Investigation drug：LORBRENA **Trial phase：Investigator Initiated**

An Investigator Sponsored Research

A real-world study to explore therapeutic changing mode of locally therapy during 1L lorlatinib treatment in unresectable ALK+ NSCLC patients

Clinical Study Protocol

Sponsor: Beijing Cancer Hospital

Principal Investigator: Jun Zhao

Version/ date: The 3.0 Version 25/09/2024

Participating units

Sponsor

Name: Beijing Cancer Hospital

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Principal Investigator: Jun Zhao

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PROTOCOL SIGNATURE PAGE

I will be in accordance with the "Drug clinical trial management norms (GCP)" provisions, the implementation of the work entrusted by the sponsors and tasks. Agree to carry out the clinical study according to the design and regulation of this protocol.

Sponsor：Beijing Cancer Hospital

Principal Investigator:

Date:

PROTOCOL SIGNATURE PAGE

1. I will personally participate in and direct the clinical study.

2. I have read the clinical trial protocol and agreed to conduct the study in accordance with the ethical and scientific principles of the Declaration of Helsinki and the GCP, modifications to the scheme are made only after notification to the sponsor and are subject to the consent of the ethics committee, unless urgent measures are required to protect the safety, rights and interests of the subject.

3. I will ensure that all subjects sign a written informed consent form before entering the study as required by the GCP.

4. I will be responsible for making medical decisions related to the trial and ensuring that participants receive appropriate treatment if adverse events occur during the trial.

5. I will ensure that the data is recorded truthfully, accurately, completely and in a timely manner. I will be supervised and inspected by inspectors or inspectors from contract research organizations to ensure the quality of clinical trials.

6. I promise to keep the subject information and related matters confidential, and I have been informed that I will be held liable for any breach of this promise.

Research Unit：

Principal Investigator:

Date:

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1. INTRODUCTION

Lung cancer is the most fatal malignancy in China, as estimated by National Cancer Center of China, [1] accounting for 828,100 new cases, and 657,000 deaths in 2016. 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] Since the first anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKI) approved in United States in 2011 and 2013 in China, the response and overall survival of ALK-positive NSCLC patients were significantly improved as compared with empiric chemotherapy.[3] Subsequently, more second-generation ALK TKIs emerged, including alectinib, brigatinib, ceritinib and ensartinib, [4-8] with notably longer median progression free survival (mPFS) and higher intracranial response rate. However, drug resistance yet develops inevitably, mostly due to ALK resistant mutation (e.g., I1171N, L1196M and G1202R),[9,10] and intracranial progression, a major cause of illness and death. [11-15]

Lorlatinib (Pfizer) is a novel third-generation ALK TKI that is more potent than second-generation ALK TKIs in biochemical and cellular assays and has the broadest coverage of ALK resistance mutations that have been identified.[9,16,17] Lorlatinib was designed to cross the blood–brain barrier in order to achieve high exposures in the central nervous system (CNS).[18,19] In phase 1 and 2 studies, lorlatinib had potent antitumor activity after the failure of previous ALK TKIs (first-generation, second-generation, or both).[19,20] In particular, lorlatinib had marked intracranial activity in previously treated patients with baseline CNS disease, including leptomeningeal disease.[11,12,20] In an ongoing China only phase 2 study, lorlatinib exhibited highly consistent antitumor activity, intracranial efficacy and safety profile as global phase 2 study in patients with progression on ALK TKIs,[21] reconfirming superior efficacy of lorlatinib in combating ALK resistance.

The CROWN trial is a global, randomized, phase 3 trial comparing lorlatinib (n=149) with crizotinib (n=147; the standard-of-care first-line treatment at the time of trial

initiation) in patients with previously untreated advanced ALK-positive NSCLC.[22] At the time of first data cutoff, the mPFS was not reached (NR; 95% confidence interval [CI], NR=NR) in the lorlatinib group, as compared with 9.3 months (95% CI, 7.6-11.1) in the crizotinib group by BICR. The percentage of patients who were alive without disease progression at 12 months was 78% in the lorlatinib group and 39% in the crizotinib group (hazard ratio, 0.28, 95% CI, 0.19-0.41); P<0.001, one-sided). The hazard ratio favored lorlatinib over crizotinib across all prespecified patient subgroups defined according to baseline characteristics and stratification factors. At the second data cutoff, the mPFS was yet NR (95% CI, NR-NR) in the lorlatinib group, as compared with 9.3 months (95% CI, 7.6-11.1 months) in the crizotinib group by BICR.[22] 24-month and 36-month PFS rate were distinctly higher in the lorlatinib group of 68.2% and 63.5%, as compared with 21.5% and 18.9% in the crizotinib group (hazard ratio, 0.27, 95% CI, 0.184-0.388). For patients with measurable brain metastases at baseline, lorlatinib achieved 72% intracranial complete response (CR) rate, and 83% intracranial objective response rate (ORR). Time to intracranial progression by BICR was remarkably longer with lorlatinib than crizotinib in the intention-to-treat population as well as in patients with and without baseline brain metastases, in which 8 out of 37 patients with baseline brain metastases and only 1 out of 112 patients without baseline brain metastases had intracranial progression after median follow-up over 36 months. This indicates that lorlatinib possesses the potential to clear existing brain metastases, meanwhile prevents new metastatic lesions in the brain.

In consideration of high intracranial activity and 63.5% PFS rate and not reached mPFS after 36.7 months follow-up in the CROWN trial,[22] ALK-positive NSCLC patients shall benefit most using lorlatinib in the first-line treatment in the clinical practice. Nevertheless, only 10 ALK+ NSCLC patients were randomized to the lorlatinib group in China mainland, and published data of clinical trials regarding first-line treatment of lorlatinib is still limited to CROWN trail. There is a vast vacancy of efficacy and safety regarding first-line lorlatinib treatment in China ALK-positive NSCLC patients. Further,

first-line resistance mechanism of lorlatinib is still ambiguous,[23] the sequencing therapy after PD of first-line lorlatinib is far from definite, and how lorlatinib benefiting ALK-positive NSCLC patients in clinical practice beyond CROWN criteria should be further explored. There is no clear answer so far to these clinically relevant questions.

In addition, recent clinical studies have shown that continuation of TKI treatment beyond progression in patients with oligometastasis NSCLC can be an effective strategy to target tumor cells that still addicted to the EGFR pathway and prevent the disease flare observed after discontinuation of the targeted agent. [24,25]Further more, for patients with oligometastases （means target lesions with residual disease ，definition a maximum of 3 organs, and no more than 5 lesions in total）, treatment should be considered in combination with local therapeutic approaches, such as surgery, local ablation or radiotherapy, to improve disease control and thereby long-term survival outcomes.[26] However, no studies have yet reported whether patients with ALK+ NSCLC can also benefit from the above treatment mode.

This real-word study is designed to prospectively explore whether local treatment (surgery, ablation, radiotherapy and others) can prolong the time to treatment discontinuation during 1L lorlatinib treatment in Chinese patients with unresectable ALK^+ NSCLC. Since this is a non-interventional study (NIS) to observe the routine practice, there will not be any study required clinical interventions or laboratory assessments. Participation in this study is not intended to change the routine treatment received as determined by their attending physicians. Patients will be treated according to the routine medical practice in terms of visit frequency and types of assessments performed.

This study will enroll patients with ALK-positive non-small cell lung cancer locally diagnosed in about 6 sites in China from study setup to about Oct 2025, as the target observation population. Patients’ effectiveness and safety data of first line treatment with lorlatinib will be collected after their first dose until the 60th month or patient death, loss to follow-up, or withdrawal from the study for any reason. The visit schedule

during study is not mandatory and follow local routine clinical practice.

The study data will be generated from the attending physician's routine clinical assessment during standard care. The data source used for data collection will be from electronic medical records/medical records or medical charts or other approved data source.

The database lock date is about Oct 2030 or the date of the death of the last enrolled patient.

2. STUDY OBJECTIVES

2.1. Objectives

Primary Objective:

- To evaluate the time-to treatment discontinuation (TTD) of lorlatinib with locally therapy in unresectable ALK-positive NSCLC patients who have received 1L lorlatinib in real-world settings;

Secondary Objectives:

- To evaluate the rwORR, rwDCR and real-world intracranial ORR, intracranial time to progression (IC-TTP) and TTP of 1L lorlatinib in real world setting ;
    - To explore the progression pattern in this therapeutic changing mode;
- To evaluate 1/2/3/4/5-year overall survival (OS) rate and OS of in each treatment cohort;
- To explore the association between the effectiveness of lorlatinib in first line for Chinese patients with ALK-positive locally advanced or metastatic NSCLC patients with baseline brain metastases (Yes or No) ， ALK Fusion Variants ([V1, V2, V3] and

TP53 mutation status [TP53 mutation, TP53 WT]) if data is available in medical records;

- To evaluate the safety and tolerability of the therapeutic changing mode;
    - To explore the adverse events (AEs), the dose modification and the reason for interruption or discontinuation of lorlatinib in first line for Chinese ALK-positive locally advanced or metastatic NSCLC recorded in medical records;
    - To evaluate patient-reported outcomes (PROs) of health-related quality of life for this therapeutic mode;
    - To describe the demographic, clinicopathological and baseline co-mutation characteristics of enrolled patients.

Exploratory Objectives:

- To explore dynamic ctDNA change during lorlatinib treatment;
- To evaluate candidate biomarkers of sensitivity or resistance to lorlatinib in no-prior ALK-TKIs treatment tumor tissue and peripheral blood if available in real world setting;

2.2. Endpoints

Primary Endpoint:

- Time-to treatment discontinuation (TTD) is defined as the time from start of treatment to the date of discontinuation of these therapeutic methods.

Secondary Endpoints:

- Effectiveness: Objective Response Rate (ORR), duration of response (DOR) and TTP based on investigator's assessment; intracranial ORR (IC-ORR), IC-time to progression (IC-TTP), progression pattern ,1/2/3/4/5-year rwOS rate and OS;
- Safety: To explore the adverse events (AEs), the dose modification and the reason

for interruption or discontinuation of lorlatinib in first line for Chinese patients with ALK-positive locally advanced or metastatic NSCLC recorded in medical records;

- Adverse Events (AEs), as graded by NCI CTCAE (National cancer Institute Common Terminology Criteria for Adverse Events) v5.0; laboratory abnormalities (as graded by NCI CTCAE v5.0); vital signs (blood pressure, pulse rate) and body weight; electrocardiograms (ECGs); echocardiogram or MUGA (multigated acquisition) scan; ophthalmologic data;

- PRO as assessed by EORTC (European Organization for Research and Treatment of Cancer) QLC-C30;

- To describe the demographic, clinicopathological and baseline co-mutation characteristics of enrolled patients.

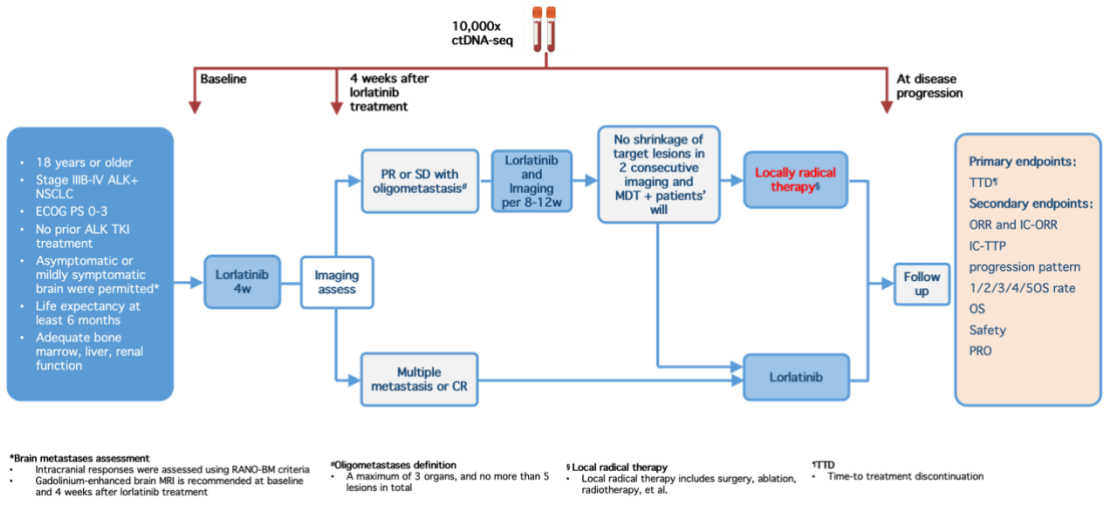
Exploratory Endpoints:

- Dynamic molecular response associated with lorlatinib treatment using ctDNA as measured by next-generation sequencing (NGS) if available in real world setting ;

- Biomarkers of sensitivity or resistance to lorlatinib in no-prior ALK-TKIs treatment tumor tissue and peripheral blood if available in real world setting;

3. STUDY DESIGN

Figure 1. Study Design



3.1 Study design

This is a prospective，observational，multi-center, parallel-group, real world study to explore therapeutic changing mode of locally therapy after 1L lorlatinib treatment in unresectable ALK-positive Non-Small Cell Lung Cancer (NSCLC). Patients with unresectable NSCLC must have no previous systemic treatment for advanced (Stage IIIB/C not amenable for multimodality treatment) or metastatic (Stage IV) disease.All subjects must have tumors that test, positive for ALK rearrangement, with methods of Ventana ALK (D5F3), fluorescence in situ hybridization (FISH), polymerase chain reaction (PCR), or next generation sequencing (NGS), or circulating tumor DNA (ctDNA) for ALK rearrangement, with method of NGS. All tumors will be of histo- and/or cytopathology consistent with NSCLC, (e.g., adenocarcinoma, Squamous-cell carcinoma, or mixed), or its pathologically accepted variants.

The study will collect and analyze effectiveness, safety, PRO of lorlatinib in first-line from approximately 100 ALK positive locally advanced or metastatic NSCLC patients from study beginning to last subject last visit across approximately 8 sites in the real-world setting in China.

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. 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).

After lorlatinib treatment for 4 weeks, patients will receive an imaging assess. The patients who achieve PR or SD with oligometastasis (refer to target lesions with residual disease, a maximum of 3 organs, and no more than 5 lesions in total) should continue lorlatinib treatment and will receive imaging assess per 8-12 weeks. If target lesions indicate stable in 2 consecutive imaging, investigators will organize MDT and comprehensively evaluate patients' will to decide and choose local therapy. The local therapy includes surgery, ablation and, radiotherapy et al. After local therapy, patients should continue taking lorlatinib. While those who achieve CR or with multiple metastasis will continue lorlatinib treatment without any local therapy.

To dynamically monitor ctDNA changes in ALK + NSCLC patients during Lorlatinib treatment; to explore the correlation between ctDNA and Lorlatinib treatment efficacy .Patients need check the ctDNA-seq (10000x) in plamsa with NGS at baseline,4weeks after lorlatinib treatment and at disease progression.

Subjects will be on lorlatinib therapy until disease progression or unacceptable toxicity, new systemic anticancer therapy instituted, withdrawal of consent, death, or investigator decision dictated by protocol compliance, whichever occurs first.

Patients received continuous daily PO dosing of lorlatinib 100mg QD with/without locally therapy, from the date of first dosing (per the current protocol) or until one of the following criteria were met (whichever occurred first): disease progression; initiation of a new anti-cancer therapy; unacceptable toxicities; global deterioration of health-related symptoms; pregnancy; withdrawal of consent; loss to follow-up; death; investigator decision dictated by protocol non-compliance; or study termination. Patients who have progressive disease (PD) (per RECIST v1.1, by investigator review) and for whom the investigator believes it is in their best interest to continue lorlatinib treatment are allowed to continue lorlatinib therapy, at the discretion of the investigator, until any alternate or additional systemic anti-cancer therapy regimen was implemented.

At the time of progression and termination of study treatment, the patients could receive

any therapy at the judgment of the investigator. This study will take 1 years to enroll subjects, and each subject will be followed up for survival status and subsequent cancer therapies up to 60 months from the date of first dosing.

Participation in this study is not intended to change the routine treatment received as determined by their attending physicians. Patients will be treated according to the routine medical practice in terms of visit frequency and types of assessments performed.

Upon site initiation, investigators will consecutively enroll eligible patients into this study after obtaining patients' informed consent. The observation period for each patient is planned to be 60 months, starting from the patients who received lorlatinib enrolled in this study and ending at the earliest occurrence of the completion of 60 months of follow-up, death, loss to follow-up, or withdrawal from the study. The study data will be generated from the attending physician's routine clinical assessment during standard care. The data source used for data collection will be from electronic medical records/medical records or medical charts or other approved data source.

The study duration will be approximately 6 years. The enrollment period is planned to be about 12 months (from first site initiation, until the planned number of patients reached). The follow-up period per patient is up to 60 months from the time patients who received lorlatinib enrolled in this study. The interim analysis will be performed when half TTD events happen. The study is expected to be closed in about Oct 2030.

Safety and effectiveness 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, and LVEF imaging. Contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) was used for tumor assessment at screening,at baseline, 4 weeks after lorlatinib treatment and then every 8-12 weeks. For patients with brain metastases,

RANO-BM criteria was used for intracranial lesions. Gadolinum-enhanced brain MRI is recommended at baseline and 4 weeeks after lorlatinib treatment.

A post-treatment follow-up visit for safety occurred at least 28 days, and no more than 35 days, after discontinuation of treatment. All patients (regardless of the reason for discontinuation from study treatment) were to be followed for subsequent anti-cancer systemic therapies and survival status approximately every 6 months from the post-treatment follow-up visit, for up to 60 months from the date of first dosing (per the current protocol). Patients with no evidence of disease progression at the time of permanent treatment discontinuation were to be followed until disease progression; for these patients, repeat tumor assessments were suggested to occur approximately every 8-12 weeks from the date of the CT/MRI at the end-of-study treatment.

Subjects should be instructed to take their medication at approximately the same time every day.

Throughout the study, there was no fixed schedule of visits and safety assessments and effectiveness assessments will follow local clinical routine.

Data Source/Data Collection:

Data will be collected from approximately 8 hospitals. The data is sourced from the hospital information system (HIS)/electronic medical record (EMR)/laboratory information system (LIS)/ picture archiving and communication system (PACS), and genetic testing report data. All data collection will be done using LinkDoc data management platform. All data are based on medical records or genetic testing reports if available. The investigators at the sites are responsible for ensuring that the required data is collected and entered into the LinkDoc data management platform.

For each patient, the attending physician will document the clinical information during the initial visit, follow-up visits, and the final visit. The attending physician will document the baseline data (demographic and baseline disease characteristics) from medical records or through an interview at an initial visit. When patients who received

lorlatinib enrolled in this study, follow-up visits are performed by investigator to collect study-related data, including data on effectiveness, tumor status, and other study required variables. A final data collection will be performed at death, withdrawal of consent, loss to follow-up, or the end of the study which is the earliest occurrence. There is no fixed visit schedule; visits will follow local routine clinical practice. Data will be collected until the 60th month after patient enrolled in this study (last follow-up time) or the death of patients due to any cause, loss to follow-up or withdrawal from the study which is the earliest occurrence.

Data type:

The clinical data collected for this study include, but is not limited to:

Collect patients' baseline demographic information (including age at diagnosis, gender, height, weight, physical examination, smoking status), ECOG score, past history, baseline disease characteristics (disease stage, molecular typing, pathological diagnosis), laboratory test results (blood routine, urine routine, blood biochemistry, coagulation function tests, electrocardiogram, echocardiography, vital signs), ALK genetic testing methods and results, test specimen types, imaging tests (tumor assessment[size, number, and location], medication treatment, adverse events, post-resistance gene testing, dose modification regimens, reasons for lorlatinib dose modification, interruption or discontinuation, PRO (if data is available in clinical practice) and survival status.

Collection and recording of SAEs and AEs will commence once the study participant has provided informed consent and terminate till 28 (and no more than 35) days after administration of the last dose of lorlatinib. After this period, only lorlatinib-related SAEs must be reported to the Pfizer. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient’s stable or chronic condition or intercurrent illness(es). All patients will be periodically contacted for survival and safety information unless the patient requests to be withdrawn from the study. Survival status is also encouraged to be confirmed through a telephone follow-up by the investigator or designee at the end of the study or withdrawal from the study.

3.2 Safety Plan

The overall safety profile and toleration of lorlatinib and locally 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 and treatment mode. Throughout the study, all patients treated with lorlatinib are followed for safety to assess the safety of lorlatinib, including AEs leading to dose modification, interruption or discontinuation of lorlatinib and other reasons for dose modification, interruption or discontinuation of lorlatinib in the medical records.

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 of the following inclusion criteria to be eligible for enrollment into the study:

1. Diagnosis:

   a. Study Population: Patients with histologically or cytologically confirmed diagnosis of locally advanced [(Stage IIIB/C not amenable for multimodality treatment) or metastatic (Stage IV) by American Joint Committee on Cancer (AJCC) v 7.0] ALK-positive NSCLC where ALK status is determined by the Ventana ALK (D5F3) Companion Diagnostic (CDx) IHC test performed on the Ventana ULTRA or XT Platforms, FISH, PCR, or next generation sequencing (NGS), or circulating tumor DNA (ctDNA).

b. Tumor Requirements: At least 1 measurable target lesion per RECIST v. 1.1 that has not been previously irradiated. Brain metastases are allowed.

2. No prior systemic treatment for advanced (Stage IIIB/C not amenable for multimodality treatment) or metastatic (Stage IV) disease.

3. Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0, 1, 2 or 3.

4. Age ≥18 years.

5. 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).

6. Life expectancy at least 6 months.

7. 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.

8. 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.

9. 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:

1. Major surgery within 4 weeks prior to randomization. Minor surgical procedures (e.g., port insertion) are not excluded, but sufficient time should have passed for adequate wound healing.

2. Radiation therapy within 2 weeks prior to enrollment, including stereotactic or partial brain irradiation. Patients who complete whole brain irradiation within 4 weeks prior to randomization or palliative radiation therapy outside of the CNS within 48 hours prior to randomization will also not be included in the study.

3. Gastrointestinal abnormalities, including inability to take oral medication; requirement for intravenous alimentation; prior surgical procedures affecting absorption including total gastric resection or lap band; active inflammatory gastrointestinal disease, chronic diarrhea, symptomatic diverticular disease; treatment for active peptic ulcer disease in the past 6 months; malabsorption syndromes.

4. Known prior or suspected severe hypersensitivity to study drugs or any component in their formulations.

5. 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.

6. 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.

7. Concurrent use of any of the following food or drugs (consult the sponsor if in doubt whether a food or a drug fall into any of the above 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).

8. 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.

9. Participation in other studies involving investigational drug(s) within 2 weeks prior to study entry and/or during study participation.

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, 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): disease progression; initiation of a new anti-cancer 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.

After lorlatinib treatment for 4 weeks, patients will receive an imaging assess. The patients who achieve PR or SD with oligometastasis(A maximum of 3 organs, and no more than 5 lesions in total) should continue lorlatinib treatment and will receive imaging assess per 8-12 weeks. If target lesions indicate stable in 2 consecutive imaging, investigators will organize MDT and comprehensively evaluate patients' will to decide and choose local therapy. The local therapy includes surgery, ablation and, radiotherapy et al. After local therapy patients should continue taking lorlatinib. While those who achieve CR or multiple metastasis will continue lorlatinib treatment without any local therapy.

Subjects who receive local therapy must observe the therapeutic plan and complete the process under the direction of investigators. They shouldn't use other drugs and methods that may influence the effects of investigational therapeutic mode.

Patients need check the ctDNA-seq (10000x)in plamsa with NGS at baseline, 4 weeks after lorlatinib treatment, and at disease progression if available.

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 in Table 1.

Table 1. 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 3 below. 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 RECIST-defined disease progression by the investigator.

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 2 below.

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

Table 2. 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.

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 -2/+2 weeks 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.

6.1 Baseline

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

Within 2 weeks prior to first study drug administration of lorlatinib, 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 first study drug administration of lorlatinib (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 first day of lorlatinib administration. In case of urine sample, pregnancy test needs to be conducted on Day 1 of lorlatinib administration 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). Subject who does not have adequate organ function will not start study treatment in the CC cohort;
    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 ≥10.0 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;
- Blood collection for a retrospective analysis for the presence of ctDNA.

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.

6.2 Study Period

6.2.1 Day 1 of the first 4 weeks

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;
- ECOG PS (see **Appendix 1**);
- Concomitant medication and AE data will be collected and reviewed.

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 8 weeks after completion of study drug).

6.2.2 Day 28 of the first 4 weeks (±2 days)

- Check the ctDNA-seq (10000x) in plamsa with NGS

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

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

- Vital signs and body weight will be measured;
- 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;
- Tumor assessments will occur at the end of the first 4 weeks and then following per 8-12 weeks. 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.

6.2.4 Local therapy

- Patients may be assigned to receive local therapy if stable of target lesions in 2 consecutive imaging during lorlatinib treatment, and the specific treatment will be at the discretion of the investigator or patients willingness.

6.2.5 Imaging

Either a CT or MRI scan (whichever was used at screening) of the tumor area will be conducted at the first 4 weeks and following per 8-12 weeks. The scan is to include the chest, Brain, liver, adrenal glands and other applicable sites of disease.

6.2.6 End of Treatment Visit

If a subject comes off treatment for progression of disease, 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.

- Vital signs and body weight will be measured;
- ECOG PS (see Appendix 1);
- Blood and urine samples will be collected (hematology, blood chemistry, coagulation, pregnancy test [if required], urinalysis;). 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;

6.2.7 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 or other medical facilities and the following assessments will be performed.

In case subjects continue on therapy after progressive disease, 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;
- 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.

6.2.8 Long-term Follow-up for Progression and Survival

Subjects with no evidence of disease progression at the time of treatment discontinuation should be followed up until disease progression, regardless of any start of subsequent cancer therapy. Repeat tumor assessments are suggested approximately every 8-12 weeks from the date of CT/MRI at the end of study treatment.

All subjects (including those who show disease progression) must be followed up for subsequent cancer therapies and survival status regardless of the reasons for discontinuation from study drug treatment approximately every 2-3 months from post treatment follow-up visit. Telephone contact or other means to obtain timely regular follow-up is recommended, including subjects who are subsequently followed by providers other than the investigator. The information for subsequent therapies collected and recorded on the LinkDoc should include enumeration of subsequent treatment, including drugs administered, date of initiation and discontinuation of each medication. Each subject will be followed up for survival status and subsequent cancer therapies up to 60 months from the date of first dosing of loraltinib.

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 Day 1 of the first 8 weeks, 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) in real world clinical practice .

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.

Post-baseline tumor assessments will be performed at the end of the first 8 weeks

then every cycle (within 7 days of the start of subsequent cycle including Day 1 of subsequent cycle), using the same method and technique used to characterize lesions identified at baseline. Imaging serves also as safety assessment to monitor/exclude pulmonary toxicity.

Subjects with no evidence of disease progression at the time of treatment discontinuation, should be followed up until disease progression, regardless of the start of any new cancer therapy. Repeat tumor assessments are suggested approximately every 4 weeks from the date of CT/MRI at the end of study treatment in the appropriate setting.

All subjects should be followed up for subsequent cancer therapies and survival status regardless of the reasons for discontinuation from study drug 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 enumeration of subsequent treatment, including drugs administered, date of initiation

and discontinuation of each drug. This may be conducted by telephone for unresponsive subjects. As per RECIST v1.1 guidelines, PR and CR do not need to be confirmed following initial response documentation. However, subjects with documented PR or CR should still be followed with regular assessments for the duration of the study to see if there is a change in status with time.

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 Blood Specimens for Circulating Nucleic Acid (CNA) Profiling

Collection of peripheral plasma samples optimized for nucleic acid analysis (e.g., circulating free DNA [ctDNA] or RNA [ctRNA]) will be mandatory for all patients at baseline, week 8. Markers that may be analyzed include, but may not be limited to ALK rearrangement, and ALK kinase domain mutations.

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 Day 1 of the first 8 weeks. In case of urine sample, pregnancy test needs to be conducted on Day 1 of the first 8 weeks 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 to the Sponsor or its designated representative. 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, and the Sponsor concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor any non-serious AE that is determined by the Sponsor to be serious will be reported by the Sponsor 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 Sponsor 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 Pfizer, 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.

9. DATA ANALYSIS/STATISTICAL METHODS

9.1 Sample Size Determination

The primary objective of this real-world study is to demonstrate that locally therapy during 1L lorlatinib is instrumental in prolonging TTD by investigator assessment per RECIST v1.1.

Approximately 100 patients who receive lorlatinib in first line are expected to be included in this study. Since this study is descriptive without specified hypothesis, the sample size is not determined based on statistical assumptions, but according to the following information: epidemiology, China marketing competition environment, marketing research report, drug availability, patient affordability, health insurance coverage, and at least 20% dropout rate. Comprehensively, the final sample size of this study is expected to reach for about 100 cases.

9.2 Effectiveness Analysis

9.2.1 Analysis Populations

The following subject populations will be assessed:

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.

Censoring for time-to-event efficacy endpoints (i.e., PFS and OS) will be elaborated in the SAT.

9.2.2 Definition of Primary Endpoint

Time-to treatment discontinuation (TTD) is defined as the time from start of treatment to the date of discontinuation of lorlatinib.

9.2.3 Analysis of Primary Endpoint

TTD will be summarized using Kaplan-Meier methods and displayed graphically. Potential influences of other demographic baseline characteristics including biomarker profile use parametrical text, $\chi 2$ or Fisher exact test .

9.2.4 Definitions of Secondary Efficacy Endpoints

Real world Intracranial Objective Response Rate is defined as the proportion of subjects with a BOR of either CR or PR of intracranial disease, where BOR is the best response recorded from the start of treatment until disease progression or start of other anticancer therapy in real world setting. As per RECIST v1.1 guidelines, PR and CR do not need to be confirmed following initial response documentation.

Real world Objective Response Rate is defined as the proportion of subjects with a BOR of either CR or PR, where BOR is the best response recorded from the start of treatment until disease progression or start of other anticancer therapy in real world setting. As per RECIST v1.1 guidelines, PR and CR do not need to be confirmed following initial response documentation.

Real world Disease control rate is defined as the proportion of patients with complete response (CR) or partial response (PR) or subjects with stable disease (SD) as per investigator assessment according to RECIST 1.1 criteria in real world setting.

Overall Survival is defined as the time from start of treatment to the date of death for any cause. In the absence of confirmation of death, survival time will be censored at the last date the subject is known to be alive.

Real world Intracranial Time To Progression is defined as the time from randomization to the date of the first documentation of objective progression of intracranial disease, based on either new brain metastases or progression of existing brain metastases in real world setting.

9.2.5 Analysis of Secondary Endpoints

rwPFS, IC-TTP and Overall Survival will be summarized using Kaplan-Meier methods and displayed graphically. The 1/2/3/4/5-year rwPFS, IC-TTP and survival probability will be estimated using Kaplan-Meier methods and the 2-sided 95% CI will be provided. Potential influences of other demographic, baseline characteristics including biomarker profile use parametrical text, $\chi 2$ or Fisher exact test. Objective Response Rate will be summarized for the SAT Population 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.

Intracranial Objective Response Rate will be summarized for the SAT Population based on the investigator's assessment. The assessment of intracranial response will be conducted on subjects with measurable and unmeasurable CNS metastases. 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.

Subgroup analysis is considered to be conducted by baseline characteristics such as CNS (Yes/No), TP53 status (Yes/No), ALK-EML4 fusion variant (V1, V2, V3) in patients with baseline who receive lorlatinib in first line. Depending on the actual sample size at the time of analysis, adjustment by either combining or re-classifying the subgroups will be applied as needed.

Subgroup comparisons, where is applicable, will be performed using the Kaplan-Meier method and the log-rank test. Statistically significant level of α=0.05 (two sides) is used for tests.

The qualitative exploratory endpoints will be categorized and summarized descriptively by count and percentage of patients. Missing data will be categorized by missing, unknown, or can't be determined.

The interim analysis will be performed when the completion of 2.5 year follow-up in late patient. The final full analysis will take place at the time of data cut-off (i.e. the completion of 60-month follow-up for all the participants).

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.

10. STUDY ORGANISATION AND COMMITTEES

10.1 Study Coordination

The study is an investigator-initiated, cooperative trial group trial.

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).

Selection Bias: Real-world study population is relatively unselected compared with randomized clinical trials in terms of stringent inclusion and exclusion criteria. However, selection bias still exists because the participants are not randomly drawn from the target population. First, patients will be recruited from particular sites that are characterized by the site's prevalent demographics, specific routine clinical practice procedures, and the different levels of experience in the investigators. Second, there is also selection bias due to loss to follow up (also known as informative censoring), which often happen when a patient can no longer be tracked due to various reasons such as hospital referral or migration.

Information Bias: Information bias due to missing data exists in almost all kinds of studies. In contrast to the prospective clinical trials, where study variables are intentionally prespecified and collected, the availability, completeness of the data in this study requires special attention since the data is originally recorded without any intervention to prevent missingness.

Generalizability: While the real-world study can include a wider population than randomized control studies, the generalizability of this study may still be affected by the geographic location of the sample study population and hospital specific characteristics and may lead to differences in variations in outcomes. The analysis

will be done for each site to validate generalizability of outcomes respective of geographic location of the participants. Furthermore, disease assessment will be based on evaluations performed by the attending physicians in real-world clinical practice. Although a significant proportion of physicians use RECIST in their clinical practice, it may still result in an inconsistent definition of tumor response and disease progression. Such information bias can be minimized to some extent by following a well-designed data management process and through appropriated definition of variables to sufficiently use available information. Lastly, no hypotheses will be tested in this study and only descriptive analysis will be performed. Thus, results cannot serve as a general conclusion on the effectiveness and safety of lorlatinib.

11. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, the Sponsor or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practice (GCP) are being followed. The monitors will review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Sponsor monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by Sponsor or companies working with or on behalf of Sponsor, and/or to inspection by appropriate regulatory authorities.

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 LinkDoc data management platform 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.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the LinkDoc data management platform and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required.

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

12.2 Record Retention

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. If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), the Sponsor should be prospectively notified. The study records must be transferred to a designee acceptable to the Sponsor, such as another investigator, another institution, or to an independent third party arranged by the Sponsor. The investigator must obtain the Sponsor’s written permission before disposing of any records, even if retention requirements have been met.

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. Copies of IRB/IEC approvals should be forwarded to the Sponsor.

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 and Sponsor 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 Sponsor forms, reports, publications, or in any other disclosures, except where required by law.

Subject names, address, birth date and other identifiable data will be replaced by an alphanumerical code consisting of a numbering system provided by the Sponsor. In case of data transfer, the Sponsor will maintain high standards of confidentiality and protection of subject personal data.

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 and the Sponsor 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.

13.5 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, the Sponsor should be informed immediately.

In addition, the investigator will inform the Sponsor immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP of which the investigator becomes aware.

14. PUBLICATION OF STUDY RESULTS

Publication of study results is discussed in the Clinical Study Agreement.

14.1 Communication of Results by the Sponsor

The Sponsor shall fulfill its commitment to publicly disclose clinical study results through posting the results of this study on www.clinicaltrials.gov (ClinicalTrials.gov).

14.2 Publications by Investigators

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

The investigator agrees that 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.

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APPENDIX 1 ECOG Performance Status

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.

APPENDIX 2 Medications with Potential PR Interval Prolongation

Effect

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

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.		

APPENDIX 3 RECIST Version 1.1

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.

CATEGORIZING LESIONS AT BASELINE

Measurable Lesions

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

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)

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

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

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

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-measurable disease

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.

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.

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.

Normal sites

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.

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.

RECORDING TUMOR ASSESSMENTS

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.

Target lesions

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.

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.

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.

Non-target disease

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’).

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

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.

Target disease

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.

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.

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.

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.

Indeterminate: Progression has not been documented, and

one or more target measurable lesions have not been assessed

or assessment methods used were inconsistent with those used at baseline

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

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

Non-target disease

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).

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

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.

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.

New Lesions

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.

Subjective Progression

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.

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

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

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

Best Overall Response

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.

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

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

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.

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

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

APPENDIX 4 PRO Instrument

- EORTC QLQ-C30 (version 3)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

Your birthdate (Day, Month, Year):

Today's date (Day, Month, Year):

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk	1	2	3	4
4.	Do you need to stay in bed or a chair during	1	2	3	4
5.	Do you need help with eating, dressing, yourself or using the toilet?	1	2	3	4
During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
6.	Were you limited in doing either your work or	1	2	3	4
7.	Were you limited in pursuing your hobbies or	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4

15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17.Have you had diarrhea?	1	2	3	4
18.Were you tired?	1	2	3	4
19.Did pain interfere with your daily activities?	1	2	3	4
20.Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21.Did you feel tense?	1	2	3	4
22.Did you worry?	1	2	3	4
23.Did you feel irritable?	1	2	3	4
24.Did you feel depressed?	1	2	3	4
25.Have you had difficulty remembering things?	1	2	3	4
26.Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27.Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28.Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

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

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7

Very poor Excellent