Target

Disease Only

Non-target Disease	New Lesions	Objective status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Indeterminate	No	Indeterminate
Unequivocal progression	Yes or No	PD
Any	Yes	PD

84.

85. Best Overall Response

86. The best overall response (BOR) is the best response recorded from the start of treatment until disease progression. This is derived from the sequence of objective statuses. Objective statuses are not considered after objective progression is documented or after start of the first anticancer treatment post discontinuation of protocol treatment. BOR for each patient will be derived as one of the following categories.

87. **Complete Response (CR)**: At least one objective status of CR documented before progression.

88. **Partial Response (PR)**: At least one objective status of PR documented before progression.

89. **Stable Disease (SD)**: At least one objective status of stable documented at least 8 weeks after start of treatment date and before progression but not qualifying as CR, PR.

90. **Progressive Disease (PD):** Objective status of progression within 12 weeks of start of treatment date, not qualifying as CR, PR or SD.

91. **Indeterminate (IND):** Progression not documented within 12 weeks after start of treatment date and no other response category applies.