TIGER-3: A Phase 3, Open-label, Multicenter, Randomized Study of Oral Rociletinib (CO-1686) Monotherapy Versus Single-agent Cytotoxic Chemotherapy in Patients with Mutant EGFR Non-small Cell Lung Cancer (NSCLC) After Failure of at Least 1 Previous EGFR-directed Tyrosine Kinase Inhibitor (TKI) and Platinum-doublet Chemotherapy

Protocol Number:	CO-1686-020
Investigational Product:	Rociletinib (CO-1686)
IND Number:	[redacted]
EUDRA CT Number:	[redacted]
Development Phase:	Phase 3
Indication Studied:	Locally advanced or metastatic NSCLC with mutant epidermal growth factor receptor (EGFR)
Sponsor Name and Address:	Clovis Oncology, Inc. 5500 Flatiron Parkway, Suite 100 Boulder, CO 80301 USA Phone Number: 303-625-5000 Facsimile Number: 303-245-0360
Responsible Medical Officer:	[redacted]
Compliance Statement:	This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, clinical research guidelines established by the Code of Federal Regulations (Title 21, CFR Parts 50, 56, and 312), and International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) Guidelines. Essential study documents will be archived in accordance with applicable regulations.
Protocol Date:	10 October 2014
Amendment 1 Date:	31 October 2014
Amendment 2 Date:	27 April 2015
Amendment 3 Date:	22 February 2016
Amendment 4 Date:	7 September 2016
[redacted]	[redacted]

CONFIDENTIALITY STATEMENT

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Protocol Approval Signature Page

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[redacted]

[redacted]

Reviewed and Approved by:

[redacted]

[redacted]

[redacted]

Protocol Acceptance Form

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[redacted] [redacted]

[redacted] [redacted]

Reviewed and Approved by:

I have carefully read this protocol and agree that it contains all of the necessary information required to conduct this study. I agree to conduct this study as described and according to the Declaration of Helsinki, ICH Guidelines for GCP, and all applicable regulatory requirements.

Investigator's Signature Date

Name (printed)

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1 SYNOPSIS

Protocol Number	CO-1686-020
Title	TIGER-3: A Phase 3, Open-label, Multicenter, Randomized Study of Oral Rociletinib (CO-1686) Monotherapy Versus Single-agent Cytotoxic Chemotherapy in Patients with Mutant EGFR Non-small Cell Lung Cancer (NSCLC) After Failure of at Least 1 Previous EGFR-directed Tyrosine Kinase Inhibitor (TKI) and Platinum-doublet Chemotherapy
Phase	Phase 3
Introduction	In mid-2015, Clovis submitted a New Drug Application for the use of rociletinib in patients with T790M-positive NSCLC. In June 2016, the FDA issued a Complete Response Letter to Clovis stating that more data is required to approve rociletinib for use outside of a clinical trial. Based on this outcome, Clovis decided to discontinue development of CO-1686 for NSCLC. Patients will be informed of this change in the development plans in an update to the informed consent form for this study. Those patients who continue to derive clinical benefit from study treatment, will be allowed to continue on study at the discretion of the Principal Investigator in an extension phase. The purpose of this protocol amendment is to add a new Extension Phase to allow patients to continue on study but to avoid unnecessary collection of data that will no longer be analyzed or required for regulatory purposes, whilst maintaining an appropriate level of safety monitoring. A new schedule of assessments for the Extension Phase as well as a complete description of procedures is provided in Appendix C. This schedule replaces all schedules of assessments in Section 9 and should be followed for all patients. In addition, this amendment also introduces the availability of N-acetyltransferase 2 (NAT2) testing for patients, an indirect indicator of the likelihood of developing hyperglycaemia or QTc prolongation. The availability and disclosure of this information to the patients' treating physician will not affect the monitoring and associated treatment guidelines for these adverse events. For patients who wish to continue rociletinib treatment post progression or for patients wish to crossover to rociletinib treatment following progression on chemotherapy it is important that a full exploration of alternative treatment options between patients and their treating physicians takes place prior to making that decision. Investigators and their staff are directed to the current Investigator's Brochure for the most current efficacy and safety data, in which integrated summaries of the latest available data can be found and supersedes all safety and efficacy data in this protocol. Rociletinib (CO-1686) is a novel, potent, small molecule irreversible TKI that selectively targets mutant forms of the epidermal growth factor receptor (EGFR) while sparing wild-type (WT) EGFR. Clovis Oncology, Inc. (Clovis) was developing rociletinib as a therapeutic agent to be administered orally to patients with mutant EGFR NSCLC. Activating EGFR mutations are key drivers of NSCLC in 10% to 15% of patients of European descent and approximately 30% of patients of East Asian descent.[1]

	Patients with the most common EGFR mutations, exon 21 L858R and deletions in exon 19, typically have good responses to therapy with first-generation EGFR inhibitors such as erlotinib or gefitinib, and also with the second generation inhibitor afatinib.[2-4] Toxicity associated with erlotinib, gefitinib, and afatinib includes skin rash and diarrhea related to inhibition of the WT-EGFR in skin and intestine, respectively.[5-7] Despite an impressive initial response to treatment, progression generally occurs after 9 to 14 months of erlotinib, gefitinib, or afatinib therapy, driven in approximately 60% of cases by a second site EGFR mutation in exon 20 called T790M (the "gatekeeper" mutation) which mediates resistance to first and second generation EGFR inhibitors.[8-10] There are no approved therapies that target T790M specifically, and standard of care remains cytotoxic chemotherapy. Yu et al reported that T790M-positive (T790M+) disease is fatal, with a median overall survival (OS) of less than 2 years.[10] Nonclinical data demonstrate that rociletinib inhibits T790M as well as the common activating mutations (L858R, del19) and has minimal inhibitory activity towards WT-EGFR at therapeutic doses. It is anticipated that rociletinib will promote cell death in tumor cells with the T790M mutation, thus driving objective tumor responses and providing therapeutic benefit in patients who have acquired T790M-mediated resistance to first generation EGFR inhibitors. In the first-in-human study, CO-1686-008, in patients with advanced EGFR mutation positive NSCLC and previous treatment with an EGFR inhibitor, no maximum tolerated dose (MTD) was observed and 3 doses levels, 500 mg twice daily (BID), 625 mg BID, and 750 mg BID, were selected for further clinical evaluation of safety, tolerability and efficacy in the expansion cohorts. Maturing data from this study suggest that patients treated with rociletinib at 500 mg BID and 625 mg BID experience responses that are comparable in frequency, depth and duration, with an overall acceptable safety profile for this advanced cancer patient population. To further describe the risk/benefit profile of the rociletinib 500 mg BID dose, patients enrolled under Protocol Amendment 2 will receive a starting dose of 500 mg BID. As expected, due to its selectivity for mutant EGFR, events typical of WT-EGFR inhibition (the combination of rash and chronic diarrhea) have not been observed with rociletinib. Furthermore, heavily pretreated patients have experienced durable Response Evaluation Criteria In Solid Tumors (RECIST) responses. The majority of these responders had most recently been treated with an EGFR-TKI. Moreover, initial clinical data suggest that rociletinib may provide clinical benefits to patients who test negative with respect to the T790M mutation and the study has been designed to specifically investigate the effectiveness of rociletinib in this group of patients. The goals of the current study (Protocol CO-1686-020) are to compare the anti-tumor efficacy and safety of oral single-agent rociletinib with that of single-agent cytotoxic chemotherapy in patients with EGFR-mutated, advanced/metastatic NSCLC after failure of at least 1 previous EGFR-directed TKI and 1 line of platinum-containing doublet chemotherapy. An additional goal will be to determine the effectiveness of rociletinib in patients who test negative with respect to the T790M mutation. Rociletinib is being developed with a companion diagnostic (Qiagen, United Kingdom) to identify patients whose tumors express activating EGFR mutations as well as the T790M resistance mutation.

Planned Number of Patients	Up to approximately 600 patients will be enrolled.
Planned Number of Sites	Up to 150 investigative sites in North America, Europe, Asia, and Australia.
Study Objectives	**Primary Objective** • To compare the anti-tumor efficacy of oral single-agent rociletinib, as measured by investigator assessment of the progression-free survival (PFS), with that of single-agent cytotoxic chemotherapy in patients with EGFR-mutated, advanced/metastatic NSCLC after failure of at least 1 previous EGFR-directed TKI and at least 1 line of platinum-containing doublet chemotherapy **Secondary Objectives** • To compare secondary measures of clinical efficacy (duration of response [DR], objective response rate [ORR], and OS) between patients randomized to rociletinib or single-agent cytotoxic chemotherapy • To compare the safety and tolerability of rociletinib with that of single-agent cytotoxic chemotherapy • To determine pharmacokinetics (PK) of rociletinib using population PK (POPPK) methods and explore correlations between PK, exposure, response, and/or safety findings in patients randomized to rociletinib **Exploratory Objectives** • To evaluate clinical benefit of continued rociletinib treatment following disease progression in patients randomized to the rociletinib arm • To evaluate clinical benefit of rociletinib treatment following disease progression in patients randomized to the comparator arm who cross over to receive rociletinib • To compare quality of life (QoL) by patient-reported outcomes (PRO) between patients randomized to rociletinib or single-agent cytotoxic chemotherapy • To evaluate concordance of mutant EGFR detection between tissue and plasma and assess rociletinib mediated alterations in mutant EGFR levels over time using circulating tumor deoxynucleic acid (ctDNA) obtained from plasma; analyze clinical endpoints based on plasma EGFR mutation test results • To explore tissue and blood-based biomarkers that may be predictive of response or primary resistance to rociletinib and investigate mechanisms of acquired resistance in the tissue and blood of patients who experience clinical progression during treatment with rociletinib
Study Endpoints	**Primary Endpoint:** • PFS according to RECIST Version 1.1[11] as determined by investigator assessment (invPFS) **Secondary Endpoints:** • ORR and DR according to RECIST Version 1.1 as determined by investigator assessment • OS

	• Treatment-emergent adverse events (AEs), laboratory abnormalities, and electrocardiogram (ECG) abnormalities • Plasma PK parameters for rociletinib based on sparse sampling **Exploratory Endpoints:** • DCR according to RECIST Version 1.1 as determined by investigator assessment • Time-to-treatment failure • OS, ORR, PFS, DR, and DCR in patients who cross over to receive rociletinib and in patients who continue to receive rociletinib beyond progression • Change from baseline in PROs using the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30), the EORTC Quality of Life Questionnaire Lung Cancer module (EORTC QLQ-LC13)[12] and the EQ-5D[13] • Change from baseline in mutant EGFR levels in ctDNA obtained from plasma • OS, ORR, PFS, DR, and DCR based on plasma EGFR mutation test results • Positive and negative percent agreement between blood and tissue results for T790M • Identify biomarkers associated with response or resistance to rociletinib
Study Design	In mid-2015, Clovis submitted a New Drug Application for the use of rociletinib in patients with T790M-positive NSCLC. In June 2016, the FDA issued a Complete Response Letter to Clovis stating that more data is required to approve rociletinib for use outside of a clinical trial. Based on this outcome, Clovis decided to discontinue development of CO-1686 for NSCLC. Patients will be informed of this change in the development plans in an update to the informed consent form for this study. Those patients who continue to derive clinical benefit from study treatment, will be allowed to continue on study at the discretion of the Principal Investigator in an extension phase. The purpose of this protocol amendment is to add a new Extension Phase to allow patients to continue on study but to avoid unnecessary collection of data that will no longer be analyzed or required for regulatory purposes, whilst maintaining an appropriate level of safety monitoring. A new schedule of assessments for the Extension Phase as well as a complete description of procedures is provided in Appendix C. This schedule replaces all schedules of assessments in Section 9 and should be followed for all patients. In addition, this amendment also introduces the availability of NAT2 testing for patients, an indirect indicator of the likelihood of developing hyperglycemia or QTc prolongation. The availability and disclosure of this information to the patient's treating physician will not affect the monitoring and associated treatment guidelines for these adverse events. For patients who wish to continue rociletinib treatment post progression or for patients wish to crossover to rociletinib treatment following progression on chemotherapy it is important that a full exploration of alternative treatment options between patients and their treating physicians takes place prior to making that decision.

	This is a Phase 3, randomized, open-label, multicenter study evaluating the safety and efficacy of oral rociletinib compared with that of single-agent cytotoxic chemotherapy, in patients with previously treated mutant EGFR NSCLC. Eligible patients are those with mutant EGFR NSCLC previously treated with at least 1 EGFR inhibitor and at least 1 line of platinum-containing chemotherapy doublet for advanced/metastatic NSCLC. After providing informed consent to participate and screening to confirm eligibility, patients will be randomized 1:1 to receive rociletinib or single-agent cytotoxic chemotherapy (investigator choice of pemetrexed, gemcitabine, docetaxel, or paclitaxel; choice of chemotherapy agent must be specified before randomization). Randomization will be stratified according to: 1. Brain metastases present versus no brain metastases present, 2. Eastern Cooperative Oncology Group (ECOG) performance status 0 versus ECOG performance status 1, 3. Territory of residence at time of randomization (East Asian versus non-East Asian). All patients will provide a tumor biopsy during screening for central determination of T790M mutation status, although the test results do not have to be available before randomization. Switching therapy after biopsy sampling is not permitted as this may impact on the T790M mutation status. However, dose reduction of the therapy adopted at that time is permitted. The treatment cycle length will be 21 days for all treatments. Treatment will continue, with tumor assessment every 6 ± 1 weeks, irrespective of regimen, until disease progression or until other withdrawal criteria are met (including completion of a single-agent chemotherapy regimen). If clinical progression is diagnosed then confirmation of disease progression with a computed tomography (CT) scan (per RECIST 1.1) will be required. Tumor scan at the End-of-Treatment Visit is not required if patient had radiographic evidence of disease progression on study, or it has been < 2 weeks since last on-study scan. In addition, a magnetic resonance imaging (MRI) may be used in place of a CT at end-of-treatment scan if required per local authorities. Patients may opt to continue to receive treatment with rociletinib following radiographic progression as outlined in the National Comprehensive Cancer Network (NCCN) guidelines for treatment of NSCLC with EGFR-TKIs if: a) the patient provides additional consent, b) the investigator feels it is in the patient's best interest, and c) the sponsor provides approval. In general, eligible patients may include those with asymptomatic systemic progression or locally symptomatic progression, such as brain metastases amenable to local treatment, with concomitant asymptomatic systemic progression or continued systemic disease control. Patients randomized to the comparator chemotherapy arm may choose to cross over to receive rociletinib upon radiological progression. As with all patients, if clinical progression is diagnosed then confirmation of disease progression with a CT/MRI scan (per RECIST 1.1) will be required along with sponsor approval before crossing over to treatment with rociletinib. When protocol-specified therapy is discontinued, and the patient has yet to progress, patients will continue to undergo scheduled tumor assessments for

	monitoring of PFS. All patients will also be followed for survival status, and subsequent NSCLC cancer therapy. Dosing may be delayed or reduced according to protocol-specified toxicity criteria. Patients will undergo serial assessments for anti-tumor efficacy, drug safety, and PROs. Sparse blood sampling for POPPK analyses will be conducted in all patients treated with rociletinib. A central laboratory will confirm presence or absence of the T790M mutation in formalin-fixed paraffin embedded (FFPE) tumor tissue (results not required prior to randomization). Local laboratories will be used for hematology and chemistry. ECGs will be performed and interpreted locally for patient care decisions; however, tracings will be collected centrally for independent evaluation. Tumor scans will be acquired by the investigative site and evaluated locally for patient treatment decisions. Scans will also be collected and stored with a central vendor and quality control performed; central reading of scans will not be done unless requested by the sponsor. Following disease progression, patients who provide additional consent will undergo tumor biopsy before subsequent-line therapy is initiated. AEs will be collected from the time the first dose of study drug is administered through to 28 days after the last protocol-specified treatment administration. Study procedure-related AEs that occur after signing of the Informed Consent Form (ICF) but before administration of study drug will also be captured.
Study Population	<u>Inclusion Criteria</u> All patients must meet all of the following inclusion criteria: 1. Histologically or cytologically confirmed metastatic or unresectable locally advanced NSCLC with radiological progression on the most recent therapy received 2. Documented evidence of a tumor with 1 or more EGFR activating mutations excluding exon 20 insertion 3. Disease progression confirmed by radiological assessment while receiving treatment with single-agent EGFR-TKI (eg, erlotinib, gefitinib, afatinib, or dacomitinib). The washout period for the single agent EGFR-TKI is a minimum of 3 days or 5 half-lives, whichever is more applicable, prior to start of treatment. 4. Multiple lines of prior treatment are permitted and there is no specified order of treatment, but in the course of their treatment history, patients must have received and have radiologically documented disease progression following: – At least 1 line of prior treatment with a single-agent EGFR TKI (eg, erlotinib, gefitinib, afatinib, or dacomitinib) o If EGFR-TKI is a component of the most recent treatment line, the washout period for the EGFR-TKI is a minimum of 3 days before the start of rociletinib treatment AND – A platinum-containing doublet chemotherapy (either progressed during therapy or completed at least 4 cycles without progression with subsequent progression after a treatment-free interval or after a maintenance treatment). o If cytotoxic chemotherapy is a component of the most recent treatment line, treatment with chemotherapy should have been

	completed at least 14 days prior to start of study treatment. When an EGFR-TKI is given in combination with platinum-containing doublet chemotherapy, treatment with the EGFR-TKI may continue until at least 3 days before start of treatment. 5. Have undergone a biopsy of either primary or metastatic tumor tissue within 60 days prior to start of treatment and have tissue available to send to sponsor laboratory or are able to undergo a biopsy during screening and provide tissue to sponsor laboratory 6. Measureable disease according to RECIST Version 1.1 7. Life expectancy of at least 3 months 8. ECOG performance status of 0 to 1 9. Age ≥ 18 years (in certain territories, the minimum age requirement may be higher eg, age ≥ 20 years in Japan and Taiwan, age ≥ 21 years in Singapore) 10. Patients should have recovered to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade ≤ 1 from any significant chemotherapy-related toxicities 11. Adequate hematological and biological function, confirmed by the following local laboratory values: <u>Bone marrow function</u> a. Absolute neutrophil count (ANC) ≥ 1.5 × 109/L b. Platelets > 100.0 × 109/L c. Hemoglobin ≥ 9 g/dL (or 5.6 mmol/L) <u>Hepatic function</u> d. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × upper limit of normal (ULN); if liver metastases, ≤ 5 × ULN e. Bilirubin ≤ 2 × ULN – Patients with documented Gilbert's syndrome and conjugated bilirubin within the normal range may be allowed into the study. In this event, it will be documented that the patient was eligible based on conjugated bilirubin levels <u>Renal function</u> f. Creatinine clearance ≥ 45 mL/min <u>Electrolytes</u> g. Potassium and magnesium within normal range. Patients may receive supplements to meet this requirement. <u>Glucose</u> h. Fasting serum glucose within normal ranges 12. Written consent on an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved ICF before any study-specific evaluation <u>Exclusion Criteria</u> Any of the following criteria will exclude patients from study participation:

	1. Any other malignancy associated with a high mortality risk within the next 5 years and for which the patients may be (but not necessarily) currently receiving treatment – Patients with a history of malignancy that has been completely treated, with no evidence of that cancer currently, are permitted to enroll in the trial provided all chemotherapy was completed > 6 months prior and/or bone marrow transplant > 2 years prior 2. Known pre-existing interstitial lung disease 3. Tumor small cell transformation by local assessment, irrespective of presence of T790M+ component 4. Patients with leptomeningeal carcinomatosis are excluded. Other central nervous system (CNS) metastases are only permitted if treated, asymptomatic, and stable (not requiring steroids for at least 2 weeks prior to randomization and the patient is neurologically stable; ie, free from new symptoms of brain metastases). If a patient has had brain metastasis treated within the previous 8 weeks, a follow-up scan should have been performed to confirm that treated metastasis remain controlled without evidence of new lesions. 5. Patients who are currently receiving treatment with any medications that have the potential to prolong the QT interval and that treatment cannot be either discontinued or switched to a different medication (known to have no effect on QT) before starting protocol-specified treatment (see http://crediblemeds.org/ for a list of QT-prolonging medications) 6. Prior treatment with rociletinib, or other drugs that target T790M+ mutant EGFR with sparing of WT-EGFR including but not limited to AZD9291, HM61713, and TAS-121 7. Any contraindications for therapy with pemetrexed, paclitaxel, gemcitabine or docetaxel unless a contraindication with respect to one of these drugs will not affect the use of any of the others as a comparator to rociletinib 8. Any of the following cardiac abnormalities or history: a. Clinically significant abnormal 12-lead ECG, QT interval corrected using Fridericia's method (QT_CF) > 450 msec b. Inability to measure QT interval on ECG c. Personal or family history of long QT syndrome d. Implantable pacemaker or implantable cardioverter defibrillator e. Resting bradycardia < 55 beats/min 9. Non-study related surgical procedures ≤ 7 days prior to randomization. In all cases, the patient must be sufficiently recovered and stable before treatment administration. 10. Females who are pregnant or breastfeeding 11. Refusal to use adequate contraception for fertile patients (females and males) while on treatment and for 6 months after the last dose of study treatment (rociletinib and chemotherapy irrespective of single cytotoxic agent used) 12. Presence of any serious or unstable concomitant systemic disorder incompatible with the clinical study, eg, substance abuse, uncontrolled intercurrent illness including: • uncontrolled diabetes

	• active infection • arterial thrombosis, and • symptomatic pulmonary embolism 13. Any other reason the investigator considers the patient should not participate in the study 14. Treatment with live vaccines initiated less than 4 weeks prior to randomization
Study Treatments	Patients will be randomized 1:1 to receive either rociletinib or single-agent cytotoxic chemotherapy (investigator choice of pemetrexed, gemcitabine, docetaxel, or paclitaxel; choice of chemotherapy agent must be specified before randomization). Rociletinib Daily oral rociletinib at 500 mg BID with 8 oz (240 mL) of water and with a meal or within 30 minutes after a meal. Treatment with rociletinib is continuous and each cycle will comprise of 21 days. For patients who started therapy with rociletinib at 625 mg BID under Protocol Amendment 1, a dose reduction to 500 mg BID is allowed, only if necessitated by unacceptable toxicity. Pemetrexed 500 mg/m^2 pemetrexed given intravenously on Day 1 of each 21-day cycle. Gemcitabine 1250 mg/m^2 gemcitabine given intravenously on Days 1 and 8 of each 21-day cycle. Docetaxel 75 mg/m^2 docetaxel (60 mg/m^2 in Asian patients) given intravenously on Day 1 of each 21-day cycle, or 35 mg/m^2 docetaxel given intravenously on a weekly basis as part of a continuous 21-day cycle; ie, dosing will be on Days 1, 8, and 15 of each 21-day cycle. Paclitaxel 80 mg/m^2 paclitaxel given intravenously as a 1 hour infusion, on a weekly basis as part of a continuous 21-day cycle; ie, dosing will be on Days 1, 8, and 15 of each 21-day cycle.
Concomitant Medications	Premedication should be administered in accordance with standard of care associated with the comparator chemotherapy. Additional supportive care may be used at the investigator's discretion and in accordance with institutional procedures.
Withdrawal Criteria	After stopping protocol-specified treatment, all patients will remain in the study and will be followed for safety (until 28 days after last dose for all AEs or until resolution for serious adverse events [SAEs]), and for survival status and subsequent therapy assessment (approximately every 2 months from the End-of-Treatment Visit until death or sponsor decision, whichever comes first). Patients who discontinue rociletinib or chemotherapy without progression should continue to be scanned every 6 weeks per protocol until disease progression occurs. Exceptions to this requirement based on local institutional or regulatory requests must be agreed in advance with the sponsor. A patient must be discontinued from protocol-prescribed therapy if any of the following apply:

	• Consent withdrawal at the patient's own request or at the request of their legally authorized representative • Radiographic progression of patient's underlying disease per RECIST 1.1, except as described in Section 5.1.3 of the protocol. If clinical progression is diagnosed then confirmation with a CT scan will be required before patient withdrawal • Any event, adverse or otherwise, that, in the opinion of the investigator, would pose an unacceptable safety risk to the patient • An intercurrent illness that, in the opinion of the investigator, would affect assessments of the clinical status to a significant degree • A positive pregnancy test at any time during the study • Noncompliance as described in Section 7.7 of the protocol • Investigator decision
Efficacy Assessments	Efficacy measures will include tumor assessments, preferably by CT scans of the chest and abdomen with appropriate slice thickness per RECIST Version 1.1. Scans of the pelvis (CT or MRI) are required if there is prior evidence of local disease or if clinically indicated (symptomatic patients). MRI scans may be carried out in patients unable to undergo CT scan or if requested by local regulatory authorities. Brain imaging (CT/MRI) is required at baseline and follow-up scans should include the brain in patients with baseline brain lesions. All sites of disease should be followed and the same imaging methodology should be used throughout the study. Tumor assessments will be carried out at screening and every 6 weeks ± 1 week from the time of randomization thereafter until tumor progression. Patients are required to have an end-of-treatment tumor scan using the same methodology used at screening unless: • The patient has radiographic evidence of disease progression while on study, or • It has been < 2 weeks since their last on-study scan In addition, an MRI may be used in place of a CT at end-of-treatment scan if required per local authorities. Patients who discontinue rociletinib or chemotherapy without progression should continue to be scanned every 6 weeks per protocol until disease progression occurs. Exceptions to this requirement based on local institutional or regulatory requests must be agreed in advance with the sponsor. If a treatment cycle is delayed, the efficacy assessments should still follow the 6-weekly calendar schedule from the time of randomization.
Safety Assessments	Safety assessments will include: • AEs • Hematology including complete blood count (CBC) and differential, clinical chemistry including glycated HbA1c and c-peptide, and urinalysis • 12-lead ECGs • Physical examination, vital signs, and body weight • Concomitant medications/procedures • ECOG performance status AEs will be classified according to the NCI CTCAE Version 4.03.[14]

Biomarker Assessments	EGFR mutational status will be assessed in matching blood and tumor tissue collected at screening from each patient. Tumor tissue from the primary tumor, or an accessible local/distal metastatic lesion, will be obtained within 60 days prior to start of treatment with study drug. The corresponding blood specimen will be obtained immediately prior to tumor specimen collection where possible. EGFR-mutational status on collected tissue and blood will be assessed by the sponsor. If sufficient tissue is available from the baseline tumor biopsy, samples will be tested for other molecular alterations, that may modulate response or resistance to EGFR-targeted therapy including but not limited to EGFR gene amplification, MET proto-oncogene (MET) amplification, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA) mutations, and expression of other growth factor receptors and their ligands. Following disease progression, patients who provide additional consent will undergo a tumor biopsy before subsequent line therapy is initiated. This tissue will be analyzed for molecular alterations that modulate resistance to EGFR-targeted therapy. For patients who provide additional consent, genomic DNA will be extracted from a blood sample in order to detect genetic polymorphisms in cytochrome P450 (CYP) isozymes and to explore the possible correlation between CYP polymorphism and drug exposure. The extracted genomic DNA from blood may additionally be compared to tumor DNA so that molecular alterations unique to the tumor that may modulate response or resistance to EGFR-targeted therapy can be unambiguously identified.
Patient-reported Outcome Assessments	PROs will be measured using the EORTC QLQ-C30, EORTC QLQ-LC13[12] and EQ-5D[13] which will be administered at screening, pre-dosing on Cycle 1 Day 1 (C1D1), then on Day 1 of every 2 cycles ± 1 week for the first 6 cycles. After Cycle 7, questionnaires will be collected every 3 cycles ± 1 week, and at the End-of-Treatment Visit.
Statistical Procedures	**Sample Size Justification** Up to approximately 600 patients will be randomized in a 1:1 ratio to receive treatment with rociletinib or single-agent cytotoxic chemotherapy. The primary objective of this study is to estimate the difference in PFS between rociletinib and single-agent cytotoxic chemotherapy. The median PFS for cytotoxic chemotherapy in this patient population is expected to be approximately 4 months[15] while the median PFS in all rociletinib patients (both T790M+ and negative) is expected to be at least 6 months. A step-down procedure will be used (see below) where PFS will first be evaluated in the T790M+ subgroup followed by all randomized patients. The total sample size for the study is based on the minimum anticipated treatment effect of 4 months versus 6 months median PFS in all patients. A total of 600 patients should result in about 400 events of progression which provides 90% power to detect a hazard ratio (HR) of 0.70 at a one-sided 0.025 significance level. The targeted number of T790M+ patients in this study is between 250 and 275 patients. A sample size of 250 T790M+ patients should result in about 170 events of progression which provides 90% power to detect a HR of 0.60 at a one-sided 0.025 significance level.

	In the event that the frequency of T790M+ patients in this trial is lower than expected, enrollment will continue until 250 T790M+ patients have been enrolled. **Efficacy Analysis** The primary and key secondary endpoints will be tested among the centrally confirmed T790M+ and all randomized patients, using an ordered step-down multiple comparisons procedure. InvPFS in the T790M+ subgroup will be tested first at a one-sided 0.025 significance level. If invPFS in the T790M+ subgroup is statistically significant then invPFS in all randomized patients will be tested at a one-sided 0.025 significance level. A sensitivity analysis of Independent Radiology Review of PFS (irrPFS) will also be conducted. The remaining key secondary efficacy analyses will also be tested using this step-down approach. Once statistical significance is not achieved for one test, the statistical significance will not be declared for all subsequent analyses in the ordered step-down procedure. Kaplan-Meier methodology will be used to summarize time to event variables. The stratified log-rank and the HR will be used for comparing the PFS distributions among the rociletinib and chemotherapy-treated patients. The stratification factors of brain metastases and territory will also be used for analysis. The ORR will be summarized with frequencies and percentages. The DR for complete response (CR) and partial response (PR) will be summarized with descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) as well as categorically. **Safety Analyses** Data from all patients who receive 1 or more doses of study medication will be included in the safety analyses. AEs, clinical laboratory information, vital signs, ECGs, ECOG performance status, body weight, and concomitant medications/procedures will be summarized. **Population PK** Sparse blood sampling for POPPK analyses will be conducted in all patients treated with rociletinib (patients randomized to receive rociletinib or those who cross over to receive rociletinib following treatment with single-agent cytotoxic chemotherapy). A specific POPPK data analysis plan will be developed and will outline the detailed approach to data handling, model development and diagnostics, individual model parameter estimation, exploration of covariate effects, and final model evaluation techniques. **Pharmacodynamic Assessment** Blood may be tested for biomarkers of response or resistance to EGFR-targeted therapy. Analysis may be performed on a subset of patients if it becomes clear that the analysis will have limited scientific value in some or if there are not enough serially collected samples from individual patients to allow for adequate biomarker evaluation.

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AAG	alpha 1-acid glycoprotein
AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0–24}$	area under the curve from time zero to 24 hours
BID	twice daily
BUN	blood urea nitrogen
C_{12h}	concentration at 12 hours post-dose
C1D1	Cycle 1 Day 1
CBC	complete blood count
CFR	Code of federal regulations
CI	confidence interval
C_{max}	maximum concentration
CNS	central nervous system
CO_2	carbon dioxide
CO-1686 free base (Fb)	free base form of CO-1686
CO-1686 HBr	hydrobromide salt formulation CO-1686
CR	complete response
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events, Version 4.03
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor

EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire
EORTC QLQ-LC13	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer module
EURTAC	EURopean TArceva® versus Chemotherapy study
FACT-L	Functional Assessment of Cancer Therapy-Lung
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FG	fasting plasma or serum glucose
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
GRAS	generally regarded as safe
HbA1c	glycated hemoglobin A1c
HCP	health care practitioner
HIPAA	Health Information Portability and Accountability Act
HR	hazard ratio
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IGF-1R	insulin-like growth factor 1 receptor
INR	international normalized ratio
invPFS	investigator determined progression-free survival
iPASS	Iressa™ Pan-ASian Study
IR	insulin receptor
IRB	Institutional Review Board
IRR	Independent Radiology Review
irrPFS	Independent Radiology Review of PFS
ITT	intent-to-treat
LD	longest diameter
MedDRA	Medical Dictionary for Drug Regulatory Activities
MET	MET proto-oncogene
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NAT2	N-acetyltransferase 2
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	not evaluable
NSAID	nonsteroidal anti-inflammatory drug

NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PIK3CA	hosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
PK	pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency
POPPK	population pharmacokinetics
PR	partial response
PROs	patient-reported outcomes
PT	preferred term
QD	once daily
QoL	quality of life
QT_CF	QT interval corrected using Fridericia's method
RECIST	Response Evaluation Criteria In Solid Tumors, Version 1.1
SAE	serious adverse event
SAS	statistical analysis software
SD	stable disease
SGLT2	sodium-glucose cotransporter 2
SOC	system organ class
SOP	standard operating procedure
SPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	elimination half-life
T790M	EGFR mutation in exon 20; "gatekeeper" mutation
T790M+	T790M-positive
TE	treatment-emergent
TKI	tyrosine kinase inhibitor
T_{max}	time to maximum concentration
TOI	trial outcome index
ULN	upper limit of normal
WBC	white blood cell
WT	wild-type
β-hCG	beta human chorionic gonadotropin

3 INTRODUCTION

CO-1686 Clinical Development Program Update

In mid-2015, Clovis submitted a New Drug Application for the use of rociletinib in patients with T790M-positive NSCLC. In June 2016, the FDA issued a Complete Response Letter to Clovis stating that more data is required to approve rociletinib for use outside of a clinical trial. Based on this outcome, Clovis decided to discontinue development of CO-1686 for NSCLC. Patients will be informed of this change in the development plans in an update to the informed consent form for this study. Those patients who continue to derive clinical benefit from study treatment, will be allowed to continue on study at the discretion of the Principal Investigator in an extension phase.

Extension Phase

The purpose of this protocol amendment is to add a new Extension Phase to allow patients to continue on study but to avoid unnecessary collection of data that will no longer be analyzed or required for regulatory purposes, whilst maintaining an appropriate level of safety monitoring. A new schedule of assessments for the Extension Phase as well as a complete description of procedures is provided in Appendix C. This schedule replaces all schedules of assessments in Section 9 and should be followed for all patients.

In addition, this amendment also introduces the availability of N-acetyltransferase 2 (NAT2) testing for patients, an indirect indicator of the likelihood of developing hyperglycaemia and QTc prolongation. The availability and disclosure of this information to the patient's treating physician will not affect the monitoring and associated treatment guidelines for these adverse events.

For patients who wish to continue rociletinib treatment post progression or for patients who wish to crossover to rociletinib treatment following progression on chemotherapy it is important that a full exploration of alternative treatment options between patients and their treating physicians takes place.

Investigators and their staff are directed to the current Investigator's Brochure for the most current efficacy and safety data, in which integrated summaries of the latest available data can be found and supersedes all safety and efficacy data in this protocol.

3.1 Mutant EGFR Non-small Cell Lung Cancer

Despite years of research and prevention strategies, lung cancer remains the most common cancer worldwide with an incidence of 1.8 million in 2012 representing 13% of all cancers, and non-small cell lung cancer (NSCLC) accounts for almost 89% of all lung cancers.[16,17] Additionally, lung cancer continues to be the most common cause of cancer-related deaths worldwide with a 5-year survival rate of less than 10% in patients with advanced disease.[18]

Cytotoxic chemotherapy has been the mainstay of treatment of patients with NSCLC; however, survival rates remain low and toxicity is significant. Recent breakthroughs in NSCLC treatment

have been a result of molecular characterization of NSCLC and development of molecularly targeted agents that have demonstrated superiority to chemotherapy in those patients whose tumors express the targeted genetic mutation.

One timely example is the recent approval of crizotinib, used to treat NSCLC patients whose tumors harbor anaplastic lymphoma kinase (ALK) rearrangements. In 2 single-arm studies of crizotinib in previously treated ALK-positive patients, the tumor response rates were 50% and 61% and the duration of responses (DR) were 42 and 48 weeks, respectively.[19,20] These response rates and the DR are significantly higher that what would be expected with chemotherapy in this patient population.[21]

Molecularly targeted therapies also have proven to be superior to chemotherapy for NSCLC patients whose tumors have mutations in the epidermal growth factor receptor (EGFR). Activating EGFR mutations are key drivers of NSCLC malignancy in 10% to 15% of patients of European descent and approximately 30% of patients of East Asian descent.[1] Two recent Phase 3 trials comparing EGFR tyrosine kinase inhibitors (TKIs) versus chemotherapy have established TKIs as the gold standard for treating EGFR-mutation-positive NCSLC. In the Iressa™ Pan-ASia Study (iPASS), treatment with gefitinib was compared with treatment with carboplatin/paclitaxel in previously-untreated NSCLC patients. In EGFR-mutation-positive patients, the response rate was significantly higher with gefitinib treatment (71.2%) than with chemotherapy (47.3%).[2] Furthermore, EGFR-mutation-positive patients experienced a significantly longer progression free survival (PFS) of 9.5 months compared with 6.3 months for those on chemotherapy.[22] Quality of life (QoL) was also evaluated in this study; more patients treated with gefitinib versus chemotherapy had clinically meaningful improvement in QoL, as assessed by the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire and the Trial Outcome Index (TOI). Although survival was an endpoint of the study, the analysis of overall survival (OS) was complicated by the fact that EGFR-mutation-positive patients assigned to the chemotherapy arm crossed over to gefitinib upon progression. A second Phase 3 randomized trial, the EURopean TArceva® (erlotinib) versus Chemotherapy (EURTAC) study, compared erlotinib treatment with chemotherapy in previously untreated patients with EGFR-mutation-positive NSCLC. Patients demonstrated a response rate of 58% in the erlotinib arm compared with 15% in the chemotherapy arm ($p < 0.0001$). Furthermore, PFS was 9.7 months in the erlotinib arm versus 5.2 months in the chemotherapy arm (hazard ratio [HR] = 0.37; $p < 0.0001$).[23] At an interim analysis, OS was 22.9 months in the erlotinib arm and 18.8 months in the chemotherapy arm (HR = 0.80; $p = 0.42$). Again, cross over from chemotherapy to erlotinib confounds interpretation of survival data in this study. These data demonstrate that gefitinib and erlotinib improve response rates and PFS compared with chemotherapy.

While the toxicity profile is also improved with first-generation TKIs compared with chemotherapy, significant toxicities do occur. Toxicities associated with both erlotinib and gefitinib includes skin rash and diarrhea related to inhibition of the wild-type (WT) EGFR in skin and intestine, respectively.[5-7]

Despite the initial response, progression occurs in most patients. In the most comprehensive analysis to date, Sequist et al analyzed serial biopsies from EGFR-mutation-positive NSCLC patients who progressed on TKIs.[24] Through this research, Sequist demonstrated that acquired resistance occurs through a number of different mechanisms, while the activating mutation is

maintained. The most common cause of progression (in 60% of patients) was found to be a second site EGFR mutation in exon 20 called T790M (the "gatekeeper" mutation), which prevents drug from binding to the receptor.[3,8,9,24] This mutation was sometimes associated with amplification of the EGFR gene as well. Some patients developed amplification of another gene that drives tumor growth (MET proto-oncogene (MET) amplification). Still others showed mutations in the phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA) gene. Interestingly, a few patients had tumors that transitioned to a small-cell lung cancer, or to a more aggressive mesenchymal cell morphology.[24]

The differences in the mechanisms of resistance have a direct impact on patient treatment algorithms; specific therapies are needed to target these different mutations or changes in cellular morphology. For patients with the T790M mutation, there are currently no approved therapies. Several compounds that target the T790M mutation are in development. Second generation TKIs such as neratinib and afatinib have been shown to be more potent than erlotinib and gefitinib against the T790M mutation *in vitro*, but only at concentrations higher than the drug concentration required to maximally inhibit WT-EGFR.[25] Consequently, although there are several compounds in development, to date they have failed to demonstrate significant anti-T790M activity in the clinic, likely because of dosing limitations caused by toxicity from WT-EGFR inhibition. Hence, patients who have progressed on first generation TKIs have limited treatment options. Assessment of post-progression survival in patients treated with EGFR-TKI indicated patients with EGFR T790M-positive (T790M+) tumors had a median post-progression survival of 1.9 years (95% confidence interval [CI], 1.6–2.6 years).[10] These patients are usually offered chemotherapy, which is known to cause increased toxicities compared with targeted therapies and does not offer a cure; progression eventually occurs. Thus, NSCLC patients who have failed treatment with TKIs and whose tumors express T790M mutation represent a group with fatal disease and unmet need.

In this patient population, rociletinib (CO-1686) was expected to provide improved activity by inhibiting a key resistance pathway. Furthermore, as rociletinib has only minimal activity against WT-EGFR, patients receiving rociletinib may not experience the toxicities noted with first generation TKIs (eg, skin rash and diarrhea). In addition, this study aims to confirm and extend in a larger cohort of patients, early findings of activity in patients who test negative for the T790M mutation.

3.2 Nonclinical Overview

Rociletinib is a novel, potent, small molecule irreversible TKI that selectively targets mutant forms of the EGFR. Clovis Oncology, Inc. (Clovis) is developing rociletinib as a therapeutic agent to be administered orally to patients with mutant EGFR NSCLC. Rociletinib inhibits the EGFR gatekeeper mutation (T790M) which is associated with clinical resistance to Tarceva® (erlotinib) and Iressa™ (gefitinib) as well as the common EGFR activating mutations (L858R, del19) and has minimal inhibitory activity towards the WT-EGFR at clinically relevant doses.

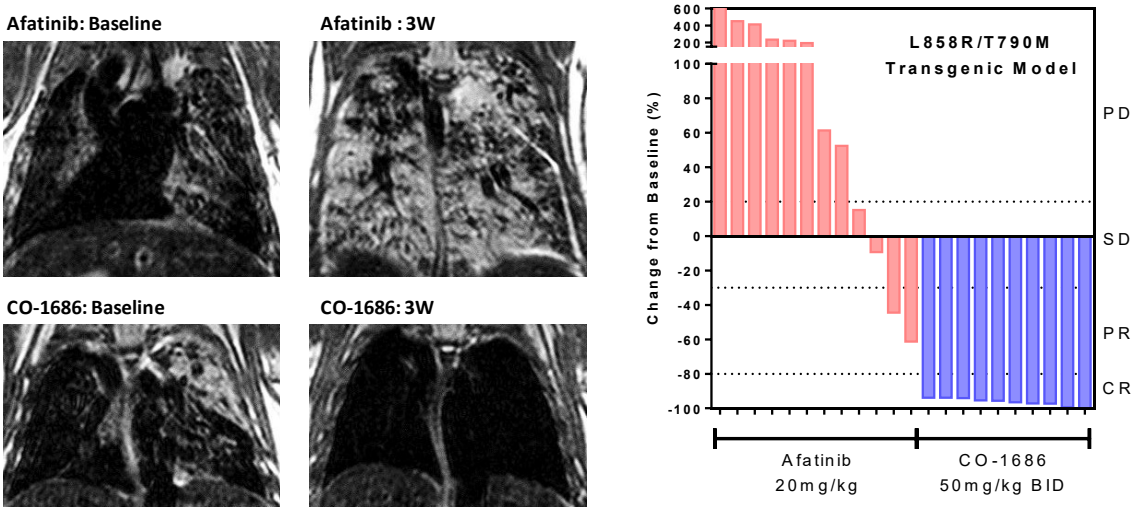
Rociletinib has been evaluated as a free base formulation (CO-1686 free base) and as a hydrobromide salt formulation (CO-1686 HBr). The pharmacologically active moiety, irrespective of formulation, is CO-1686.

3.2.1 Pharmacology

Rociletinib exhibits nonclinical antitumor activity as a single agent in cell lines expressing the most common activating and T790M EGFR mutations. The *in vitro* activity of rociletinib was evaluated against common and rare lung-cancer associated EGFR mutants. Rociletinib was active against del19, L858R, G719S (an exon 19 insertion mutant), and L861Q, but not against an exon 20 insertion. Therefore, patients with exon 20 insertions have been excluded from participation in this study.

At clinically achievable doses, rociletinib shows potent activity in the NCI-H1975 ($EGFR^{L858R/T790M}$) and primary LUM1868 ($EGFR^{L858R/T790M}$) subcutaneous xenograft models.[26] In addition, the efficacy of rociletinib was examined in an $EGFR^{L858R/T790M}$ transgenic model and compared with that of afatinib. Complete responses (CRs) were observed in all mice treated with rociletinib, with very limited activity in the afatinib group (Figure 3-1).

Figure 3-1: Rociletinib Generates Complete Responses in L858R/T790M Transgenic Model



Abbreviations: BID = twice daily; CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

3.2.2 Metabolism

In liver microsomes, rociletinib was slowly metabolized, with cytochrome P450 (CYP) 2C8 playing a role, and CYP2D6 playing a minor role at most. There is no evidence to suggest the involvement of the polymorphically-expressed CYP2C9 and CYP2C19 in rociletinib metabolism, implying a low potential for ethnic sensitivity variability in humans. Rociletinib is a substrate and an inhibitor of P-glycoprotein (P-gp) and caution should be exercised when rociletinib is co-administered with P-gp inhibitors and inducers (see Section 8.4 for further information). Caution should also be exercised in patients receiving oral rociletinib and requiring concomitant medication with warfarin (Coumadin), nonsteroidal anti-inflammatory drugs (NSAIDs), or clopidogrel, as rociletinib moderately inhibited CYP2C8, CYP2C9, and CYP2C19 activities *in vitro* (see Section 8.3 for further information).

3.2.3 Safety Pharmacology and Toxicology

Safety pharmacology and toxicology studies were carried out in rats and dogs with the rociletinib formulation of CO-1686 HBr.

Primary indices of toxicity in rats included dose-dependent clinical signs (thinning haircoat [females], squinting, pale ears or body, and hunched posture), loss in body weight, and decreased body weight gain and food consumption. Increased neutrophil count, decreased white blood cell (WBC) count, lymphocyte count, and red blood cell parameters were also noteworthy. Squinting was observed in high dose rats administered rociletinib and was associated with atrophy of meibomian gland in the eyelid; both effects were reversible. The correlate of this finding in humans is dry eye. Other microscopic findings after 28 days of repeated-dosing in rats included minimal-to-moderate atrophy of other glands (Harderian gland, mammary gland, and prostate). Pathological findings were minor glandular atrophy in all 4 tissues which was reversible and principally occurred in the high-dose group. Only minor effects were observed with rociletinib on hematopoietic tissue.

Primary indices of toxicity in dogs included dose-related clinical signs which included abnormal feces (liquid and/or non-formed feces), vomiting, and redness of gingiva and lips. These observations were not considered adverse due to the overall good health of the animals. All clinical observations were reversible, except for non-formed feces. There was no microscopic correlation associated with the redness of gingiva or lips.

No evidence of elevated serum glucose levels were observed in the rat and dog studies. There were no rociletinib-related cardiac safety or neurobehavioral findings from the Good Laboratory Practice (GLP) repeat-dose toxicity studies. Rociletinib did not have any genotoxic activity in 2 *in vitro* assays, and was not phototoxic when evaluated in a phototoxicity study with Long Evans pigmented rats.

Please refer to the Investigator's Brochure for detailed information on the nonclinical program.

3.3 Clinical Experience with Rociletinib

Four studies are currently ongoing (CO-1686-008, CO-1686-018, CO-1686-019, CO-1686-022) and 1 clinical study has been completed (CO-1686-016).

Ongoing studies:

- CO-1686-008 (TIGER-X) is a 2-part, open-label, safety, pharmacokinetic (PK), and preliminary efficacy study of rociletinib in patients with advanced NSCLC. The study consists of 2 parts. Part 1 is a Phase 1 dose escalation phase to determine the maximum tolerated dose (MTD) and is fully enrolled. The Phase 2 part of the study is the expansion portion in previously-treated NSCLC patients who have documented evidence of an activating mutation in the EGFR gene and evidence of the T790M mutation based on prospective testing for T790M, and is currently enrolling
- CO-1686-018 is a Phase 1, open-label, safety, PK, and preliminary efficacy study of rociletinib in Japanese patients with advanced NSCLC

- CO-1686-019 (TIGER-2) is a single arm, open-label, safety and efficacy study of rociletinib as second line EGFR-directed TKI therapy in patients with mutant EGFR NSCLC with the T790M mutation
- CO-1686-022 (TIGER-1) is a randomized, open-label, Phase II study of CO-1686 or erlotinib as first-line treatment of patients with EGFR-mutant advanced non-small cell lung cancer (NSCLC)

Completed study:

- CO-1686-016 was a Phase 1, PK, safety and tolerability study in healthy adult male subjects that was completed in order to evaluate 3 formulations of rociletinib CO-1686 HBr, and to support introduction of the CO-1686 HBr formulation into protocol CO-1686-008

3.3.1 Safety of Rociletinib from Clinical Studies

Preliminary safety data are presented for the ongoing CO-1686-008 and completed CO-1686-016 studies. One hundred and ninety patients have received at least 1 dose of rociletinib as of 04 June 2014; 42 healthy male volunteers (Study CO-1686-016) and 148 patients with advanced NSCLC (Study CO-1686-008). The overall safety data presented here are for patients who received rociletinib in Study CO-1686-008 and included in the clinical database, as of the cut-off date of 04 June 2014.

3.3.1.1 Study CO-1686-008 – Ongoing Phase 1/2 Study

CO-1686-008 is an ongoing 2-part, open-label, safety, PK, and preliminary efficacy study of rociletinib in patients with advanced NSCLC. As of 04 June 2014, 148 patients with advanced NSCLC have received at least 1 dose of rociletinib. In the initial stage of the study, 57 patients were treated with rociletinib administered as CO-1686 free base capsules at doses ranging from 150 mg up to 1800 mg daily. Subsequently, CO-1686 HBr tablets were introduced into the study to be used in the later dose escalation cohorts. Ninety-one patients have been treated with rociletinib administered as HBr tablets at doses of 500 mg twice daily (BID; N = 18), 625 mg BID (N = 17), 750 mg BID (N = 50) and 1000 mg BID (N = 6). At the time of this summary, preliminary safety data are available in the clinical database for 148 patients.

DOSE-LIMITING TOXICITIES (DLTS)

Enrollment of patients to the dose escalation phase was completed in February 2014 with a DLT rate of < 33% at all evaluated doses. The DLT evaluable population included all patients who had completed Cycle 1, and who were enrolled while the dose escalation part of the study was ongoing. The most frequently reported DLT was hyperglycemia/glucose tolerance impaired which occurred at a similar frequency (11% to 25%) across all rociletinib dose levels with the CO-1686 HBr formulation (500 mg BID, 625 mg BID, 750 mg BID, and 1000 mg BID). Hyperglycemia can be effectively managed with the addition of anti-hyperglycemic therapy and/or dose reductions. Guidance for the management of hyperglycemia associated with rociletinib treatment is provided in Section 7.4.1.

SERIOUS ADVERSE EVENTS (SAEs) AND DEATHS

A total of 43 patients experienced at least 1 SAE and 17 patients have reported an SAE assessed as related to study drug. Treatment-related SAEs are summarized in Table 3-1. The most commonly reported treatment-related SAE was hyperglycemia (reported in 6% of patients). Four patients (3%) experienced an SAE of vomiting and 3 patients (2%) experienced an SAE of nausea. All other treatment-related SAEs occurred in 2 or fewer patients.

To date, there have been 11 deaths while on study or within 28 days after the last dose of rociletinib. Eight deaths were reported as due to progression of NSCLC, 1 death due to pulmonary embolism, 1 death due to pneumonia, and 1 death of unknown cause. At this stage, a causal relationship with rociletinib cannot be ruled out for the death of unknown cause, all other deaths were reported as unrelated to study drug.

Table 3-1: Treatment-related Serious Adverse Events Reported in Patients in Study CO-1686-008

System Organ Class Preferred Term	< 900 BID FB (N = 38)	900 BID FB (N = 19)	500 BID HBr (N = 18)	625 BID HBr (N = 17)	750 BID HBr (N = 50)	1000 BID HBr (N = 6)	Overall (N = 148)
Number of Patients with at Least 1 Treatment-related Treatment-emergent SAE							
Overall	4 (10.5%)	1 (5.3%)	4 (22.2%)	3 (17.6%)	4 (8.0%)	1 (16.7%)	17 (11.5%)
Cardiac Disorders							
Pericarditis	1 (2.6%)	0	0	0	0	0	1 (0.7%)
Gastrointestinal Disorders							
Diarrhea	1 (2.6%)	1 (5.3%)	0	0	0	0	2 (1.4%)
Nausea	1 (2.6%)	0	1 (5.6%)	0	1 (2.0%)	0	3 (2.0%)
Pancreatitis	0	0	1 (5.6%)	0	0	0	1 (0.7%)
Vomiting	2 (5.3%)	0	1 (5.6%)	0	1 (2.0%)	0	4 (2.7%)
Infections and Infestations							
Gastroenteritis	0	0	0	0	1 (2.0%)	0	1 (0.7%)
Investigations							
ECG QT prolonged	0	0	0	1 (5.9%)	1 (2.0%)	0	2 (1.4%)
ECG T wave inversion	0	0	0	0	1 (2.0%)	0	1 (0.7%)
Transaminases increased	0	1 (5.3%)	0	0	0	0	1 (0.7%)
Metabolism and Nutrition Disorders							
Combined terms of hyperglycemia	1 (2.6%)	0	4 (22.2%)	1 (5.9%)	2 (4.0%)	1 (16.7%)	9 (6.1%)
Decreased appetite	0	1 (5.3%)	0	0	0	0	1 (0.7%)
Hypoglycemia	1 (2.6%)	0	0	0	0	0	1 (0.7%)
Hypokalemia	0	0	0	1 (5.9%)	0	0	1 (0.7%)
Respiratory, Thoracic, and Mediastinal Disorders							
Pneumonitis	0	0	0	1 (5.9%)	0	0	1 (0.7%)

Abbreviations: BID = twice daily; ECG = electrocardiogram; FB = CO-1686 free base; HBr = CO-1686 hydrobromide; N = number of patients; SAE = serious adverse event; TE = treatment-emergent.

TREATMENT-RELATED ADVERSE EVENTS (AEs)

Of the 148 patients treated with rociletinib as of the data cut-off date, 124 patients (84%) had at least 1 AE and 111 patients (75%) had an AE considered to be possibly, probably, or definitely related to rociletinib.

The most frequently reported AEs (≥ 20% of patients), regardless of causality or severity, were nausea (40%); AEs associated with blood glucose increases (39%; including Medical Dictionary for Regulatory Activities [MedDRA] preferred terms [PTs] blood glucose elevated, glucose tolerance impaired, and hyperglycemia); fatigue (26%); diarrhea (26%); and decreased appetite (22%).

AEs considered to be related to rociletinib and reported in > 5% of patients overall are summarized by system organ class (SOC), PT, and dose level in Table 3-2. The most frequently reported treatment-related AEs (≥ 20% of patients), regardless of severity, were nausea (28%); increased blood glucose, combined terms as in previous paragraph (33%); and fatigue (20%).

The majority of AEs have been mild or moderate in severity. Rociletinib selectively inhibits mutant EGFR, and as expected, the syndrome of dose related WT-driven rash and diarrhea has not been observed. All reported events of diarrhea were either Grade 1 or Grade 2.

The most common skin reaction reported in patients treated with EGFR-TKIs is a follicular acneiform eruption. In Study CO-1686-008, rash, irrespective of causality, was reported infrequently (overall 6 patients [4%]) and all events were mild. In Study CO-1686-008, only 1 report of dermatitis acneiform and 1 report of follicular rash have been reported to date.

There have been 2 AEs of pneumonitis and 1 SAE of pneumonitis, all assessed as related to rociletinib by the investigator. Patients recovered after steroid therapy, and patients were not rechallenged with rociletinib.

ELECTROCARDIOGRAM (ECG) CHANGES

Rociletinib exposure is associated with QT_C prolongation. The effect takes several days to develop, and is not seen on Day 1 of therapy. Patients with low baseline resting heart rates appear to be at a higher risk for QT_C prolongation during treatment with rociletinib. Typically, the abnormality is evident by Day 15 of therapy, and the increase remains stable with continued dosing. QT_C intervals longer than 500 msec have been observed in 10 patients (7.6%). In clinical studies of rociletinib, all cases of QT_C prolongation have been asymptomatic and no cases of ventricular dysrhythmia or torsades de pointes have been observed.

Prolonged QT_C is managed effectively by dose reduction.

Table 3-2: Treatment-related Adverse Events Reported in at Least 5% of Patients in Study CO-1686-008

System Organ Class Preferred Term	< 900 BID FB (N = 38)	900 BID FB (N = 19)	500 BID HBr (N = 18)	625 BID HBr (N = 17)	750 BID HBr (N = 50)	1000 BID HBr (N = 6)	Overall (N = 148)
Number of Patients with at Least 1 Treatment-related TEAE							
Overall	**28 (73.7%)**	**18 (94.7%)**	**16 (88.9%)**	**15 (88.2%)**	**28 (56.0%)**	**6 (100.0%)**	**111 (75.0%)**
Gastrointestinal Disorders							
Diarrhea	6 (15.8%)	6 (31.6%)	4 (22.2%)	4 (23.5%)	6 (12.0%)	2 (33.3%)	28 (18.9%)
Nausea	8 (21.1%)	6 (31.6%)	6 (33.3%)	7 (41.2%)	12 (24.0%)	3 (50.0%)	42 (28.4%)
Vomiting	5 (13.2%)	2 (10.5%)	3 (16.7%)	4 (23.5%)	4 (8.0%)	0	18 (12.2%)
General Disorders and Administration Site Conditions							
Fatigue	9 (23.7%)	6 (31.6%)	5 (27.8%)	3 (17.6%)	5 (10.0%)	1 (16.7%)	29 (19.6%)
Investigations							
Electrocardiogram QT prolonged	0	2 (10.5%)	0	2 (11.8%)	5 (10.0%)	3 (50.0%)	12 (8.1%)
Metabolism and Nutrition Disorders							
Combined terms of hyperglycemia	4 (10.5%)	6 (31.6%)	11 (61.1%)	10 (58.8%)	14 (28.0%)	4 (66.7%)	49 (33.1%)
Decreased appetite	1 (2.6%)	6 (31.6%)	4 (22.2%)	3 (17.6%)	2 (4.0%)	2 (33.3%)	18 (12.2%)
Musculoskeletal and Connective Tissue Disorders							
Muscle spasms	3 (7.9%)	4 (21.1%)	3 (16.7%)	0	3 (6.0%)	0	13 (8.8%)
Myalgia	3 (7.9%)	4 (21.1%)	2 (11.1%)	0	1 (2.0%)	1 (16.7%)	11 (7.4%)

Abbreviations: BID = twice daily; FB = CO-1686 free base; HBr = CO-1686 hydrobromide; N = number of patients; TEAE = treatment-emergent adverse event.

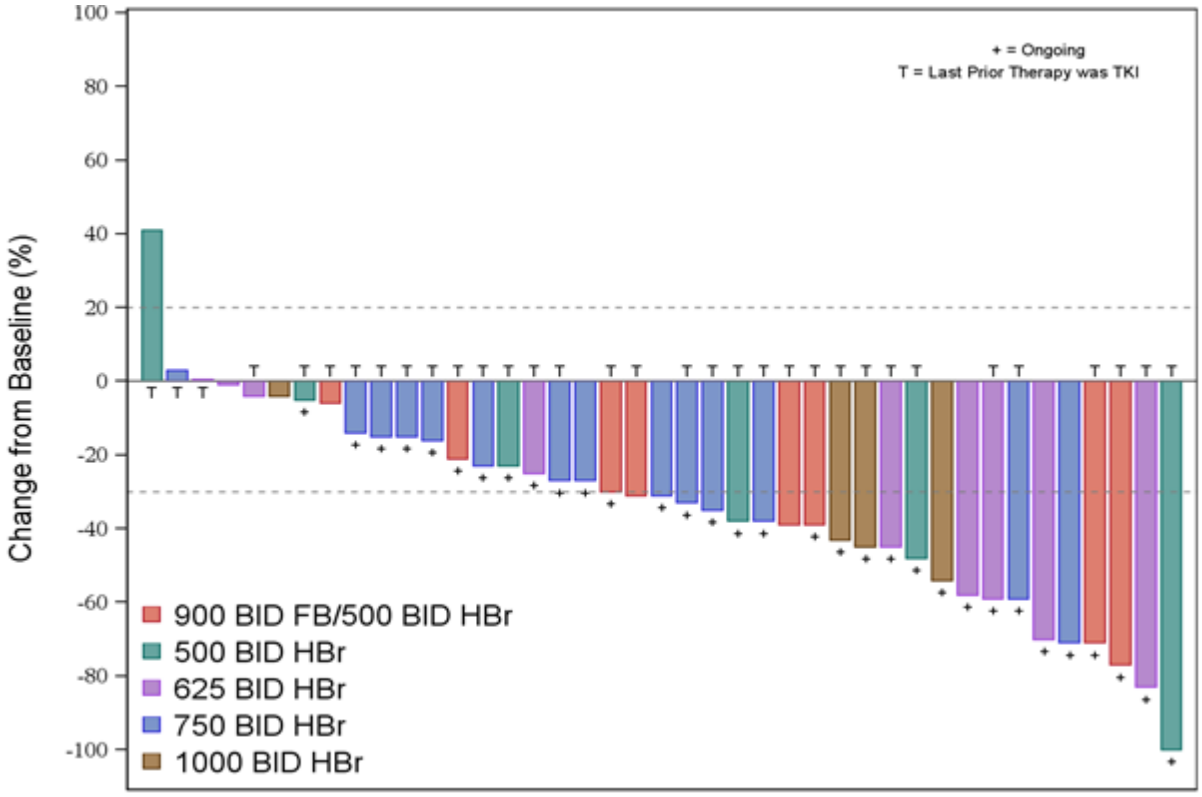
3.3.2 Activity of Rociletinib from Clinical Studies

3.3.2.1 Study CO-1686-008 – Ongoing Phase 1/2 Study

CO-1686-008 is a 2-part, open-label, safety, PK, and preliminary efficacy study of rociletinib in patients with advanced NSCLC. The dose escalation phase of the study has been completed.

Although the primary objectives of Phase 1 of Study CO-1686-008 were to evaluate the safety, toxicity, and PK profile of rociletinib, encouraging signals of activity have been observed in an EGFR-mutation-positive patient population previously treated with one or more lines of an EGFR-TKI (eg, erlotinib, gefitinib, afatinib) and chemotherapy. A preliminary analysis of efficacy has been conducted using objective response rate (ORR), DR, and PFS as efficacy parameters. There is robust evidence of activity for rociletinib across the therapeutic doses (Figure 3-2) for patients confirmed as T790M+ by central testing, with 22 of 40 patients achieving a Response Evaluation Criteria In Solid Tumors (RECIST) partial response (PR) as of the data cut-off date (Table 3-3). The ORR in this group of patients is 55% and the disease control rate (DCR) is approximately 92%.

Figure 3-2: Target Lesion Response in Centrally Confirmed T790M+ Patients



Abbreviations: BID = twice daily; FB = CO-1686 free base; HBr = CO-1686 hydrobromide; T790M+ = T790M-positive; T = last prior therapy was a tyrosine kinase inhibitor; + = ongoing.

Table 3-3: Best Response, Objective Response, and Disease Control Rate in T790M+ Patients

	900 mg BID FB (N = 8)	500 mg BID HBr (N = 6)	625 mg BID HBr (N = 9)	750 mg BID HBr (N = 13)	1000 mg BID HBr (N = 4)	Overall (N = 40)
Best Response						
PR	6 (75.0%)	3 (50.0%)	5 (55.6%)	5 (38.5%)	3 (75.0%)	22 (55%)
SD	2 (25.0%)	2 (33.3%)	2 (22.2%)	8 (61.5%)	1 (25.0%)	15 (45.5%)
PD	0 (0.0%)	1 (16.7%)	2 (22.2%)	0 (0.0%)	0 (0.0%)	3 (9.0%)
Objective Response (CR, PR)	6 (75.0%)	3 (50.0%)	5 (55.6%)	5 (38.5%)	3 (75.0%)	22 (55%)
Disease Control Rate (CR, PR, SD)	8 (100.0%)	5 (83.3%)	7 (77.8%)	13 (100.0%)	4 (100.0%)	37 (92.5%)

Abbreviations: BID = twice daily; CR = complete response; FB = CO-1686 free base; HBr = CO-1686 hydrobromide; N= number of patients; PD = progressive disease; PR = partial response; SD = stable disease; T790M+ = T790M-positive.

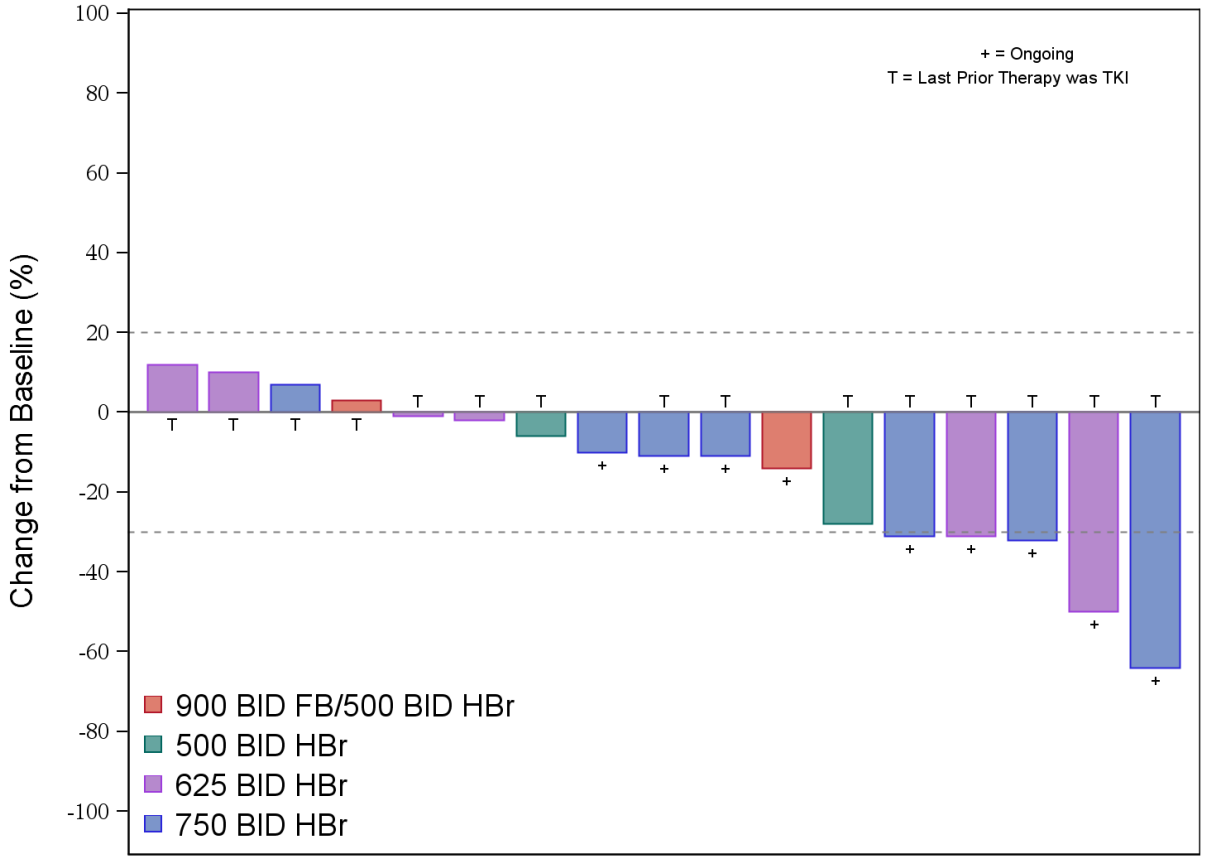
Data shown are for patients with measurable disease at baseline.

Some (29.4%) evaluable T790M-negative patients, with at least a Cycle 2 scan measurement, achieved a target lesion response as of the data cut-off date (Figure 3-3). These data suggest that although the benefit is more modest than in patients with T790M+ disease, rociletinib is active in patients with T790M-negative disease. Response rate and PFS in the T790M-negative group are longer than would be expected for single-agent cytotoxic chemotherapy in relapsed disease in an unselected population (data specific to T790M-negative patients are not available). Response rates of less than 10% with PFS under 3 months have been described for pemetrexed and docetaxel monotherapy (Alimta® label).

Rociletinib activity in T790M-negative patients could be explained by several factors including heterogeneous clones of cells within the tumor, with only T790M-negative clones captured within the biopsy sample, or a small fraction of T790M+ cells falling out with the sensitivity limit of the assay.

The data support including T790M-negative patients in randomized studies, to characterize the signal further, and to establish whether rociletinib is more active than available therapies.

Figure 3-3: Best Response for Target Lesions in T790M-negative Patients



Abbreviations: BID = twice daily; FB = CO-1686 free base; HBr = CO-1686 hydrobromide; T = last prior therapy was a tyrosine kinase inhibitor; + = ongoing.

3.3.3 Pharmacokinetics of Rociletinib

3.3.3.1 Study CO-1686-016 – Completed Phase 1 Study

In healthy volunteers (Study CO-1686-016), maximum concentration (C_{max}) and area under the curve from time zero to 24 hours ($AUC_{0–24}$) of rociletinib increased with ascending single doses of the rociletinib formulation of CO-1686 HBr (50 mg to 1000 mg), with rociletinib plasma levels increasing in a less than dose proportional manner above 125 mg.

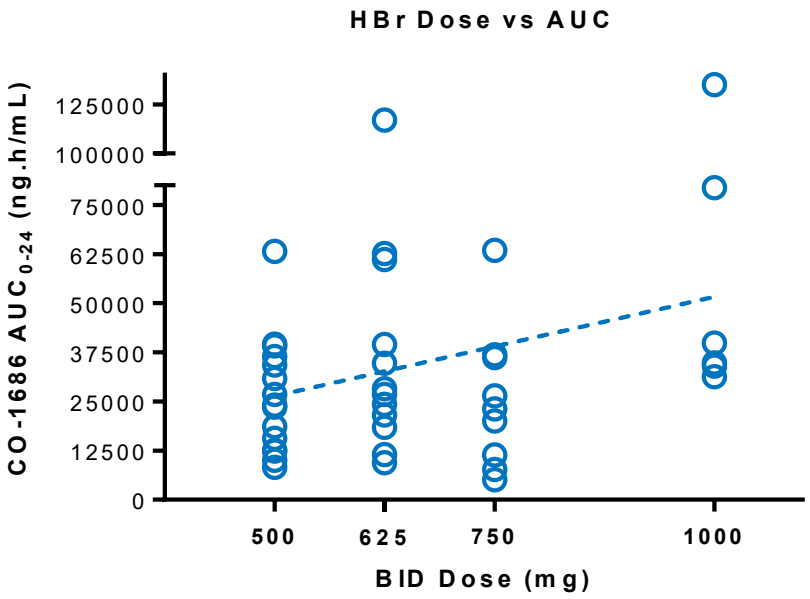
The single-dose PK of rociletinib was compared in the fasted and fed state, and it was concluded that a high-fat meal increased the plasma drug concentrations from 3 to 12 hours postdose with a mean increase of 172% at 12 hours postdose (C_{12h}: –22% to +400%) and a mean increase of 77% in $AUC_{0–24}$ (+10% to 146%) with no change in half-life ($T_{1/2}$); a slight mean increase of 12% in C_{max} was observed and a delayed time to maximum concentration (T_{max}) was seen in a majority of subjects.

Six healthy subjects were dosed, in the fed state, with 500 mg BID rociletinib for 4 days. PK profiles of rociletinib following morning and evening dosing were similar, with low intra-subject variability (Day 1 and Day 4 comparison). There was no accumulation of rociletinib.

3.3.3.2 Study CO-1686-008 – Ongoing Phase 1/2 Study

In the patient study (CO-1686-008), PK following HBr salt administration were available from a total of 51 patients (11 started at 500 mg BID, 10 switched from CO-1686 free base to 500 mg BID HBr, 15 started at 625 mg BID, 9 started at 750 mg BID, and 6 started at 1000 mg BID). CO-1686 HBr showed increased absorption and thus higher exposure than free base. The median T_{max} was 1.5 to 3.25 hours and $T_{1/2}$ ranged from 1.7 to 4.7 hours. Following CO-1686 HBr administration, exposure (measured as C_{max} and $AUC_{0–24}$) increased approximately dose-proportionally from 500 mg to 1000 mg BID (Figure 3-4).

Figure 3-4: Individual Rociletinib $AUC_{0–24}$ on Day 1 Following 500 mg to 1000 mg CO-1686 HBr BID



Abbreviations: AUC = area under the curve; BID = twice daily; HBr = CO-1686 hydrobromide.

3.4 Rationale for Current Study

As noted previously, there are limited treatment options for mutant EGFR NSCLC patients who have failed treatment with first generation TKIs and platinum-containing cytotoxic chemotherapy. Single-agent cytotoxic chemotherapy has limited efficacy and significant toxicity in the second or third-line setting. Consequently, these patients represent a group with fatal disease and unmet need.

With potent nonclinical activity against activating EGFR mutations and the T790M resistance mutation, minimal inhibitory activity towards the WT, and with activity in clinical studies in

both T790M+ and T790M-negative populations, rociletinib may provide a tolerable and effective therapy for a patient population with few alternative treatment options.

The goals of the current study (Protocol CO-1686-020) are to compare the anti-tumor efficacy and safety of oral single-agent rociletinib with that of single-agent cytotoxic chemotherapy in patients with EGFR-mutated advanced/metastatic NSCLC after failure of at least 1 previous EGFR-directed TKI and one line of platinum-containing doublet chemotherapy.

An additional goal will be to determine the effectiveness of rociletinib in patients who test negative with respect to the T790M mutation, given initial findings suggestive of a clinical benefit of rociletinib in these patients.

In the first-in-human study, CO-1686-008, in patients with advanced EGFR mutation positive NSCLC and previous treatment with an EGFR inhibitor, no MTD was observed and 3 dose levels, 500 mg BID, 625 mg BID, and 750 mg BID, were selected for further clinical evaluation of safety, tolerability and efficacy in the expansion cohorts. Maturing data from this study suggest that patients treated with rociletinib at 500 mg BID and 625 mg BID experience responses that are comparable in frequency, depth and duration, with an overall acceptable safety profile for this advanced cancer patient population. To further describe the risk/benefit profile of the rociletinib 500 mg BID dose, patients enrolled under Protocol Amendment 2 will receive a starting dose of 500 mg BID.

4 STUDY OBJECTIVES AND ENDPOINTS

4.1 Objectives

4.1.1 Primary Objective

- To compare the anti-tumor efficacy of oral single-agent rociletinib, as measured by investigator assessment of the PFS, with that of single-agent cytotoxic chemotherapy in patients with EGFR-mutated, advanced/metastatic NSCLC after failure of at least 1 previous EGFR-directed TKI and at least 1 line of platinum-containing doublet chemotherapy

4.1.2 Secondary Objectives

- To compare secondary measures of clinical efficacy (DR, ORR and OS) between patients randomized to rociletinib or single-agent cytotoxic chemotherapy
- To compare the safety and tolerability of rociletinib with that of single-agent cytotoxic chemotherapy
- To determine PK of rociletinib using population PK (POPPK) methods and explore correlations between PK, exposure, response, and/or safety findings in patients randomized to rociletinib

4.1.3 Exploratory Objectives

- To evaluate clinical benefit of continued rociletinib treatment following disease progression in patients randomized to the rociletinib arm
- To evaluate clinical benefit of rociletinib treatment following disease progression in patients randomized to the comparator arm who cross over to receive rociletinib
- To compare QoL by patient-reported outcomes (PRO) between patients randomized to rociletinib or single-agent cytotoxic chemotherapy
- To evaluate concordance of mutant EGFR detection between tissue and plasma and assess rociletinib mediated alterations in mutant EGFR levels over time using circulating tumor DNA (ctDNA) obtained from plasma; analyze clinical endpoints based on plasma EGFR mutation test results
- To explore tissue and blood-based biomarkers that may be predictive of response or primary resistance to rociletinib and investigate mechanisms of acquired resistance in the tissue and blood of patients who experience clinical progression during treatment with rociletinib

4.2 Endpoints

4.2.1 Primary Endpoint

- Progression-free survival (PFS) according to RECIST Version 1.1 as determined by investigator assessment (invPFS)

4.2.2 Secondary Endpoints

- ORR and DR according to RECIST Version 1.1 as determined by investigator assessment
- OS
- Treatment-emergent AEs, laboratory abnormalities, and ECG abnormalities
- Plasma PK parameters for rociletinib based on sparse sampling

4.2.3 Exploratory Endpoints

- DCR according to RECIST Version 1.1 as determined by investigator assessment
- Time–to-treatment failure
- OS, ORR, PFS, DR, and DCR in patients who cross over to receive rociletinib and in patients who continue to receive rociletinib beyond progression
- Change from baseline in PROs using the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30), the EORTC Quality of Life Questionnaire Lung Cancer module (EORTC QLQ-LC13) and the EQ-5D
- Change from baseline in mutant EGFR levels in ctDNA obtained from plasma
- OS, ORR, PFS, DR, and DCR based on plasma EGFR mutation test results
- Positive and negative percent agreement between blood and tissue results for T790M
- Identify biomarkers associated with response or resistance to rociletinib

5 STUDY DESIGN

5.1 Overall Study Design and Plan

This is a Phase 3, randomized, open-label, multicenter study evaluating the safety and efficacy of oral rociletinib compared with single-agent cytotoxic chemotherapy in patients with previously treated mutant EGFR NSCLC. Eligible patients are those with mutant EGFR NSCLC previously treated with at least 1 EGFR inhibitor and at least 1 line of platinum-containing chemotherapy doublet for advanced/metastatic NSCLC.

After providing consent to participate and screening to confirm eligibility for participation in the study, patients will be randomized 1:1 to receive either oral rociletinib or single-agent cytotoxic chemotherapy (investigator choice of pemetrexed, gemcitabine, docetaxel, or paclitaxel; choice of chemotherapy agent must be specified before randomization). Randomization will be stratified according to:

1. Brain metastases present versus no brain metastases present
2. Eastern Cooperative Oncology Group (ECOG) performance status 0 versus ECOG performance status 1
3. Territory of residence at time of randomization (East Asian versus non-East Asian).

All patients will provide a tumor biopsy during screening for central determination of T790M mutation status in formalin-fixed paraffin-embedded (FFPE) tumor tissue, although the test result does not have to be available before randomization. Switching therapy after biopsy sampling is not permitted as this may impact on the T790M mutation status. However, dose reduction of the therapy adopted at that time is permitted.

The treatment cycle length will be 21 days for all treatments. See Section 7.3 for further details of the dosing schedules. Dosing may be delayed or reduced according to protocol-specified toxicity criteria. Protocol-specified treatment will continue, with tumor assessment every 6 ± 1 weeks, irrespective of regimen, until there is disease progression by RECIST Version 1.1 or unacceptable toxicity as assessed by the investigator or until other withdrawal criteria are met (including completion of a single agent chemotherapy regimen). If clinical progression is diagnosed then confirmation of disease progression with a computed tomography (CT) scan (per RECIST 1.1) will be required. Patients may opt to continue to receive treatment with rociletinib following radiographic progression as outlined in the National Comprehensive Cancer Network (NCCN) guidelines for treatment of NSCLC with EGFR-TKIs if: a) the patient provides additional consent, b) the investigator feels it is in the patient's best interest, and c) the sponsor provides approval. In general, eligible patients may include those with asymptomatic systemic progression or locally symptomatic progression, such as brain metastases amenable to local treatment, with concomitant asymptomatic systemic progression or continued systemic disease control.

Patients randomized to the comparator chemotherapy arm may choose to cross over to receive rociletinib upon radiological progression. As with all patients, if clinical progression is diagnosed then confirmation of disease progression with a CT/magnetic resonance imaging (MRI) scan (per

RECIST Version 1.1) will be required along with sponsor approval before crossing over to treatment with rociletinib.

When protocol-specified therapy is discontinued, and the patient has yet to progress, patients will continue undergo scheduled tumor assessments for monitoring of PFS. All patients will also be followed for survival status, and subsequent NSCLC cancer therapy until death or sponsor decision, whichever comes first.

5.1.1 Screening Period

After providing consent to participate, patients will undergo screening assessments within 35 days prior to randomization to rociletinib or single-agent cytotoxic chemotherapy. Patients will be monitored for AEs from the time the first dose of study medication is administered through to 28 days after the last protocol-specified treatment administration. Study-procedure-related AEs that occur after signing of the Informed Consent Form (ICF) but before administration of study treatment will also be collected.

5.1.2 Randomization

Following confirmation of patient eligibility by the investigator, patients will be centrally randomized in a 1:1 ratio to receive oral rociletinib or single-agent cytotoxic chemotherapy (investigator choice of pemetrexed, gemcitabine, docetaxel, or paclitaxel). The choice of chemotherapy agent must be specified by the investigator before randomization. At least 5 daily doses of folic acid must be taken preceding the first dose of pemetrexed. If the investigator selects pemetrexed as the comparator option for a patient, then folic acid supplementation may begin prior to randomization, if necessary, to ensure that Cycle 1 Day 1 (C1D1) is not delayed while premedication is completed. Patients can continue receiving treatment with a single-agent EGFR-TKI (eg, erlotinib, gefitinib, afatinib, or dacomitinib) until 3 days before C1D1.

5.1.3 Treatment Period

During the treatment period, patients will receive either oral single agent rociletinib or investigator choice of single-agent pemetrexed, gemcitabine, docetaxel, or paclitaxel chemotherapy. Treatment cycles are 21 days long, with dosing initiating within 3 days after randomization (C1D–3), on C1D1.

Rociletinib will be administered daily to patients at 500 mg BID (see Section 7.3.1). Treatment with rociletinib is continuous and each cycle will comprise of 21 days. In each cycle, the first dose of rociletinib will be taken in clinic, with the remaining doses self-administered by the patient at home. Patients will take rociletinib with 8 oz (240 mL) of water and with a meal or within 30 minutes after a meal. No dose escalation above the starting dose is allowed.

For patients who started therapy with rociletinib at 625 mg BID under Protocol Amendment 1, a reduction in dose to 500 mg BID is allowed, only if necessitated by unacceptable toxicity.

The choice of single-agent cytotoxic chemotherapy is at the discretion of the investigator from amongst the regimens described in this protocol. The treatment cycle length will be 21 days. The dosing regimens for the 4 chemotherapy comparators are as follows:

Chemotherapy Agent	Dosing Regimen
Pemetrexed	500 mg/m^2 intravenously on Day 1 of each 21-day cycle
Gemcitabine	1250 mg/m^2 intravenously on Days 1 and 8 of each 21-day cycle
Docetaxel	*Two possible dosing regimens:*
	75 mg/m^2 intravenously on Day 1 of each 21-day cycle (Note: dose will be 60 mg/m^2 in Asian patients)
	35 mg/m^2 intravenously on a weekly basis as part of a continuous 21-day cycle; (ie, dosing will be on Days 1, 8, and 15 of each 21-day cycle)
Paclitaxel	80 mg/m^2 intravenously as a 1 hour infusion, on a weekly basis as part of a continuous 21-day cycle; (ie, dosing will be on Days 1, 8, and 15 of each 21-day cycle)

See Section 7.3.2 for further dosing details.

All patients will undergo serial assessments for anti-tumor efficacy, drug safety, and PRO. Sparse blood sampling for POPPK analyses will be conducted in all patients treated with rociletinib. Tumor scans will be acquired by the investigative site and evaluated locally for patient treatment decisions. Scans will also be collected and stored with a central vendor and quality control performed; central reading of scans will not be done unless requested by the sponsor. AEs will be collected from the time of first dose of study treatment until 28 days after the last protocol-specified treatment administration. Study procedure-related AEs that occur after signing of the ICF but before administration of study treatment will also be collected. Local laboratories will be used for hematology and chemistry. ECGs will be performed and interpreted locally for patient care decisions; however, tracings will be collected centrally for independent evaluation. ECGs will be read by the central ECG reader, within 1 day for screening ECGs and within 3 days for ECGs at other times.

Protocol-specified treatment will continue until there is disease progression by RECIST Version 1.1 or unacceptable toxicity as assessed by the investigator. If clinical progression is diagnosed then confirmation of disease progression with a CT scan (per RECIST Version 1.1) will be required.

Patients may opt to continue to receive treatment with CO-1686 following radiographic progression, as outlined in the NCCN guidelines for treatment of NSCLC with EGFR-TKIs[27] if the patient provides additional consent and the investigator believes it is in the best interest of the patient, in consideration of the potential risks and benefits, the current status of the rociletinib development program, and alternative treatment options. The investigator should inform the sponsor of their decision prior to starting post-progression treatment. In general, eligible patients may include those with asymptomatic systemic progression or locally symptomatic progression, such as brain metastases amenable to local treatment, with concomitant asymptomatic systemic progression or continued systemic disease control. This must be discussed with, and approved by, the sponsor and will be reviewed on a case-by-case basis. If a patient continues treatment post-progression, all study assessments including efficacy assessments, safety assessments, QoL

administration, and blood collection for biomarker analysis and companion diagnostic development should continue per protocol. The patient should be discontinued from treatment once it is clear that no further clinical benefit can be achieved.

Following disease progression, patients who provide additional consent will undergo tumor biopsy before subsequent-line therapy is initiated.

5.1.4 End-of-Treatment

All patients should return to the clinic for end-of-treatment assessments 28 ± 7 days after the last dose of oral rociletinib or single-agent cytotoxic chemotherapy has been administered. Patients in the cross over portion of the study will only have 1 End-of-Treatment Visit after discontinuation of cross over rociletinib. Patients who continue treatment with rociletinib after radiological progression will likewise only have 1 End-of-Treatment Visit after discontinuation of rociletinib.

The trial will be completed when all enrolled patients have discontinued treatment in this protocol and completed the End-of-Treatment follow-up Visit.

5.1.5 Follow-up

All patients will be followed up at approximately every 2 months, starting at the End-of-Treatment Visit, to monitor survival status until death or sponsor decision, whichever comes first. After discontinuation of protocol-specified treatment, subsequent anticancer therapy use will be recorded. If the patient discontinues treatment before progression, then scans should continue until progression according to the protocol schedule of every 6 ± 1 weeks.

5.1.6 Extension Phase

In mid-2015, Clovis submitted a New Drug Application for the use of rociletinib in patients with T790M-positive NSCLC. In June 2016, the FDA issued a Complete Response Letter to Clovis stating that more data is required to approve rociletinib for use outside of a clinical trial. Based on this outcome, Clovis decided to discontinue development of CO-1686 for NSCLC. Patients will be informed of this change in the development plans in an update to the informed consent form for this study. Those patients who continue to derive clinical benefit from study treatment will be allowed to continue on study at the discretion of the Principal Investigator in an extension phase.

The purpose of this protocol amendment is to add a new Extension Phase to allow patients to continue on study but to avoid unnecessary collection of data that will no longer be analyzed or required for regulatory purposes, whilst maintaining an appropriate level of safety monitoring. A new schedule of assessments for the Extension Phase as well as a complete description of procedures has been provided in Appendix C. This schedule will replace all schedules of assessments in Section 9 and should be followed for all patients.

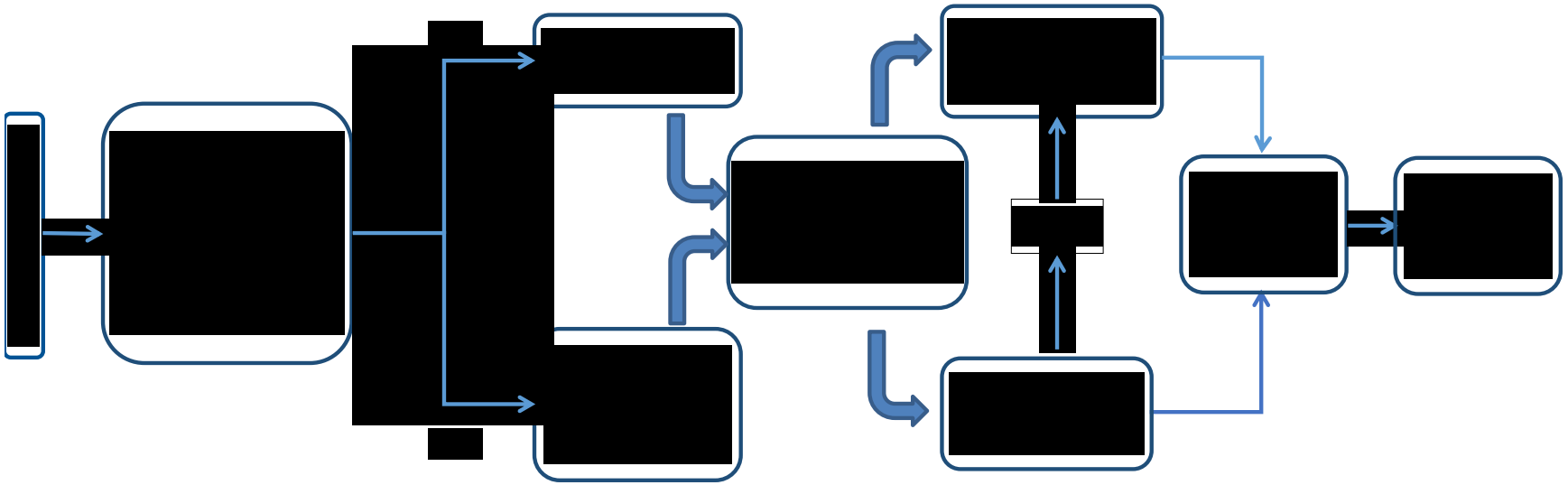
For patients who wish to continue rociletinib treatment post progression or for patients who wish to crossover to rociletinib treatment following progression on chemotherapy it is important that a

full exploration of alternative treatment options between patients and their treating physicians takes place.

5.2 Study Schema

The study schema in Figure 5-1 summarizes the treatment design of the study.

Figure 5-1: Study Schema



Abbreviations: OS = overall survival; PD = progressive disease per RECIST Version 1.1; R = randomization; RECIST = Response Evaluation Criteria In Solid Tumors, Version 1.1.

Screening: Biopsy or surgical resection of primary or metastatic lesions within 60 days prior to start of treatment.

Randomization: Patients will be allocated to rociletinib or comparator on 1:1 ratio.

6 STUDY POPULATION

6.1 Number of Patients and Sites

The total enrollment planned for this study is up to approximately 600 patients. There will be up to 150 investigative sites in North America, Europe, Asia, and Australia.

6.2 Inclusion Criteria

All patients must meet all of the following inclusion criteria:

1. Histologically or cytologically confirmed metastatic or unresectable locally advanced NSCLC with radiological progression on the most recent therapy received
2. Documented evidence of a tumor with 1 or more EGFR activating mutations excluding exon 20 insertion
3. Disease progression confirmed by radiological assessment while receiving treatment with single agent EGFR-TKI (eg, erlotinib, gefitinib, afatinib, or dacomitinib). The washout period for the single agent EGFR-TKI is a minimum of 3 days or 5 half-lives, whichever is more applicable, prior to start of treatment.
4. Multiple lines of prior treatment are permitted and there is no specified order of treatment, but in the course of their treatment history, patients must have received and have radiologically documented disease progression following:
   - At least 1 line of prior treatment with a single-agent EGFR TKI (eg, erlotinib, gefitinib, afatinib, or dacomitinib)
     - If EGFR-TKI is a component of the most recent treatment line, the washout period for the EGFR-TKI is a minimum of 3 days before the start of rociletinib treatment

   AND

   - A platinum-containing doublet chemotherapy (either progressed during therapy or completed at least 4 cycles without progression with subsequent progression after a treatment-free interval or after a maintenance treatment).
     - If cytotoxic chemotherapy is a component of the most recent treatment line, treatment with chemotherapy should have been completed at least 14 days prior to start of study treatment. When an EGFR-TKI is given in combination with platinum-containing doublet chemotherapy, treatment with the EGFR-TKI may continue until at least 3 days before start of treatment.
5. Have undergone a biopsy of either primary or metastatic tumor tissue within 60 days prior to start of treatment and have tissue available to send to sponsor laboratory or are able to undergo a biopsy during screening and provide tissue to sponsor laboratory
6. Measureable disease according to RECIST Version 1.1
7. Life expectancy of at least 3 months
8. ECOG performance status of 0 to 1

9. Age ≥ 18 years (in certain territories, the minimum age requirement may be higher eg, age ≥ 20 years in Japan and Taiwan, age ≥ 21 years in Singapore)
10. Patients should have recovered to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade ≤ 1 from any significant chemotherapy-related toxicities.
11. Adequate hematological and biological function, confirmed by the following local laboratory values:

    Bone marrow function

    a. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
    b. Platelets > 100.0 × 109/L
    c. Hemoglobin ≥ 9 g/dL (or 5.6 mmol/L)

    Hepatic function

    d. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × upper limit of normal (ULN); if liver metastases, ≤ 5 × ULN
    e. Bilirubin ≤ 2 × ULN
       – Patients with documented Gilbert's syndrome and conjugated bilirubin within the normal range may be allowed into the study. In this event, it will be documented that the patient was eligible based on conjugated bilirubin levels

    Renal function

    f. Creatinine clearance ≥ 45 mL/min

    Electrolytes

    g. Potassium and magnesium within normal range. Patients may receive supplements to meet this requirement

    Glucose

    h. Fasting serum glucose within normal ranges
12. Written consent on an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved ICF before any study specific evaluation

6.3 Exclusion Criteria

Any of the following criteria will exclude patients from study participation:

1. Any other malignancy associated with a high mortality risk within the next 5 years and for which the patients may be (but not necessarily) currently receiving treatment
   – Patients with a history of malignancy that has been completely treated, with no evidence of that cancer currently, are permitted to enroll in the trial provided all chemotherapy was completed > 6 months prior and/or bone marrow transplant > 2 years prior

2. Known pre-existing interstitial lung disease
3. Tumor small cell transformation by local assessment, irrespective of presence of T790M+ component
4. Patients with leptomeningeal carcinomatosis are excluded. Other central nervous system (CNS) metastases are only permitted if treated, asymptomatic, and stable (not requiring steroids for at least 2 weeks prior to randomization and the patient is neurologically stable; ie, free from new symptoms of brain metastases). If a patient has had brain metastasis treated within the previous 8 weeks, a follow up scan should have been performed to confirm that treated metastasis remain controlled without evidence of new lesions.
5. Patients who are currently receiving treatment with any medications that have the potential to prolong the QT interval and that treatment cannot be either discontinued or switched to a different medication (known to have no effect on QT) before starting protocol-specified treatment (see http://crediblemeds.org/ for a list of QT-prolonging medications)
6. Prior treatment with rociletinib, or other drugs that target T790M+ mutant EGFR with sparing of WT-EGFR including but not limited to AZD9291, HM61713, and TAS-121
7. Any contraindications for therapy with pemetrexed, paclitaxel, gemcitabine or docetaxel unless a contraindication with respect to one of these drugs will not affect the use of any of the others as a comparator to rociletinib
8. Any of the following cardiac abnormalities or history:
    a. Clinically significant abnormal 12-lead ECG, QT interval corrected using Fridericia's method (QTCF) > 450 msec
    b. Inability to measure QT interval on ECG
    c. Personal or family history of long QT syndrome
    d. Implantable pacemaker or implantable cardioverter defibrillator
    e. Resting bradycardia < 55 beats/min
9. Non-study related surgical procedures ≤ 7 days prior to randomization. In all cases, the patient must be sufficiently recovered and stable before treatment administration
10. Females who are pregnant or breastfeeding
11. Refusal to use adequate contraception for fertile patients (females and males) while on treatment and for 6 months after the last dose of study treatment (rociletinib and chemotherapy irrespective of single cytotoxic agent used)
12. Presence of any serious or unstable concomitant systemic disorder incompatible with the clinical study, eg, substance abuse, uncontrolled intercurrent illness including:

- uncontrolled diabetes
- active infection
- arterial thrombosis, and
- symptomatic pulmonary embolism

13. Any other reason the investigator considers the patient should not participate in the study
14. Treatment with live vaccines initiated less than 4 weeks prior to randomization

6.4 Criteria for Rociletinib Cross-over Treatment Eligibility Following Radiological Progression on or After Comparator Arm Therapy

To be eligible for participation in the cross over part of the study, patients must fulfil the following criteria:

1. Have documented radiological progression per RECIST 1.1 during or following completion of comparator arm therapy (single agent cytotoxic chemotherapy)
2. Have adequate hematological and biological function, confirmed by the following local laboratory values:

   Bone marrow function

   a. ANC $\geq 1.5 \times 10^9$/L
   b. Platelets $> 100.0 \times 10^9$/L
   c. Hemoglobin ≥ 9 g/dL (or 5.6 mmol/L)

   Hepatic function

   d. AST and ALT $\leq 3 \times$ ULN; if liver metastases, $\leq 5 \times$ ULN
   e. Bilirubin $\leq 2 \times$ ULN (except for patients with documented Gilbert's disease and conjugated bilirubin)

   Renal function

   f. Creatinine clearance ≥ 45 mL/min

   Electrolytes

   g. Potassium and magnesium within normal range. Patients may receive supplements to meet this requirement.

   Glucose

   h. Fasting serum glucose within normal ranges
3. Written consent on an IRB/IEC-approved ICF

In addition, any of the following will exclude patients from participation in the cross over part:

1. Patients who are currently receiving treatment with any medications that have the potential to prolong the QT interval and that treatment cannot be either discontinued or switched to a different medication (known to have no effect on QT) before starting rociletinib (see http://crediblemeds.org/ for a list of QT-prolonging medications)
2. Any of the following cardiac abnormalities or history:
   a. Clinically significant abnormal 12-lead ECG, QTCF > 450 msec

b. Inability to measure QT interval on ECG

c. Personal or family history of long QT syndrome

d. Implantable pacemaker or implantable cardioverter defibrillator

e. Resting bradycardia < 55 beats/min

3. Presence of any serious or unstable concomitant systemic disorder incompatible with the clinical study, eg, substance abuse, uncontrolled intercurrent illness including:
   - uncontrolled diabetes
   - active infection
   - arterial thrombosis, and
   - symptomatic pulmonary embolism
4. A positive pregnancy test in females of childbearing potential
5. Any other reason the Investigator considers the patient should not participate in the cross over study

6.5 Patients or Partners of Patients of Reproductive Potential

Pregnancy is an exclusion criterion and women of childbearing potential must not be considering getting pregnant during the study. Female patients who are more than 2 years postmenopausal or have had a hysterectomy will not be considered of childbearing potential. Female patients of childbearing potential must have a negative serum pregnancy less than 3 days before randomization. Since there is a 3 day window between randomization and C1D1, a urine pregnancy test must be performed on C1D1 to confirm that the patient is not pregnant before dosing. Both values should be entered in the electronic case report form (eCRF). Another serum pregnancy test will be performed at the End-of-Treatment Visit, and during screening for patients who chose to cross over from comparator arm therapy to receive rociletinib.

Patients of reproductive potential (males and females) must practice an adequate method of contraception during treatment and for 6 months after the last dose of study treatment (rociletinib and chemotherapy irrespective of the single cytotoxic agent used). Adequate contraception is defined as:

- Abstinence - Complete abstinence, acceptable only when it is the usual and preferred lifestyle of the patient, periodic abstinence (eg, calendar, symptothermal, post-ovulation methods) is not acceptable; or
- Double-barrier protection (ie, condom plus spermicide in combination with a diaphragm, cervical/vault cap, or intrauterine device).

Patients will be instructed to notify the investigator if pregnancy is discovered either during or within 6 months of completing treatment. This also applies to male patients whose partners become pregnant while the patient is on study or within the 6-month period after the last dose of study drug.

6.6 Waivers of Inclusion/Exclusion Criteria

No waivers of these inclusion or exclusion criteria will be granted by the investigator and the sponsor or its designee for any patient enrolling into the study.

7 DESCRIPTION OF STUDY TREATMENTS AND DOSE MODIFICATIONS

7.1 Description of Study Treatments

7.1.1 Rociletinib

Rociletinib is provided as yellow, film-coated tablets for oral administration in two dosage strengths made from the same drug blend. The strengths are achieved by adjusting the total tablet weight. The strengths are differentiated by tablet shapes: the 125 mg strength is a round tablet and the 250 mg strength is an oval tablet. Each tablet consists of CO-1686 HBr drug substance, silicified microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, copovidone, magnesium stearate and hypromellose based film coat. Excipients used are generally regarded as safe (GRAS). Tablets are packaged along with desiccant in high density polyethylene bottles closed with a child-resistant cap. Tablets will be supplied to the study sites by the sponsor. Rociletinib tablets should be stored in their original packaging at 15°C to 30°C (59°F to 86°F).

Child-resistant bottles containing rociletinib tablets are labeled according to applicable regulations for investigational products. Patients should be advised not to split or crush tablets. Additionally, patients should be advised not to take tablets with chips or other gross visual defects. Defective tablets should be returned to the study site and reported to the sponsor.

7.1.2 Single-agent Cytotoxic Chemotherapy

The comparator product is single agent cytotoxic chemotherapy: investigator choice of pemetrexed, gemcitabine, docetaxel, or paclitaxel. Commercially available pemetrexed, gemcitabine, docetaxel, and paclitaxel will be either procured by investigational centers or be supplied by the sponsor. Each product will be stored in accordance with manufacturer's product labeling.

7.2 Method of Assigning Patients to Treatment Groups

Patients will be randomized 1:1 to receive oral rociletinib or single-agent cytotoxic chemotherapy (investigator choice of pemetrexed, gemcitabine, docetaxel, or paclitaxel; choice of chemotherapy agent must be specified before randomization). Randomization will be stratified according to:

1. Brain metastases present versus no brain metastases present
2. ECOG performance status 0 versus ECOG performance status 1
3. Territory of residence at time of randomization (East Asian versus non-East Asian).

7.3 Preparation and Administration of Protocol-specified Treatment

7.3.1 Rociletinib

Rociletinib will be administered daily at 500 mg BID. Treatment with rociletinib is continuous and each cycle will comprise of 21 days. The first dose will be administered at the clinic during the visit on Day 1 of each cycle, then the patient should take rociletinib at home, at approximately the same time each day. Patients should take rociletinib as directed by the treating physician. Each dose should be taken with 8 oz (240 mL) of water and with a meal or within 30 minutes after a meal. Tablets should be swallowed whole.

For patients who started therapy with rociletinib at 625 mg BID under Protocol Amendment 1, a reduction in dose to 500 mg BID is allowed, only if necessitated by unacceptable toxicity.

If a patient misses a dose (ie, does not take it within 6 hours of the scheduled time), he or she should resume taking rociletinib with their next scheduled dose. Missed or vomited doses will not be made up.

The investigator or designee will be responsible for distributing the appropriate strength(s) of oral rociletinib tablets to all patients. A sufficient number of tablets will be provided to the patient to last until the next scheduled visit. Patients will be instructed to record daily doses taken or not taken at home in a patient diary, and will be instructed to bring their rociletinib tablets and diary to the next scheduled clinic visit for reconciliation by site personnel.

Supportive care should be given if required to manage AEs per institutional guidelines. Prophylactic treatment is not required.

7.3.2 Single-agent Cytotoxic Chemotherapy

The choice of single-agent cytotoxic chemotherapy is at the discretion of the investigator from amongst the regimens described in this protocol and must be specified and documented before randomization. The following treatment and premedication regimens are recommended for the comparator regimens; however, locally approved premedication protocols may be followed at the investigator's discretion.

7.3.2.1 Pemetrexed

Pemetrexed will be administered to patients intravenously in clinic at 500 mg/m^2 over 10 minutes on Day 1 of each 21-day cycle.

A corticosteroid should be given the day before, on the day of, and on the day after pemetrexed administration. The corticosteroid should be equivalent to 4 mg of dexamethasone administered orally BID.

Patients treated with pemetrexed should also receive vitamin supplementation. Patients should take oral folic acid or a multivitamin containing folic acid (350 to 1000 micrograms) on a daily basis. At least 5 daily doses of folic acid must be taken preceding the first dose of pemetrexed. If pemetrexed is considered as a chemotherapy choice, then folic acid supplementation may begin

prior to randomization to minimize treatment delay. Dosing should continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Patients should also receive an intramuscular injection of vitamin B12 (1000 micrograms) in the week preceding the first dose of pemetrexed and once every 3 cycles thereafter. Subsequent vitamin B12 injections may be given on the same day as pemetrexed.

Complete blood counts (CBC), including platelet counts, should be performed on all patients receiving pemetrexed. Patients should be monitored before each dose and on Days 8 and 15 of each cycle. Patients should not begin a new cycle of treatment unless the ANC is ≥ 1500 cells/mm^3, the platelet count is $\geq 100{,}000$ cells/mm^3, and creatinine clearance is ≥ 45 mL/min. Pemetrexed should not be administered to patients whose creatinine clearance is < 45 mL/min using the standard Cockcroft and Gault formula:

$$\text{Males: } \frac{[140 - \text{Age in years}] \times \text{Actual Body Weight (kg)}}{72 \times \text{Serum Creatinine (mg/dL)}} = \text{mL/min}$$

$$\text{Females: Estimated creatinine clearance for males} \times 0.85$$

Caution should be exercised when administering pemetrexed concurrently with NSAIDs to patients whose creatinine clearance is < 80 mL/min.

7.3.2.2 Gemcitabine

Gemcitabine will be administered to patients intravenously in clinic at 1250 mg/m^2 over 30 minutes on Days 1 and 8 of each 21-day cycle.

Patients receiving gemcitabine should be monitored prior to each dose with a CBC, including differential and platelet count. Laboratory evaluation of renal and hepatic function, including transaminases and serum creatinine, should be performed prior to initiation of therapy and periodically thereafter. Gemcitabine should be administered with caution in patients with evidence of significant renal or hepatic impairment.

7.3.2.3 Docetaxel

There is a choice of 2 dosing regimens for docetaxel:

- Docetaxel administered intravenously in clinic at 75 mg/m^2 (60 mg/m^2 for Asian patients) over 1 hour on Day 1 of each 21-day cycle

Or

- Docetaxel administered intravenously in clinic at 35 mg/m^2 over 1 hour on a weekly basis as part of a continuous 21-day cycle; ie, dosing will be on Days 1, 8, and 15 of each 21-day cycle

All patients should be premedicated with corticosteroids, such as oral dexamethasone 16 mg per day (eg, 8 mg BID) for 3 days starting 1 day prior to docetaxel administration, in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

7.3.2.4 Paclitaxel

Paclitaxel will be administered to patients intravenously in clinic at 80 mg/m^2 as a 1 hour infusion, on a weekly basis as part of a continuous 21-day cycle; ie, dosing will be on Days 1, 8, and 15 of each 21-day cycle.

All patients should be premedicated prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of dexamethasone 20 mg administered orally approximately 12 and 6 hours before paclitaxel, diphenhydramine (or its equivalent) 50 mg intravenously, 30 to 60 minutes prior to paclitaxel, and cimetidine 300 mg or ranitidine 50 mg intravenously, 30 to 60 minutes before paclitaxel.

Patients who experienced severe hypersensitivity reactions to paclitaxel should not be rechallenged with the drug. Paclitaxel should not be administered to patients with baseline neutrophil counts of less than 1500 cells/mm^3. Frequent monitoring of blood counts should be performed during paclitaxel treatment. Patients should not be re-treated with subsequent cycles of paclitaxel until neutrophils recover to a level > 1500 cells/mm^3 and platelets recover to a level > 100,000 cells/mm^3.

If a patient develops significant conduction abnormalities during paclitaxel infusion, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel.

7.4 Dose Modifications of Protocol-specified Treatment

7.4.1 Rociletinib

No dose escalation above the starting dose is allowed. Two dose reduction steps are allowed for each patient. The dose reductions are from 500 mg BID (starting dose) to 375 mg BID, then to 250 mg BID. The dose of rociletinib should not be reduced below 250 mg BID without prior sponsor approval.

For NCI CTCAE Version 4.03 Grade 3 or 4 hematologic and non-hematologic toxicities (except for nausea/vomiting, alopecia, QTc prolongation and hyperglycemia), the dose should be initially reduced to 375 mg BID and, if persistent, to 250 mg BID for subsequent doses if the investigator and sponsor do not believe treatment discontinuation is required. Re-escalation of dose after resolution of AEs must be discussed and approved by sponsor prospectively.

If a patient continues to experience toxicity after these dose reduction steps, or if dosing with rociletinib is interrupted for > 14 consecutive days due to toxicity, treatment should be discontinued unless otherwise agreed between the investigator and the sponsor before re-introduction of study drug.

7.4.1.1 Management of Prolonged QT_C

ECGs will be measured throughout the study as described in the protocol. Readings for QT_C prolongation will be based on the average seen in the ECGs for each time point. Patients are required to have within-normal-range potassium and magnesium at enrollment, and these electrolytes should be maintained within range during rocilenitib treatment, if necessary using supplementation. If QT_C prolongation of CTCAE Grade 3 is observed, rociletinib will be withheld until the event has improved to Grade 1. Rociletinib can then be re-started at a reduced dose after sponsor approval. After 2 dose reduction evaluations, if CTCAE Grade 3 or above QT_C prolongation recurs, then rociletinib will be discontinued unless agreed with the sponsor that additional dose reductions can be evaluated. If QT_C prolongation changes of CTCAE Grade 4 are observed at any time, rociletinib will be discontinued permanently.

7.4.1.2 Management of Hyperglycemia

Rociletinib causes hyperglycemia in some patients secondary to inhibition of the insulin-like growth factor 1 receptor (IGF-1R) and insulin receptor (IR) kinases by a metabolite. Therefore, some patients will require addition of a glucose lowering medication and patients with pre-existing diabetes may require more frequent monitoring and/or adjustments of diabetic medication. Clinical experience with rociletinib suggests hyperglycemia generally occurs within the first 3 weeks of treatment, leading to the need for more intensive glucose monitoring during the first several weeks of the study. In Phase 1/2 clinical trial experience, increased nausea, vomiting, decreased appetite, diarrhea, muscle cramps and fatigue have been reported in patients with hyperglycemia. Such patients must be closely monitored including assessment of fasting glucose levels and early initiation of anti-hyperglycemic therapy. As rociletinib-induced hyperglycemia is mediated through insulin resistance, agents that suppress glucose synthesis (metformin), increase sensitivity to insulin (glitazones) or increase glucose excretion (sodium-glucose cotransporter 2 [SGLT2] inhibitors) are expected to be more effective than those that increase plasma insulin (sulphonylureas or exogenous insulin). Metformin has been used most frequently in rociletinib clinical studies and is, therefore, recommended as the initial agent to manage hyperglycemia in patients with normal renal function. In addition, preliminary data from the ongoing Study CO-1686-008 suggest that starting metformin at the same time rociletinib therapy is initiated may prevent development of rociletinib-induced hyperglycemia. For all patients, irrespective of whether they are receiving metformin prophylactically or therapeutically, glucose monitoring should be conducted according to the following schedule:

Fasting glucose will be measured at the following visits: screening, C1D1, C1D4 (± 1 day), C1D8 (± 1 day), C1D15 (± 1 day), C2D1, C2D15 (± 1 day), C3D1, C4D1, C5D1, CND1… and End-of-Treatment Visit.

The following guidelines for management of hyperglycemia are based on experience in the Phase 1 study. Whilst the blood glucose thresholds for intervention outlined below should be followed, management of individual patients should be based on local practices and the treating physician’s judgment. In all cases, the prescribing information should be followed and maximum approved dose of anti-hyperglycemic agent should not be exceeded.

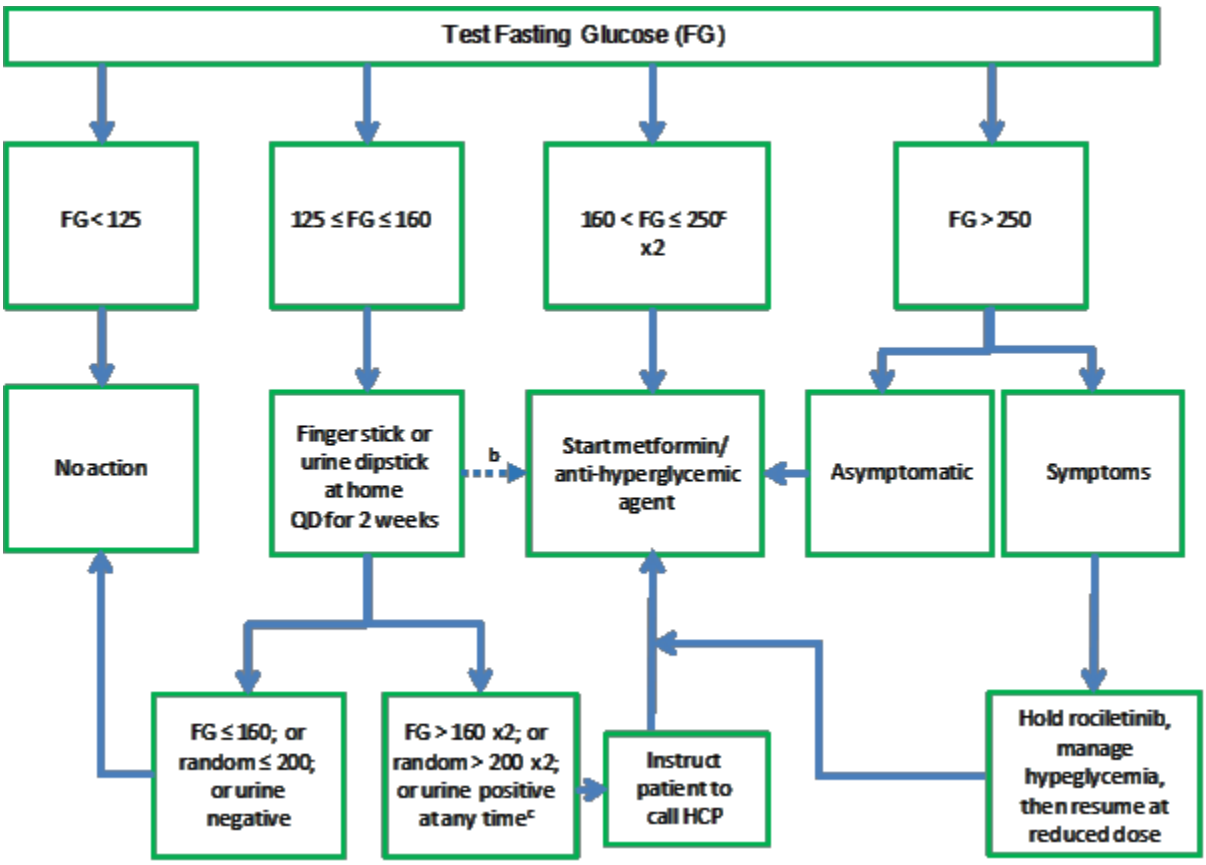
1. Additional monitoring outside of per protocol schedule is not needed if fasting glucose is < 125 mg/dL (< 6.94 mmol/L).
2. If fasting glucose ≥ 125 mg/dL (≥ 6.94 mmol/L) and ≤ 160 mg/dL (≤ 8.88 mmol/L), patients will be asked to perform self-monitoring of blood glucose using finger stick blood testing (preferred choice) or urine dipstick testing (a urine dipstick can show a false-positive glucosuria in patients taking SGLT2 inhibitors). Initiation of anti-hyperglycemic therapy with metformin or anti-hyperglycemic agent of choice should be considered at this time, particularly for patients with symptoms of increased nausea, vomiting, decreased appetite, diarrhea, muscle cramps and fatigue. Tests should be performed at home QD for at least 2 weeks, taking note of time, fasted/fed state, and glucose levels in a monitoring log provided. Patients should bring this monitoring log to scheduled visits and review with the treating physician. If patient observes at home 2 or more fasting blood glucose measurements > 160 mg/dL (> 8.88 mmol/L), and/or 2 or more random blood glucose measurements > 200 mg/dL (> 11.01 mmol/L) (or a combination of the 2), or 2 or more positive urine glucose tests before their next scheduled clinic visit, they should call their health care practitioner (HCP), inform the study site, and schedule a visit as soon as possible with the treating physician. Treatment with metformin or anti-hyperglycemic agent of choice should be started.
3. If fasting blood glucose > 160 mg/dL (≥ 8.88 mmol/L) and ≤ 250 mg/dL (≤ 13.87 mmol/L) on more than 2 occasions, start metformin or anti-hyperglycemic agent of choice. Patients should perform self-monitoring of blood glucose using finger stick blood testing or urine dipstick testing. Finger stick tests should be performed at home QD for at least 2 weeks, making note of time, fasted/fed state and glucose levels in a monitoring log provided. Patients should bring this monitoring log to scheduled visits and review with treating physician.
4. If fasting glucose > 250 mg/dL (> 13.87 mmol/L), and the patient is not symptomatic, manage as for Step 3 above. If the patient is symptomatic, then hold rociletinib and bring glucose under control acutely, if necessary using insulin with conversion to metformin or anti-hyperglycemic agent of choice once plasma glucose is controlled. Once patient is asymptomatic and deemed appropriate for additional therapy, rociletinib may be re-introduced at a reduced dose, with concomitant metformin/anti-hyperglycemic agent of choice. Patients should perform self-monitoring of blood glucose using finger stick blood testing or urine dipstick testing. Finger stick tests should be performed at home BID for at least 2 weeks, before breakfast and before dinner, taking note of time, fasted/fed state and glucose levels in a monitoring log provided. Patients should bring this monitoring log to scheduled visits and review with the treating physician.

Metformin is contraindicated in patients with renal disease or renal dysfunction, among others, and use should follow the package insert and approved label. In order to minimize known gastrointestinal (GI) toxicity associated with metformin use, the extended release form and taking medication at bedtime are recommended to improve tolerability.[28] Additional recommendations to avoid GI toxicity with metformin include starting treatment at a reduced dose (500 mg QD) for 72 hours, increasing to 500 mg BID for 72 hours, and if necessary, and increasing up to 1000 mg BID. If plasma glucose is not adequately controlled with the regimen outlined above, then consider adding pioglitazone or an SGLT-2 inhibitor and consider consultation with an endocrinologist.

End-of-Treatment

When rociletinib is discontinued, the need and use of anti-diabetic medications should be reassessed and the patient monitored and treated appropriately in order to minimize the possible hypoglycemia which may result.

Figure 7-1: Guidelines for Management of Hyperglycemia[a]



Abbreviations: FG = fasting plasma or serum glucose (in mg/dL); HCP = health care practitioner; QD = once daily.

[a] Guidelines intend to assist in managing patients that are non-diabetic at study start only.

[b] Consider initiation of anti-hyperglycemic therapy, particularly for patients with symptoms of increased nausea, vomiting, decreased appetite, diarrhea, muscle cramps and fatigue.

[c] For patients with a single elevation, fasting glucose can be repeated at the next regularly scheduled assessment.

7.4.2 Single-agent Cytotoxic Chemotherapy

Investigators can follow institutional guidelines or local dose reduction protocols for the comparator chemotherapy agents, otherwise investigators must follow the guidelines indicated in the protocol.

7.4.2.1 Pemetrexed

Hematological toxicities should be managed as follows:

Hematological Toxicity	Dose of Pemetrexed
Nadir ANC < 500/mm^3 and nadir platelets ≥ 50,000/mm^3	75% of previous dose
Nadir platelets < 50,000/mm^3 regardless of nadir ANC	75% of previous dose
Nadir platelets < 50,000/mm^3 with bleeding (CTCAE Grade 2) regardless of nadir ANC	50% of previous dose

Abbreviations: ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria for Adverse Events, Version 4.03.

If patients develop non-hematological toxicities ≥ Grade 3 (excluding neurotoxicity), pemetrexed should be withheld until resolution to less than or equal to the patient's pretherapy value. Treatment should be resumed according to the guidelines in the table below.

Non-hematological Toxicity	Dose of Pemetrexed
Any Grade 3 or 4 toxicity, except mucositis and neurotoxicity	75% previous dose
Any diarrhea requiring hospitalization (irrespective of grade) or Grade 3 or 4 diarrhea	75% previous dose
Grade 3 or 4 mucositis	50% previous dose

If patients develop neurotoxicity, treatment should be modified as follows:

CTCAE Grade	Dose of Pemetrexed
1	100% previous dose
2	100% previous dose
3, 4	Discontinue

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events, Version 4.03.

Pemetrexed therapy should be discontinued if a patient experiences any hematological or non-hematological Grade 3 or 4 toxicity after 2 dose reductions or immediately if Grade 3 or 4 neurotoxicity is observed.

7.4.2.2 Gemcitabine

Dose reduction within a treatment cycle should proceed as follows:

When the Day 8 dose is delayed more than 5 days because of toxicity, then that dose will be omitted and the next scheduled dose will be administered on time.

The criteria for step-wise dose reduction during a treatment cycle are as follows:

Within Cycle Dose Reduction Steps			
ANC, × 10^9/L		**Platelet Count, × 10^9/L**	**Percent of Full Dose During Cycle**
≥ 1.0	And	≥ 100	100
0.5 to 0.99	And/or	50 to 99	75
< 0.5	And/or	< 50	Hold

Abbreviations: ANC = absolute neutrophil count.

For other hematological and non-hematological toxicities of Grade 3/4 (except for nausea/vomiting and alopecia), the investigator should consider a dose reduction to 75%, and, if persistent, to 50% for subsequent doses. Once the dose has been reduced within a treatment cycle, treatment continues at that dose level; no dose escalation is possible during that cycle.

Dose reduction between treatment cycles should proceed as follows:

Treatment cycles may be delayed owing to drug-related toxicity or in the event of either ANC < 1.5 × 10^9/L or platelet count < 100 × 10^9/L. Delays of > 3 weeks require treatment to be permanently discontinued.

Occurrence of Grade 4 neutropenia lasting ≥ 7 days, febrile neutropenia, Grade 4 thrombocytopenia, or Grade 3 with clinically significant coagulopathy in the previous cycle require new cycles to start at 75% of the starting dose; recurrent febrile neutropenia requires starting new cycles at 50% of the starting dose.

7.4.2.3 Docetaxel

Docetaxel should be administered when the neutrophil count is ≥ 1500 cells/mm^3.

Three-weekly schedule:

In patients who experience either febrile neutropenia, neutrophil count < 500 cells/mm^3 for more than 1 week, severe or cumulative cutaneous reactions, severe peripheral neuropathy, or Grade 3 non-hematological toxicity during docetaxel therapy, treatment should be withheld until resolution of the toxicity and the subsequent dose of docetaxel should be reduced from 75 to 55 mg/m^2. If the patient continues to experience these reactions at 55 mg/m^2, the treatment should be discontinued.

If ≥ Grade 3 neuropathy occurs, docetaxel should be permanently discontinued

Weekly schedule:

If Grade 3 toxicity occurs, the dose of docetaxel should be reduced to 75 to 50% of the initial dose based on investigator assessment. If the patient continues to experience toxicity at a reduced dose, the treatment should be discontinued.

7.4.2.4 Paclitaxel

Adjust dose according to the following schedule:

Toxicity	CTCAE Grade	Adjustment
Febrile neutropenia	Any	Reduce paclitaxel to 65 mg/m^2
Peripheral neuropathy	Grade 2	Reduce paclitaxel to 65 mg/m^2
Peripheral neuropathy	Grade 3	Discontinue
Other	≥ Grade 3 excluding alopecia, nausea/vomiting/ diarrhea controlled by medication	Hold until Grade 1. If toxicity recurs on re-starting, reduce dose to 65 mg/m^2

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events, Version 4.03.

In addition, if any other Grade 3 AEs occur, the dose of paclitaxel should be reduced to 75 to 50% of the of the initial dose. Paclitaxel should not be repeated until the neutrophil count is at least 1500 cells/mm^3 and the platelet count is at least 100,000 cells/mm^3.

For all treatment regimens, additional supportive care may be used at the investigator's discretion and in accordance with institutional procedures.

7.4.2.5 For All Chemotherapy Regimens

If febrile neutropenia, Grade 4 thrombocytopenia for ≥ 7 days, or thrombocytopenia with bleeding occurs then no dose re-escalation is permitted.

7.5 Accountability of Protocol-specified Treatment

Study personnel will maintain accurate records of rociletinib and single-agent cytotoxic chemotherapy shipments/receipts (if provided by sponsor), administration, and drug reconciliation. The study site is responsible for the return or destruction of the study drugs as required. A drug management system will manage sponsor supplied study drug inventory at all sites. The system will be required to manage study treatment requests and shipments.

Any rociletinib or sponsor-provided cytotoxic chemotherapy accidentally or deliberately destroyed must be accounted for. All bottles of sponsor-provided study drug must be accounted for before their destruction at the study center. Unused bottles of sponsor-provided study drug should be destroyed locally. If destruction at the site is not possible, supply should be returned to the drug depot. During the course of the study and at completion of the study, the number of bottles of sponsor-provided study drug shipped, destroyed, and returned must be reconciled.

7.6 Blinding/Masking of Treatment

This is an open-label study; therefore, the investigational products will not be blinded or masked.

7.7 Treatment Compliance

7.7.1 Rociletinib

Documentation of dosing will be recorded in a study specific diary card provided by the sponsor (or designee). Study site personnel will enter the scheduled daily doses and the number of tablets to be taken each day. Study site personnel will review the dosing information with the patient (or legally authorized representative) on scheduled clinic visit days. Patients (or legally authorized representative) will be asked to record dosing information for oral rociletinib taken at home in the diary card and to bring the diary card and all unused tablets with them to scheduled clinic visits. A compliance check and tablet count for returned material will be performed by study personnel. Study site personnel will record compliance information on the eCRF and retain the diary card in the patient's medical record.

7.7.2 Single-agent Cytotoxic Chemotherapy

Chemotherapy (investigator choice of single-agent pemetrexed, gemcitabine, docetaxel, or paclitaxel) will be administered in the study clinic by study personnel and therefore treatment compliance is assured.

8 PRIOR AND CONCOMITANT THERAPIES

Medications known to produce QT prolongation should be avoided during the study whilst treatment is ongoing. If a drug that has the potential to cause QT prolongation is indicated to control AEs (eg, $5HT_3$ inhibitor for nausea/vomiting) and the investigator believes that the patient is benefiting from study therapy, then additional ECGs should be done to monitor for potential QT_C changes. The use of such concomitant medications and an appropriate ECG monitoring plan should be agreed between the investigator and sponsor. Acceptable antiemetics with low potential to affect QT_C include phenothiazines and corticosteroids.

All procedures performed and medications used during the study must be documented on the eCRF.

8.1 Anticancer or Experimental Therapy

No other anticancer therapies (including radiation, hormonal treatment [except corticosteroids and megestrol acetate], antibody or other immunotherapy or other experimental drugs) of any kind will be permitted while the patient is participating in the study.

Palliative radiation therapy intended to provide relief of cancer-related symptoms is permitted while the patient is on study, as long as there is no evidence of disease progression according to RECIST Version 1.1. Treatment should be withheld while the patient is undergoing radiotherapy.

Additionally, a patient who continues treatment post-progression may undergo radiation or other procedures to specific lesions post-progression, if the patient continues to benefit from treatment overall. See Section 5.1.3 for more details.

8.2 Hematopoietic Growth Factors and Blood Products

Erythropoietin, darbepoetin alfa, and/or hematopoietic colony-stimulating factors for treatment of cytopenias should be administered according to institutional guidelines. Prophylactic use of these agents is not permitted.

Transfusion thresholds for blood product support will be in accordance with institutional guidelines.

8.3 CYP450 Isozyme Inhibitors and Inducers

Caution should be exercised in patients receiving oral rociletinib and requiring concomitant medication with warfarin (Coumadin), NSAIDs, or clopidogrel, as rociletinib moderately inhibited CYP2C8, CYP2C9, and CYP2C19 activities *in vitro*. Patients taking warfarin who are enrolled in the study are required to have international normalized ratio (INR) monitored regularly per standard clinical practice. Preliminary data from an ongoing definitive CYP inhibition study revealed that rociletinib also moderately inhibited CYP3A4. As such, caution should be exercised in patients receiving rociletinib and the following CYP3A4 substrates with

narrow therapeutic range: alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimis, and terfenadine.

8.4 P-gp Substrates, Inhibitors, and Inducers

Because rociletinib is a P-gp inhibitor *in vitro*, caution should be exercised in patients receiving oral rociletinib and requiring concomitant medication with digoxin, a P-gp substrate. Patients taking digoxin who are enrolled in the study are required to have digoxin levels monitored regularly via standard clinical practice.

Rociletinib is a P-gp substrate and thus, P-gp inhibitors have the potential to increase rociletinib exposure. As such, caution should be exercised in patients receiving rociletinib and the following P-gp inhibitors: amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, and verapamil.

Conversely, P-gp inducers have the potential to decrease rociletinib exposure. Caution should be exercised in patients receiving rociletinib and the following P-gp inducers: avasimibe, carbamazepine, phenytoin, rifampin, St John's wort, and tipranavir/ritonavir.

8.5 Other Concomitant Medications

Therapies considered necessary for the patient's well-being may be given at the discretion of the investigator and in accordance with institutional procedures, and should be documented on the eCRF. Other concomitant medications, except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems, should be avoided.

Medications for nausea to consider, that are not associated with QT prolongation, include:

- Steroids (dexamethasone, methylprednisolone)
- Benzodiazepines
- Aprepitant
- Select anticholinergic agents (scopolamine)
- Trimethobenzamide
- Cannabinoids

Palonosetron is currently not listed on crediblemeds.org and a thorough QTc study showed no QTc effect. However, as rare cases of QTc prolongation have been reported, a more frequent ECG monitoring schedule should be adopted if used with rociletinib.

Because rociletinib is absorbed optimally in an acidic environment, proton pump inhibitors or H_2 blockers should be used with caution. If gastric acid blockade is required, short acting antacids are preferred.

Herbal and complementary therapies should not be encouraged because of unknown side effects and potential drug interactions, but any taken by the patient should be documented appropriately on the eCRF.

Yellow fever vaccine is strictly contraindicated in accordance with the pemetrexed Summary of Product Characteristics (SPC).

9 STUDY PROCEDURES

Table 9-1 summarizes the schedule of assessments for patients randomized to receive treatment with oral rociletinib. For patients randomized to receive single agent cytotoxic chemotherapy, the schedules of assessments are summarized in Table 9-2. Table 9-3 summarizes the schedule of assessments for patients who cross over to receive oral rociletinib after progressing on single-agent cytotoxic chemotherapy. Patients who continue to receive rociletinib after radiological progression should continue to follow the procedures as outlined in Table 9-1 without change.

All procedures and assessments are to be completed within ± 1 day of the scheduled time point and are synchronized with administration day (C1D1) of oral rociletinib or single-agent cytotoxic chemotherapy unless otherwise indicated.

Table 9-1: Schedule of Assessments for Patients Randomized to Rociletinib

	Consent	Screening		Randomization[a]	Treatment Period (Daily dosing)[b]							Post-treatment Period	
Procedure[c]	**Before Any Screening Procedures**	**Cycle 1 Day -35 to Day -3**	**Cycle 1 Day -14 to Day –3**	**Cycle 1 Day –3 (C1D–3)**	**Cycle 1 Day 1 (C1D1)[c]**	**Cycle 1 Day 4 ± 1 Day**	**Cycle 1 Day 8 ± 1 Day**	**Cycle 1 Day 15 ± 1 Day**	**Cycle 2 Day 1 (21 ± 3 days after C1D1)**	**Cycle 2 Day 15 ± 1 Day**	**Cycle 3 +, Day 1 (every 21 ± 3 days)**	**End of Treatment Visit (28 ± 7 days after last dose)**	**Follow-up (every 2 months for survival and subsequent therapy starting at end of treatment)**
Informed consent	X												
Random-ization[a]				X									
Medical/ oncology history		X											
Physical examination			X		X				X		X	X	
Vital signs[d], height (screening only), weight, ECOG PS			X (including height)		X				X		X	X	
Previous/ concomitant medications and procedures		X			X				X		X	X	
Contraceptive counseling[e]		X										X	
Local serum pregnancy test[f]			X									X	

Table 9-1: Schedule of Assessments for Patients Randomized to Rociletinib *(Cont.)*

	Consent	Screening		Randomization[a]	Treatment Period (Daily dosing)[b]							Post-treatment Period	
Procedure[c]	**Before Any Screening Procedures**	**Cycle 1 Day -35 to Day -3**	**Cycle 1 Day -14 to Day –3**	**Cycle 1 Day –3 (C1D–3)**	**Cycle 1 Day 1 (C1D1)[c]**	**Cycle 1 Day 4 ± 1 Day**	**Cycle 1 Day 8 ± 1 Day**	**Cycle 1 Day 15 ± 1 Day**	**Cycle 2 Day 1 (21 ± 3 days after C1D1)**	**Cycle 2 Day 15 ± 1 Day**	**Cycle 3 +, Day 1 (every 21 ± 3 days)**	**End of Treatment Visit (28 ± 7 days after last dose)**	**Follow-up (every 2 months for survival and subsequent therapy starting at end of treatment)**
Local urine pregnancy test[f]					X								
Local hematology (CBC and differential)			X		X				X		X	X	
Local fasting serum chemistry[h]			X		X	Fasting glucose only	Fasting glucose only	Fasting glucose only	X	Fasting glucose only	X	X	
Local urinalysis[i]			X										
Tumor scans, including brain imaging at screening[j]		X			Tumor scans performed every 6 ± 1 weeks during treatment, from C1D1							X	(X - if patient discontinues before progression)
PGx blood sample					X (optional; additional consent required)								

Table 9-1: Schedule of Assessments for Patients Randomized to Rociletinib *(Cont.)*

	Consent	Screening		Randomization[a]	Treatment Period (Daily dosing)[b]							Post-treatment Period	
Procedure[c]	**Before Any Screening Procedures**	**Cycle 1 Day -35 to Day -3**	**Cycle 1 Day -14 to Day –3**	**Cycle 1 Day –3 (C1D–3)**	**Cycle 1 Day 1 (C1D1)[c]**	**Cycle 1 Day 4 ± 1 Day**	**Cycle 1 Day 8 ± 1 Day**	**Cycle 1 Day 15 ± 1 Day**	**Cycle 2 Day 1 (21 ± 3 days after C1D1)**	**Cycle 2 Day 15 ± 1 Day**	**Cycle 3 +, Day 1 (every 21 ± 3 days)**	**End of Treatment Visit (28 ± 7 days after last dose)**	**Follow-up (every 2 months for survival and subsequent therapy starting at end of treatment)**
Tumor/ metastasis biopsy for biomarker/ EGFR mutational status[k]		X (within 60 days of C1D1)										X (optional; additional consent required)	
Blood for biomarker testing and exploratory research[l]		X			X				X		X	X	
Adverse events[m]		X	X	X	X				X		X	X	
Rociletinib dispensing/ administration					X				X		X		
Patient diary[n]					X				X		X	X	
ECG[o]		X			X			X	X		X	X	
Blood for sparse PK sampling and AAG serum levels[p]									X		X (Cycle 3 to 7 inclusive only)		

Table 9-1: Schedule of Assessments for Patients Randomized to Rociletinib *(Cont.)*

	Consent	Screening		Randomization[a]	Treatment Period (Daily dosing)[b]							Post-treatment Period	
Procedure[c]	**Before Any Screening Procedures**	**Cycle 1 Day -35 to Day -3**	**Cycle 1 Day -14 to Day –3**	**Cycle 1 Day –3 (C1D–3)**	**Cycle 1 Day 1 (C1D1)[c]**	**Cycle 1 Day 4 ± 1 Day**	**Cycle 1 Day 8 ± 1 Day**	**Cycle 1 Day 15 ± 1 Day**	**Cycle 2 Day 1 (21 ± 3 days after C1D1)**	**Cycle 2 Day 15 ± 1 Day**	**Cycle 3 +, Day 1 (every 21 ± 3 days)**	**End of Treatment Visit (28 ± 7 days after last dose)**	**Follow-up (every 2 months for survival and subsequent therapy starting at end of treatment)**
Quality of life questionnaires [q]			X		X						X (every 2 cycles ± 1 week until C7D1, then every 3 cycles ± 1 week)	X	
Survival status												X	X
Subsequent therapies for NSCLC												X	X

Abbreviations: AAG = alpha 1-acid glycoprotein; AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; β-hCG = beta human chorionic gonadotropin; BUN = blood urea nitrogen; C1D1 = Cycle 1 Day 1; CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer core quality of life questionnaire; EORTC QLQ-L13 = European Organisation for Research and Treatment of Cancer quality of life questionnaire lung cancer module; FFPE = formalin-fixed paraffin-embedded; HbA1c = glycated hemoglobin (A1c); ICF = informed consent form; PD = pharmacodynamic; PGx = pharmacogenomic; PK = pharmacokinetic; POPPK = population pharmacokinetics; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors, Version 1.1; TKI = tyrosine kinase inhibitor; WBC = white blood cells.

[a] C1D1 must be 3 days after randomization to allow patients in the pemetrexed chemotherapy arm enough time for folic acid and B12 treatment prior to therapy.

[b] Rociletinib will be administered orally BID at 500 mg/dose with 8 oz (240 mL) of water and with a meal or within 30 minutes after a meal.

[c] Unless specified, procedure is completed ± 1 day of scheduled time point and is synchronized with C1D1 of rociletinib.

[d] Vital signs (blood pressure, pulse, and temperature) taken pre-dose on C1D1, and without reference to dose at every subsequent visit. All vital signs will be obtained after the patient has been resting for at least 5 minutes. Height is only required once at screening.

Table 9-1: Schedule of Assessments for Patients Randomized to Rociletinib *(Cont.)*

	Consent	Screening		Randomization[a]	Treatment Period (Daily dosing)[b]							Post-treatment Period	
Procedure[c]	**Before Any Screening Procedures**	**Cycle 1 Day -35 to Day -3**	**Cycle 1 Day -14 to Day –3**	**Cycle 1 Day –3 (C1D–3)**	**Cycle 1 Day 1 (C1D1)[c]**	**Cycle 1 Day 4 ± 1 Day**	**Cycle 1 Day 8 ± 1 Day**	**Cycle 1 Day 15 ± 1 Day**	**Cycle 2 Day 1 (21 ± 3 days after C1D1)**	**Cycle 2 Day 15 ± 1 Day**	**Cycle 3 +, Day 1 (every 21 ± 3 days)**	**End of Treatment Visit (28 ± 7 days after last dose)**	**Follow-up (every 2 months for survival and subsequent therapy starting at end of treatment)**

[e] Fertile male patients and female patients of childbearing potential are to continue using effective contraception for 6 months after the last dose of rociletinib and report any pregnancies during this period.

[f] Serum β-hCG (evaluated by local laboratories) will be performed only on women of childbearing potential ≤ 3 days before randomization. An additional urine pregnancy test must be performed locally and results obtained prior to dosing on C1D1 to confirm that the patient is not pregnant before dosing.

[g] Includes hemoglobin, hematocrit, CBC, and differential (with ANC), and platelet count ≤ 14 days before randomization. Blood will be analyzed at a local laboratory and must be reviewed by the investigator before starting each new cycle of rociletinib administration. Additional tests may be performed at the investigator's discretion.

[h] Includes c-peptide, total protein, albumin, creatinine, BUN or urea, total bilirubin, alkaline phosphatase, ALT, AST, fasting glucose, sodium, potassium, magnesium, chloride, CO_2, calcium, phosphorus, and total cholesterol ≤ 14 days before randomization during screening and prior to starting each new cycle of rociletinib administration. Fasting glucose required on Cycle 1 Day 4 ± 1 day, Cycle 1 Day 8 ± 1 day, Cycle 1 Day 15 ± 1 day, and Cycle 2 Day 15 ± 1 day for patients taking rociletinib only (not required for patients taking chemotherapy). HbA1c will be measured ≤ 14 days before randomization during screening and on Day 1 of every other treatment cycle (Cycles 3, 5, 7, etc.). Samples will be analyzed by a local laboratory. Glucose must be measured following an 8 hour fast (no food or liquid other than water).

[i] Includes dipstick for protein, glucose, blood, pH, and ketones. If dipstick findings are abnormal, then a microscopic evaluation will be performed to assess the abnormal findings.

[j] Tumor scans obtained within 35 days before randomization may be used as the baseline scans. Scans will include the chest and abdomen (preferably CT scans with appropriate slice thickness per RECIST Version 1.1), using the same methods throughout the study that were used to detect lesions at baseline. Scans of the pelvis (CT or MRI) are required if there is prior evidence of local disease or if clinically indicated (symptomatic patients). Other studies (MRI, X-ray) may be performed if required. Brain imaging (CT/MRI) is required at baseline. Patients with brain lesions at screening should have the brain lesions followed throughout the study at the scheduled time points. Tumor scans will be performed during screening, then every 6 weeks ± 1 week from the time of randomization thereafter (Day 1 of Cycles 3, 5, 7, etc.) until tumor progression. Patients are required to have an end-of-treatment tumor scan using the same methodology used at screening unless the patient has radiographic evidence of disease progression while on study or it has been < 2 weeks since their last on-study scan. In addition, an MRI may be used in place of a CT for the end-of-treatment scan if required per local authorities. For patients with clinical progression, radiographic assessment should be performed to document evidence of radiographic progression. Patients who discontinue treatment without progression should continue to be scanned every 6 weeks per protocol until disease progression occurs. Exceptions to this requirement based on local institutional or regulatory requests must be agreed in advance with the sponsor. If a treatment cycle is delayed, the tumor scans should still follow the 6-weekly calendar schedule from the time of randomization. Scans will be evaluated locally for patient treatment decisions. Scans will also be stored with a central vendor and quality control performed; central reading of scans will not be done unless requested by the sponsor.

Table 9-1: Schedule of Assessments for Patients Randomized to Rociletinib *(Cont.)*

	Consent	Screening		Randomization[a]	Treatment Period (Daily dosing)[b]							Post-treatment Period	
Procedure[c]	**Before Any Screening Procedures**	**Cycle 1 Day -35 to Day -3**	**Cycle 1 Day -14 to Day –3**	**Cycle 1 Day –3 (C1D–3)**	**Cycle 1 Day 1 (C1D1)[c]**	**Cycle 1 Day 4 ± 1 Day**	**Cycle 1 Day 8 ± 1 Day**	**Cycle 1 Day 15 ± 1 Day**	**Cycle 2 Day 1 (21 ± 3 days after C1D1)**	**Cycle 2 Day 15 ± 1 Day**	**Cycle 3+, Day 1 (every 21 ± 3 days)**	**End of Treatment Visit (28 ± 7 days after last dose)**	**Follow-up (every 2 months for survival and subsequent therapy starting at end of treatment)**

[k] Biopsy of either primary or metastatic tissue to confirm EGFR mutational status, including EGFR T790M, and for the development of a validated tissue-based EGFR T790M test. Randomization of a given patient will be based on local mutational testing and independent of the patient's T790M status. Tissue material must be obtained within 60 days prior to start of treatment and following progression on the most recent EGFR-TKI therapy and at least 1 previous platinum-based chemotherapy. T790M assessment will be performed by a central laboratory. At progression and/or end of treatment (prior to initiating a new line of treatment), a tumor biopsy will be performed if the patient provides additional consent. All tumor tissue will be processed locally as FFPE tissue. Exploratory biomarker analysis will be done if FFPE tissue is available after T790M testing and diagnostic test validation. Refer to the Laboratory Manual for specimen handling instructions.

[l] Blood sampling for biomarker testing and exploratory research/pharmacodynamic assessment will be collected at screening (before biopsy, or at least 7 days AFTER the biopsy); predose on C1D1, then predose on Day 1 of every subsequent cycle, and at the End-of-Treatment Visit. Refer to the Laboratory Manual for sample processing details.

[m] Patients will be monitored for AEs from the time the first dose of rociletinib is administered through to 28 days after the last dose. Study procedure-related AEs that occur after signing of the ICF but before administration of rociletinib will also be collected. On C1D1, AEs will be monitored pre- and postdose.

[n] Patient diaries will be dispensed on C1D1. They should be collected and reviewed for compliance at each visit. No diary will be dispensed at end of treatment.

[o] ECGs in triplicate, 10-second tracings > 2 minutes apart. Taken anytime during screening, predose on C1D1, predose and 2 hours after dose on C1D15, then predose on Day 1 of every subsequent cycle (every 21 ± 3 days), and at end of treatment after treatment is discontinued. ECGs will be performed and interpreted locally for patient care decisions; however, tracings will be collected centrally for independent evaluation.

[p] Blood samples will be drawn for POPPK analysis at 21 ± 3 day intervals for the first 6 months (Day 1 of Cycles 2 to 7 inclusive) in all patients treated with rociletinib. The sample can be predose (eg, if the study visit is early in the day) or postdose (if the visit is late in the morning or in the afternoon). The blood draw time relative to the last rociletinib dosing time will be recorded at each PK sample occasion for each patient. Serum samples for AAG analysis will be collected on the same day as PK samples. Central laboratories will be used for bioanalysis of plasma rociletinib and 3 metabolites levels and AAG measurement. Refer to the Laboratory Manual for details on collection and processing of blood PK and AAG samples.

[q] QoL questionnaires (EORTC QLQ-C30 and EORTC QLQ-L13) and the EQ-5D preference-based health instrument will be collected at screening, predose on C1D1, then every 2 cycles ± 1 week for the first 6 cycles (Day 1 of Cycles 3, 5, 7 ± 1 week inclusive). After Cycle 7, questionnaires will be collected every 3 cycles ± 1 week (Day 1 of Cycle 10, 13, 16, etc. ± 1 week), and at the End-of-Treatment Visit.

Table 9-2: Schedule of Assessments for Patients Randomized to Single-agent Cytotoxic Chemotherapy

	Consent	Screening		Randomization	Chemotherapy Cycles[a]						Post-treatment Period	
Procedure[b]	**Before Any Screening Procedures**	**Cycle 1 Day –35 to Day –3**	**Cycle 1 Day –14 to Day –3**	**Cycle 1 Day -3 (C1D–3)**	**Cycle 1 Day 1 (C1D1)[c]**	**Cycle 1 Day 8 ± 1 Day**	**Cycle 1 Day 15 ± 1 Day**	**Cycle X+, Day 1 (every 21 ± 3 days)**	**Cycle X+ Day 8 ± 1 Day**	**Cycle X+ Day 15 ± 1 Day**	**End-of-Treatment Visit (28 ± 7 days after last dose)**	**Follow-up (every 2 months for survival and subsequent therapy starting at end of treatment)**
Informed consent	X											
Randomization				X								
Begin folic acid/plan B12 injection[p]				X								
Medical/onco-logy history		X										
Physical examination			X		X			X			X	
Vital signs[d], height (screening only), weight, ECOG PS			X (including height)		X			X			X	
Previous/ concomitant medications and procedures		X			X			X			X	
Contraceptive counseling[e]		X									X	
Local serum pregnancy test[f]			X								X	
Local urine pregnancy test[f]					X							

Table 9-2: Schedule of Assessments for Patients Randomized to Single-agent Cytotoxic Chemotherapy *(Cont.)*

	Consent	Screening		Randomization	Chemotherapy Cycles[a]						Post-treatment Period	
Procedure[b]	**Before Any Screening Procedures**	**Cycle 1 Day –35 to Day –3**	**Cycle 1 Day –14 to Day –3**	**Cycle 1 Day -3 (C1D–3)**	**Cycle 1 Day 1 (C1D1)[c]**	**Cycle 1 Day 8 ± 1 Day**	**Cycle 1 Day 15 ± 1 Day**	**Cycle X+, Day 1 (every 21 ± 3 days)**	**Cycle X+ Day 8 ± 1 Day**	**Cycle X+ Day 15 ± 1 Day**	**End-of-Treatment Visit (28 ± 7 days after last dose)**	**Follow-up (every 2 months for survival and subsequent therapy starting at end of treatment)**
Local hematology CBC and differential[g]			X		X	X	X	X	X	X	X	
Local fasting serum chemistry[h]			X		X			X			X	
Local urinalysis[i]			X									
Tumor scans, including brain imaging at screening[j]		X			Tumor scans performed every 6 ± 1 weeks during treatment, from C1D1						X	(X - if patient discontinues before progression)
Tumor/ metastasis biopsy for biomarker/EGFR mutational status[k]		X (within 60 days of C1D1)									X (optional; additional consent required)	
Blood for biomarker testing and exploratory research[l]		X			X			X			X	
Adverse events[m]		X	X	X	X	X	X	X	X	X	X	

Table 9-2: Schedule of Assessments for Patients Randomized to Single-agent Cytotoxic Chemotherapy *(Cont.)*

	Consent	Screening		Randomization	Chemotherapy Cycles[a]						Post-treatment Period	
Procedure[b]	**Before Any Screening Procedures**	**Cycle 1 Day –35 to Day –3**	**Cycle 1 Day –14 to Day –3**	**Cycle 1 Day -3 (C1D–3)**	**Cycle 1 Day 1 (C1D1)[c]**	**Cycle 1 Day 8 ± 1 Day**	**Cycle 1 Day 15 ± 1 Day**	**Cycle X+, Day 1 (every 21 ± 3 days)**	**Cycle X+ Day 8 ± 1 Day**	**Cycle X+ Day 15 ± 1 Day**	**End-of-Treatment Visit (28 ± 7 days after last dose)**	**Follow-up (every 2 months for survival and subsequent therapy starting at end of treatment)**
Chemotherapy administration					X	Xq	Xq	X	Xq	Xq		
ECG[n]		X			X			X			X	
Quality of life questionnaires[o]			X		X			X (every 2 cycles ± 1 week until C7D1, then every 3 cycles ± 1 week)			X	
Survival status											X	X
Subsequent therapies for NSCLC											X	X

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; β-hCG = beta human chorionic gonadotropin; BUN = blood urea nitrogen; C1D1 = Cycle 1 Day 1; CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer core quality of life questionnaire; EORTC QLQ-L13 = European Organisation for Research and Treatment of Cancer quality of life questionnaire lung cancer module; FFPE = formalin-fixed paraffin-embedded; HbA1c = glycated hemoglobin (A1c); ICF = informed consent form; PD = pharmacodynamic; PK = pharmacokinetic; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors, Version 1.1; TKI = tyrosine kinase inhibitor; WBC = white blood cells.

Table 9-2: Schedule of Assessments for Patients Randomized to Single-agent Cytotoxic Chemotherapy *(Cont.)*

	Consent	Screening		Randomization	Chemotherapy Cycles[a]						Post-treatment Period	
Procedure[b]	**Before Any Screening Procedures**	**Cycle 1 Day –35 to Day –3**	**Cycle 1 Day –14 to Day –3**	**Cycle 1 Day -3 (C1D–3)**	**Cycle 1 Day 1 (C1D1)[c]**	**Cycle 1 Day 8 ± 1 Day**	**Cycle 1 Day 15 ± 1 Day**	**Cycle X+, Day 1 (every 21 ± 3 days)**	**Cycle X+ Day 8 ± 1 Day**	**Cycle X+ Day 15 ± 1 Day**	**End-of-Treatment Visit (28 ± 7 days after last dose)**	**Follow-up (every 2 months for survival and subsequent therapy starting at end of treatment)**

[a] Pemetrexed will be administered to patients intravenously at 500 mg/m^2 on Day 1 of each 21-day cycle.
Gemcitabine will be administered to patients intravenously at 1250 mg/m^2 on Days 1 and 8 of each 21-day cycle.
Docetaxel will be administered to patients intravenously at 75 mg/m^2 (60 mg/m^2 in Asian patients) on Day 1 of each 21-day cycle, or at 35 mg/m^2 on a weekly basis as part of a continuous 21-day cycle (ie, dosing will be on Days 1, 8, and 15 of each 21-day cycle).
Paclitaxel will be administered to patients intravenously at 80 mg/m^2 as a 1 hour infusion, on a weekly basis as part of a continuous 21-day cycle (ie, dosing will be on Days 1, 8, and 15 of each 21-day cycle).

[b] Unless specified, procedure is completed ± 1 day of scheduled time point and is synchronized with administration day C1D1 of chemotherapy.

[c] C1D1 must be 3 days after randomization to allow patients in the pemetrexed chemotherapy arm enough time for folic acid and B12 treatment prior to therapy.

[d] Vital signs (blood pressure, pulse, and temperature, ECOG PS) taken pre-dose on C1D1, and without reference to dose at every subsequent visit. All vital signs will be obtained after the patient has been resting for at least 5 minutes. Height is only required once at screening.

[e] Fertile male patients and female patients of childbearing potential are to continue using effective contraception for 6 months after the last dose of chemotherapy and report any pregnancies during this period.

[f] Serum β-hCG (evaluated by local laboratories) will be performed only on women of childbearing potential ≤ 3 days before randomization. An additional urine pregnancy test must be performed locally and results obtained prior to dosing on C1D1 to confirm that the patient is not pregnant before dosing.

[g] Includes hemoglobin, hematocrit, CBC, and differential (with ANC), and platelet count ≤ 14 days before randomization. Blood will be analyzed at a local laboratory and must be reviewed by the investigator before starting each new cycle of chemotherapy administration. Additional tests may be performed at the investigator's discretion.

[h] Includes c-peptide, total protein, albumin, creatinine, BUN or urea, total bilirubin, alkaline phosphatase, ALT, AST, fasting glucose, sodium, potassium, magnesium, chloride, CO_2, calcium, phosphorus, and total cholesterol ≤ 14 days before randomization during screening and prior to starting each new cycle of chemotherapy. HbA1c will be measured ≤ 14 days before randomization during screening and on Day 1 of every other treatment cycle (Cycles 3, 5, 7, etc.). Samples will be analyzed by a local laboratory. Glucose must be measured following an 8 hour fast (no food or liquid other than water).

[i] Includes dipstick for protein, glucose, blood, pH, and ketones. If dipstick findings are abnormal, then a microscopic evaluation will be performed to assess the abnormal findings.

Table 9-2: Schedule of Assessments for Patients Randomized to Single-agent Cytotoxic Chemotherapy *(Cont.)*

	Consent	Screening		Randomization	Chemotherapy Cycles[a]						Post-treatment Period	
Procedure[b]	**Before Any Screening Procedures**	**Cycle 1 Day –35 to Day –3**	**Cycle 1 Day –14 to Day –3**	**Cycle 1 Day -3 (C1D–3)**	**Cycle 1 Day 1 (C1D1)[c]**	**Cycle 1 Day 8 ± 1 Day**	**Cycle 1 Day 15 ± 1 Day**	**Cycle X+, Day 1 (every 21 ± 3 days)**	**Cycle X+ Day 8 ± 1 Day**	**Cycle X+ Day 15 ± 1 Day**	**End-of-Treatment Visit (28 ± 7 days after last dose)**	**Follow-up (every 2 months for survival and subsequent therapy starting at end of treatment)**

j Tumor scans obtained within 35 days before randomization may be used as the baseline scans. Scans will include the chest and abdomen (preferably CT scans with appropriate slice thickness per RECIST Version 1.1), using the same methods throughout the study that were used to detect lesions at baseline. Scans of the pelvis (CT or MRI) are required if there is prior evidence of local disease or if clinically indicated (symptomatic patients). Other studies (MRI, X-ray) may be performed if required. Brain imaging (CT/MRI) is required at baseline. Patients with brain lesions at screening should have the brain lesions followed throughout the study at the scheduled time points. Tumor scans will be performed during screening, then every 6 weeks ± 1 week from the time of randomization thereafter (Day 1 of Cycles 3, 5, 7, etc.) until tumor progression. Patients are required to have an end-of-treatment tumor scan using the same methodology used at screening unless the patient has radiographic evidence of disease progression while on study or it has been < 2 weeks since their last on-study scan. In addition, an MRI may be used in place of a CT for the end-of-treatment scan if required per local authorities. For patients with clinical progression, radiographic assessment should be performed to document evidence of radiographic progression. Patients who discontinue treatment without progression should continue to be scanned every 6 weeks per protocol until disease progression occurs. Exceptions to this requirement based on local institutional or regulatory requests must be agreed in advance with the sponsor. If a treatment cycle is delayed, the tumor scans should still follow the 6-weekly calendar schedule from the time of randomization. Scans will be evaluated locally for patient treatment decisions. Scans will also be stored with a central vendor and quality control performed; central reading of scans will not be done unless requested by the sponsor.

k Biopsy of either primary or metastatic tissue to confirm EGFR mutational status, including EGFR T790M, and for the development of a validated tissue-based EGFR T790M test. Randomization of a given patient will be based on local mutational testing and independent of the patient's T790M status. Tissue material must be obtained within 60 days prior to start of treatment and following progression on the most recent EGFR-TKI therapy and at least one previous platinum-based chemotherapy. T790M assessment will be performed by a central laboratory. At progression and/or end of treatment (prior to initiating a new line of therapy), a tumor biopsy will be performed if the patient provides additional consent. All tumor tissue will be processed locally as FFPE tissue. Exploratory biomarker analysis will be done if FFPE tissue is available after T790M testing and diagnostic test validation. Refer to the Laboratory Manual for specimen handling instructions.

l Blood sampling for biomarker testing and exploratory research/PD assessment will be collected at screening (before biopsy, or at least 7 days AFTER the biopsy); pre-dose on C1D1, then pre-dose on Day 1 of every subsequent cycle, and at the End-of-Treatment Visit. Refer to the Laboratory Manual for sample processing details.

m Patients will be monitored for AEs from the time the first dose of chemotherapy is administered through to 28 days after the last dose. Study procedure-related AEs that occur after signing of the ICF but before administration of chemotherapy will also be collected. On C1D1, AEs will be monitored pre- and postdose.

n ECGs in triplicate, 10-second tracings > 2 minutes apart. Taken anytime during screening, predose on C1D1, then predose on Day 1 of every subsequent cycle (every 21 ± 3 days), and at end of treatment after treatment is discontinued. ECGs will be performed and interpreted locally for patient care decisions; however, tracings will be collected centrally for independent evaluation.

o QoL questionnaires (EORTC QLQ-C30 and EORTC QLQ-L13) and the EQ-5D preference-based health instrument will be collected at screening, predose on C1D1, then every 2 cycles ± 1 week for the first 6 cycles (Day 1 of Cycles 3, 5, 7 ± 1 week inclusive). After Cycle 7, questionnaires will be collected every 3 cycles ± 1 week (Day 1 of Cycle 10, 13, 16, etc. ± 1 week), and at end of treatment.

Table 9-2: Schedule of Assessments for Patients Randomized to Single-agent Cytotoxic Chemotherapy *(Cont.)*

	Consent	Screening		Randomization	Chemotherapy Cycles[a]						Post-treatment Period	
Procedure[b]	**Before Any Screening Procedures**	**Cycle 1 Day –35 to Day –3**	**Cycle 1 Day –14 to Day –3**	**Cycle 1 Day -3 (C1D–3)**	**Cycle 1 Day 1 (C1D1)**[c]	**Cycle 1 Day 8 ± 1 Day**	**Cycle 1 Day 15 ± 1 Day**	**Cycle X+, Day 1 (every 21 ± 3 days)**	**Cycle X+ Day 8 ± 1 Day**	**Cycle X+ Day 15 ± 1 Day**	**End-of-Treatment Visit (28 ± 7 days after last dose)**	**Follow-up (every 2 months for survival and subsequent therapy starting at end of treatment)**

[p] At least 5 daily doses of folic acid must be taken preceding the first dose of pemetrexed and dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Folic acid must be taken before starting pemetrexed. If the investigator selects pemetrexed as the comparator option for a patient, then folic acid supplementation may begin prior to randomization, if necessary, to ensure that C1D1 is not delayed while premedication is completed. Patients should also receive an intramuscular injection of vitamin B12 (1000 micrograms) in the week preceding the first dose of pemetrexed and once every 3 cycles thereafter. Subsequent vitamin B12 injections may be given on the same day as pemetrexed.

[q] All chemotherapy agents will be administered on Day 1 of each 21-day cycle. In addition, gemcitabine, docetaxel at the 35 mg/m^2 dose, and paclitaxel will be administered on Day 8 of each 21-day cycle; and docetaxel at the 35 mg/m^2 dose and paclitaxel will also be administered on Day 15 of each 21-day cycle. This does not apply to pemetrexed and docetaxel at the 75 mg/m^2 dose, which will only be administered on Day 1 of each 21-day cycle.

Table 9-3: Schedule of Assessments for Patients who Cross Over to Rociletinib After Chemotherapy

	Consent	Screening		Treatment Period (Daily dosing)[a]							Post-treatment Period	
Procedure[b]	**Before Any Screening Procedures**	**Day –35 to Day –1**	**Day –14 to Day –1**	**XO-Cycle 1 Day 1 (XO-C1D1)[c]**	**XO-Cycle 1 Day 4 ± 1 Day**	**XO-Cycle 1 Day 8 ± 1 Day**	**XO-Cycle 1 Day 15 ± 1 Day**	**XO-Cycle 2 Day 1 (21 ± 3 days after C1D1)**	**XO-Cycle 2 Day 15 ± 1 day**	**XO-Cycle 3+, Day 1 (every 21 ± 3 days)**	**End of Treatment visit (28 ± 7 days after last dose)**	**Follow-up (every 2 months for survival and subsequent therapy starting at end of treatment)**
Cross over informed consent	X											
Physical examination			X	X				X		X	X	
Vital signs[d], height (screening only), weight, ECOG PS			X (including height)	X				X		X	X	
Previous/concomitant medications and procedures		X		X				X		X	X	
Contraceptive counseling[e]		X									X	
Local serum pregnancy test[f]			X								X	
Local urine pregnancy test[f]				X								
Local hematology, CBC and differential[g]			X	X				X		X	X	
Local fasting serum chemistry[h]			X	X	Fasting glucose only	Fasting glucose only	Fasting glucose only	X	Fasting glucose only	X	X	
Tumor scans, including brain imaging at screening[i]		X		Tumor scans performed every 6 ± 1 weeks during treatment, from XO-C1D1							X	(X - if patient discontinues before progression

Table 9-3: Schedule of Assessments for Patients who Cross Over to Rociletinib After Chemotherapy *(Cont.)*

	Consent	Screening		Treatment Period (Daily dosing)[a]							Post-treatment Period	
Procedure[b]	**Before Any Screening Procedures**	**Day –35 to Day –1**	**Day –14 to Day –1**	**XO-Cycle 1 Day 1 (XO-C1D1)[c]**	**XO-Cycle 1 Day 4 ± 1 Day**	**XO-Cycle 1 Day 8 ± 1 Day**	**XO-Cycle 1 Day 15 ± 1 Day**	**XO-Cycle 2 Day 1 (21 ± 3 days after C1D1)**	**XO-Cycle 2 Day 15 ± 1 day**	**XO-Cycle 3+, Day 1 (every 21 ± 3 days)**	**End of Treatment visit (28 ± 7 days after last dose)**	**Follow-up (every 2 months for survival and subsequent therapy starting at end of treatment)**
PGx blood sample				X (optional; additional consent required)								
Tumor/metastasis biopsy for biomarker/EGFR mutational status[j]											X (optional; additional consent required)	
Blood for biomarker testing and exploratory research[k]		X		X				X		X	X	
Adverse events[l]		X	X	X				X		X	X	
Rociletinib dispensing/administration				X				X		X		
Patient diary[m]				X				X		X	X	
ECG[n]		X		X			X	X		X	X	
Blood for sparse PK sampling and AAG serum levels[o]								X		X (Cycle 3 to 7 inclusive only)		

Table 9-3: Schedule of Assessments for Patients who Cross Over to Rociletinib After Chemotherapy *(Cont.)*

	Consent	Screening		Treatment Period (Daily dosing)[a]							Post-treatment Period	
Procedure[b]	**Before Any Screening Procedures**	**Day –35 to Day –1**	**Day –14 to Day –1**	**XO-Cycle 1 Day 1 (XO-C1D1)[c]**	**XO-Cycle 1 Day 4 ± 1 Day**	**XO-Cycle 1 Day 8 ± 1 Day**	**XO-Cycle 1 Day 15 ± 1 Day**	**XO-Cycle 2 Day 1 (21 ± 3 days after C1D1)**	**XO-Cycle 2 Day 15 ± 1 day**	**XO-Cycle 3+, Day 1 (every 21 ± 3 days)**	**End of Treatment visit (28 ± 7 days after last dose)**	**Follow-up (every 2 months for survival and subsequent therapy starting at end of treatment)**
Quality of life questionnaires[p]			X	X						X (every 2 cycles ± 1 week until XO-C7D1, then every 3 cycles ± 1 week)	X	
Survival status											X	X
Subsequent therapies for NSCLC											X	X

Abbreviations: AAG = alpha 1-acid glycoprotein; AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; β-hCG = beta human chorionic gonadotropin; BUN = blood urea nitrogen; C1D1 = Cycle 1 Day 1; CT = computed tomography; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer core quality of life questionnaire; EORTC QLQ-L13 = European Organisation for Research and Treatment of Cancer quality of life questionnaire lung cancer module; FFPE = formalin-fixed paraffin-embedded; HbA1c = glycated hemoglobin (A1c); ICF = informed consent form; PD = pharmacodynamic; PGx = pharmacogenomic; PK = pharmacokinetic; POPPK = population pharmacokinetics; MRI = magnetic resonance imaging; NSCLC = non-small cell lung cancer; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors, Version 1.1; WBC = white blood cells, XO = cross over.

[a] Rociletinib will be administered BID at 500 mg/dose with 8 oz (240 mL) of water and with a meal or within 30 minutes after a meal.

[b] Unless specified, procedure is completed ± 1 day of scheduled time point and is synchronized with administration day of rociletinib (XO-C1D1).

[c] Procedures required on XO-C1D1 may be omitted if completed ≤ 3 days earlier during the screening period.

[d] Vital signs (blood pressure, pulse, and temperature, and ECOG PS) taken predose on XO-C1D1, and without reference to dose at every subsequent visit. All vital signs will be obtained after the patient has been resting for at least 5 minutes. Height is only required once at screening.

Table 9-3: Schedule of Assessments for Patients who Cross Over to Rociletinib After Chemotherapy *(Cont.)*

	Consent	Screening		Treatment Period (Daily dosing)[a]							Post-treatment Period	
Procedure[b]	**Before Any Screening Procedures**	**Day –35 to Day –1**	**Day –14 to Day –1**	**XO-Cycle 1 Day 1 (XO-C1D1)[c]**	**XO-Cycle 1 Day 4 ± 1 Day**	**XO-Cycle 1 Day 8 ± 1 Day**	**XO-Cycle 1 Day 15 ± 1 Day**	**XO-Cycle 2 Day 1 (21 ± 3 days after C1D1)**	**XO-Cycle 2 Day 15 ± 1 day**	**XO-Cycle 3+, Day 1 (every 21 ± 3 days)**	**End of Treatment visit (28 ± 7 days after last dose)**	**Follow-up (every 2 months for survival and subsequent therapy starting at end of treatment)**

e Fertile male patients and female patients of childbearing potential are to continue using effective contraception for 6 months after the last dose of rociletinib and report any pregnancies during this period.

f Serum β-hCG (evaluated by local laboratories) will be performed only on women of childbearing potential ≤ 3 days before XO-C1D1. An additional urine pregnancy test must be performed locally and results obtained prior to dosing on XO-C1D1 to confirm that the patient is not pregnant before dosing.

g Includes hemoglobin, hematocrit, CBC, and differential (with ANC), and platelet count ≤ 14 days before XO-C1D1. Blood will be analyzed at a local laboratory and must be reviewed by the investigator before start of each new cycle of rociletinib administration. Additional tests may be performed at the investigator's discretion.

h Includes c-peptide, total protein, albumin, creatinine, BUN or urea, total bilirubin, alkaline phosphatase, ALT, AST, fasting glucose, sodium, potassium, magnesium, chloride, CO_2, calcium, phosphorus, and total cholesterol ≤ 14 days before XO-C1D1 and prior to starting each new cycle of rociletinib administration. Fasting glucose required on XO-Cycle 1 Day 4 ± 1 day, XO-Cycle 1 Day 8 ± 1 day, XO-Cycle 1 Day 15 ± 1 day, and XO-Cycle 2 Day 15 ± 1 day. HbA1c will be measured ≤ 14 days before XO-C1D1 and on Day 1 of every other treatment cycle (XO-Cycles 3, 5, 7, etc.). Samples will be analyzed by a local laboratory. Glucose must be measured following an 8 hour fast (no food or liquid other than water).

i Tumor scans obtained at progression on/after comparator arm treatment should be used as XO-screening scans. Scans will include the chest and abdomen (preferably CT scans with appropriate slice thickness per RECIST Version 1.1), using the same methods throughout the study that were used to detect lesions at baseline. Scans of the pelvis (CT or MRI) are required if there is prior evidence of local disease or if clinically indicated (symptomatic patients). Other studies (MRI, X-ray) may be performed if required. Tumor scans will then be performed every 6 weeks ± 1 week from the time of crossover (Day 1 of XO-Cycles 3, 5, 7, etc.) until tumor progression. Patients are required to have an end of treatment tumor scan using the same methodology used at screening unless the patient has radiographic evidence of disease progression while on study or it has been < 2 weeks since their last on-study scan. In addition, an MRI may be used in place of a CT for the end-of-treatment scan if required per local authorities. For patients with clinical progression, radiographic assessment should be performed to document evidence of radiographic progression. Patients who discontinue treatment without progression should continue to be scanned every 6 weeks per protocol until disease progression occurs. Exceptions to this requirement based on local institutional or regulatory requests must be agreed in advance with the sponsor. If an XO-treatment cycle is delayed, the tumor scans should still follow the 6-weekly calendar schedule from the time of crossover. Scans will be evaluated locally for patient treatment decisions. Scans will also be stored with a central vendor and quality control performed; central reading of scans will not be done unless requested by the sponsor.

j A tumor biopsy will be performed (prior to initiating a new line of therapy) if the patient provides additional consent. All tumor tissue will be processed locally as FFPE tissue. Exploratory biomarker analysis will be done if FFPE tissue is available after T790M testing and diagnostic test validation. Refer to the Laboratory manual for specimen handling instructions.

k Blood sampling for biomarker testing and exploratory research/PD assessment will be collected at screening, predose on XO-C1D1, then pre-dose on Day 1 of every subsequent cycle, and at the End of Treatment Visit. Refer to the Laboratory Manual for sample processing details.

Table 9-3: Schedule of Assessments for Patients who Cross Over to Rociletinib After Chemotherapy *(Cont.)*

	Consent	Screening		Treatment Period (Daily dosing)[a]							Post-treatment Period	
Procedure[b]	**Before Any Screening Procedures**	**Day –35 to Day –1**	**Day –14 to Day –1**	**XO-Cycle 1 Day 1 (XO-C1D1)[c]**	**XO-Cycle 1 Day 4 ± 1 Day**	**XO-Cycle 1 Day 8 ± 1 Day**	**XO-Cycle 1 Day 15 ± 1 Day**	**XO-Cycle 2 Day 1 (21 ± 3 days after C1D1)**	**XO-Cycle 2 Day 15 ± 1 day**	**XO-Cycle 3+, Day 1 (every 21 ± 3 days)**	**End of Treatment visit (28 ± 7 days after last dose)**	**Follow-up (every 2 months for survival and subsequent therapy starting at end of treatment)**

[l] AEs will be collected from the time of the first dose of study therapy through to 28 days after the last dose of rociletinib.

[m] Patient diaries should be collected and reviewed for compliance at each visit. No diary will be dispensed at end of treatment.

[n] ECGs in triplicate, 10-second tracings > 2 minutes apart. Taken anytime during screening, pre-dose on XO-C1D1, pre-dose and 2 hours after dose on XO-C1D15, then pre-dose on Day 1 of every subsequent XO-cycle (every 21 ± 3 days), and at end of treatment after treatment is discontinued. ECGs will be performed and interpreted locally for patient care decisions; however, tracings will be collected centrally for independent evaluation.

[o] Blood samples will be drawn for POPPK analysis at 21 ± 3 day intervals for the first 6 months (Day 1 of Cycles 2 to 7 inclusive) in all patients treated with rociletinib. The sample can be pre-dose (eg, if the study visit is early in the day) or post-dose (if the visit is late in the morning or in the afternoon). The blood draw time relative to the last rociletinib dosing time will be recorded at each PK sample occasion for each patient. Serum samples for AAG analysis will be collected on the same day as PK samples. Central laboratories will be used for bioanalysis of plasma rociletinib and 3 metabolites levels and AAG measurement. Refer to the Laboratory Manual for details on collection and processing of blood PK and AAG samples.

[p] QoL questionnaires (EORTC QLQ-C30, and EORTC QLQ-L13) and the EQ-5D preference-based health instrument will be collected at screening, pre-dose on XO-C1D1, then every 2 cycles ± 1 week for the first 6 cycles (Day 1 of XO-Cycles 3, 5, 7 ± 1 week inclusive). After XO-Cycle 7, questionnaires will be collected every 3 cycles ± 1 week (Day 1 of XO-Cycle 10, 13, 16, etc. ± 1 week), and at end of treatment.

9.1 Screening Period (All Patients)

Following written informed consent, and unless otherwise specified, the following assessments should be carried out during the 35-day period before randomization. Assessments carried out before the patient signs informed consent are acceptable only if confirmed to have been standard of care.

To be performed **≤ 60 days prior to start of treatment**:

- Biopsy or surgical resection of primary or metastatic lesions ≤ 60 days prior to start of treatment. To ensure adequate viable tumor tissue is obtained, image-guided biopsies should be achieved with 18- to 20-gauge cutting needles to provide 1 to 3 cores measuring 1 to 1.5 cm in length. In addition, the biopsy must be of solid tumor tissue; ascites is not acceptable.

To be performed **≤ 35 days prior to randomization**:

- Documented evidence of a tumor with an EGFR activating mutation known to be associated with rociletinib drug sensitivity (exon 19 deletion, L858R, G719X, L861Q, T790M, and S768I) as determined by testing of the NSCLC tumor using an appropriate laboratory technique
- Medical history, including demographic information (birth date, race, gender, etc.) smoking status, and oncology history including date of cancer diagnosis, prior cancer treatment, and any surgical procedures
- Prior and concomitant medications
- Prior treatment for NSCLC
- Contraceptive counseling
- Study procedure-related AEs
- 12-lead ECG (in triplicate, 10-second tracings > 2 minutes apart)
- Tumor assessments of the chest and abdomen (preferably CT scans with appropriate slice thickness per RECIST Version 1.1), using the same methods throughout the study that were used to detect lesions at baseline. Scans of the pelvis (CT or MRI) are required if there is prior evidence of local disease or if clinically indicated (symptomatic patients). Assessments should consist of clinical examination and appropriate imaging techniques (CT scans with appropriate slice thickness per RECIST Version 1.1); MRI scans may be carried out in patients unable undergo CT scan or if requested by local regulatory authorities. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study.
- Brain imaging (CT/MRI) is required at baseline. Baseline brain lesions are only permitted if treated, asymptomatic, and stable (not requiring steroids for at least 2 weeks prior to randomization and the patient is neurologically stable; ie, free from new symptoms of brain metastases).
- Blood sampling for biomarker/EGFR mutational testing and exploratory research that may lead to development of a plasma-based EGFR test. Detailed sample handling instructions are provided in the Laboratory Manual.

To be performed **≤ 14 days prior to randomization**:

- Physical examination by body system, height, and weight
- ECOG performance status
- Vital signs (blood pressure, pulse, and temperature)
- Local hematology (hemoglobin, hematocrit, CBC and differential [with ANC], and platelet count)
- Local fasting serum chemistry (c-peptide, total protein, albumin, creatinine, blood urea nitrogen [BUN] or urea, total bilirubin, alkaline phosphatase, ALT, AST, fasting glucose, sodium, potassium, magnesium, chloride, carbon dioxide [CO_2], calcium, phosphorus, total cholesterol and glycated HbA1c
- Local urinalysis performed on freshly voided clean sample (dipstick for protein, glucose, blood, pH, and ketones). If dipstick findings are abnormal based on Investigator judgment, then a microscopic evaluation will be performed to assess the abnormal findings
- Study procedure-related AEs
- QoL Questionnaires (EORTC QLQ-C30 and EORTC QLQ-LC13) and the EQ-5D

To be performed **≤ 3 days prior to randomization**:

- Serum pregnancy test (by local laboratory) ≤ 3 days prior to randomization for women of childbearing potential

9.1.1 Screening for Patients who Cross Over to Rociletinib Having Progressed On or After Comparator Arm Therapy

The following baseline assessments will be established prior to the first dose of oral rociletinib and ≤ 35 days following radiographic progression on single-agent cytotoxic chemotherapy. Patients will be required to sign a cross over ICF before screening procedures begin.

To be performed **≤ 35 days prior to XO-C1D1**:

- Prior and concomitant medications
- Contraceptive counseling
- Study procedure-related AEs
- 12-lead ECG (in triplicate, 10-second tracings > 2 min apart)
- Tumor scans, including brain imaging at screening: scans used to determine radiographic progression on single agent cytotoxic chemotherapy will be used as baseline scans in cross over
- Blood sampling for biomarker/EGFR mutational testing and exploratory research

To be performed **≤ 14 days prior to XO-C1D1**:

- Physical examination by body system, height, and weight

- ECOG performance status
- Vital signs (blood pressure, pulse, and temperature)
- Local hematology (CBC and differential) and fasting serum chemistry (including HbA1c and a fasting glucose measurement)
- Study procedure-related AEs
- QoL Questionnaires (EORTC QLQ-C30 and EORTC QLQ-L13) and EQ-5D

To be performed **≤ 3 days prior to XO-C1D1**:

- Serum pregnancy test (by local laboratory) ≤ 3 days prior to randomization for women of childbearing potential

9.2 Randomization

Randomization will occur 3 days before initiation of study treatment (C1D1). All patients randomized to the comparator arm and selected to receive pemetrexed are required to take at least 5 doses of folic acid preceding the first dose of pemetrexed. Folic acid must be taken before starting pemetrexed. If the investigator selects pemetrexed as the comparator option for a patient, then folic acid supplementation may begin prior to randomization, if necessary, to ensure that C1D1 is not delayed while premedication is completed.

Patients are not required to be present in the clinic for randomization to occur but sites should be mindful of the 3 day difference between randomization and C1D1 for all patients when planning visits. Patients can continue receiving treatment with a single-agent EGFR-TKI (eg, erlotinib, gefitinib, afatinib, or dacomitinib) until 3 days before C1D1.

Before enrolling a patient, all eligibility criteria must be satisfied. Before enrolling a patient onto the rociletinib cross-over period following progression on or after comparator arm chemotherapy treatment, all eligibility criteria for entry to the cross over period must be satisfied.

9.3 Treatment Period

During the treatment period, patients will receive either oral rociletinib tablets or infusions of a single agent cytotoxic chemotherapy, as directed.

Oral rociletinib should be taken BID at 500 mg/dose with 8 oz (240 mL) of water and with a meal or within 30 minutes after a meal. In each cycle, the first dose of rociletinib will be taken in clinic, with the remaining doses self-administered by the patient at home. Patients will record the dose and timing of administration of oral rociletinib whilst at home in their daily dosing diary.

For patients who started therapy with rociletinib at 625 mg BID under Protocol Amendment 1, a reduction in dose to 500 mg BID is allowed, only if necessitated by unacceptable toxicity.

The choice of single-agent cytotoxic chemotherapy is at the discretion of the investigator from amongst the regimens described in this protocol. See the table in Section 5.1.3 and Section 7.3.2 for dosing details.

Unless otherwise specified, all patients will undergo the following procedures and assessments.

9.3.1 Patients Randomized to Rociletinib or Who Cross Over to Rociletinib Having Progressed On or After Comparator Arm Therapy

9.3.1.1 Cycle 1 Day 1 (C1D1) and Cross Over Cycle 1 Day 1 (XO-C1D1)

Patients will be required to take their first dose of rociletinib at the clinic with 8 oz (240 mL) of water and with a meal or within 30 minutes after a meal. The following procedures will be carried out pre- and post-dose.

Predose Assessments	**Postdose Assessments**
Physical examination Weight ECOG performance status Vital signs (blood pressure, pulse, and temperature) Urine pregnancy test (with negative result) Concomitant medications and procedures Local hematology (CBC and differential and fasting serum chemistry (includes fasting glucose) Blood sampling for biomarker/EGFR mutational testing and exploratory research Pharmacogenomic blood sample Rociletinib tablets will be dispensed to the patient Patient diary dispensed 12-lead ECG, 5 to 10 minutes before dosing (in triplicate, 10-second tracings > 2 minutes apart) QoL questionnaires (EORTC QLQ-C30, EORTC QLQ-LC13) and EQ-5D	AEs experienced by the patient since dosing will be documented Concomitant medications administered since dosing will be recorded

Enough rociletinib tablets (and diary cards) will be dispensed to the patient for daily dosing until the next study clinic visit.

9.3.1.2 Cycle 1 Day 4 and Cross Over Cycle 1 Day 4 (XO-C1D4) (± 1 Day)

The following procedures will be carried out:

- Fasting glucose

9.3.1.3 Cycle 1 Day 8 and Cross Over Cycle 1 Day 8 (XO-C1D8) (± 1 Day)

The following procedures will be carried out:

- Fasting glucose

9.3.1.4 Cycle 1 and Cycle 2 Day 15 and Cross Over Cycle 1 and Cycle 2 Day 15 (XO-C1D15 and XO-C2D15) (± 1 Day)

The following procedures will be carried out:

- Fasting glucose
- 12-lead ECG (in triplicate, 10-second tracings > 2 minutes apart; Cycle 1 Day 15 and cross over Cycle 1 Day 15 only)

9.3.1.5 Cycle 2 Day 1 and Cross Over Cycle 2 Day 1 (21 ± 3 Days After C1D1 and XO-C1D1) and Cycle 3+ Day 1 and Cross Over Cycle 3+ Day 1 (every 21 ± 3 Days Thereafter)

The following procedures will be carried out at 21 ± 3 day intervals:

- Physical examination
- Weight
- ECOG performance status
- Vital signs (blood pressure, pulse, and temperature)
- 12-lead ECG (in triplicate, 10-second tracings > 2 minutes apart)
- Local hematology (CBC and differential) and fasting serum chemistry (includes fasting glucose). HbA1c will be measured every other cycle (Day 1 of Cycles 3, 5, 7, etc.) after initiating rociletinib treatment.
- Blood sampling for biomarker/EGFR mutational testing and exploratory research
- Serum alpha 1-acid glycoprotein (AAG) samples and PK blood sample (Cycles 2 to 7 and cross over Cycles 2 to 7 inclusive only; Section 9.6.3)
- Concomitant medication and procedures since last visit
- AE monitoring
- Collection and review of patient diary
- QoL questionnaires (EORTC QLQ-C30 and EORTC QLQ-LC13) and the EQ-5D will be collected at screening, predose on C1D1 and XO-C1D1, then every 2 cycles ± 1 week for the first 6 cycles (Day 1 of Cycles 3, 5, 7 ± 1 week inclusive). After Cycle 7, questionnaires will be collected every 3 cycles ± 1 week (Day 1 of Cycle 10, 13, 16 ± 1 week, etc) and at end of treatment.
- Rociletinib tablets will be dispensed to the patient
- Patient diary will be dispensed to the patient
- Tumor assessments will be carried out every 6 weeks ± 1 week from the time of randomization until tumor progression (see Section 9.6.2.1)

9.3.2 Patients Randomized to Single-agent Cytotoxic Chemotherapy

9.3.2.1 Cycle X Day 1

The choice of single-agent cytotoxic chemotherapy is at the discretion of the investigator (pemetrexed, gemcitabine, docetaxel or paclitaxel). All chemotherapy agents will be administered to the patients at the clinic intravenously on Day 1 of each 21-day cycle:

- Pemetrexed will be administered at 500 mg/m^2
- Gemcitabine will be administered at 1250 mg/m^2
- Docetaxel will be administered either at 75 mg/m^2 (60 mg/m^2 for Asian patients) or at 35 mg/m^2
- Paclitaxel will be administered at 80 mg/m^2 as a 1 hour infusion

The following procedures will be carried out pre and postdose.

Predose Assessments	**Postdose Assessments**
Physical examination Weight ECOG performance status Vital signs (blood pressure, pulse, and temperature) Urine pregnancy test (with negative result) Concomitant medications and procedures Local hematology (CBC and differential) and fasting serum chemistry (includes fasting glucose) Blood sampling for biomarker/EGFR mutational testing and exploratory research AE monitoring 12-lead ECG, 5 to 10 minutes before dosing (in triplicate, 10-second tracings > 2 minutes apart) QoL questionnaires (EORTC QLQ-C30, EORTC QLQ-LC13) and EQ-5D Chemotherapy administration	AEs experienced by the patient since dosing will be documented Concomitant medications administered since dosing will be recorded

Tumor assessments will be carried out every 6 weeks ± 1 week from the time of randomization until tumor progression (see Section 9.6.2.1).

9.3.2.2 Cycle X Day 8 (± 1 Day)

If selected as the comparator option, gemcitabine, docetaxel, and paclitaxel will be administered at the clinic intravenously on Day 8 of each 21-day cycle:

- Gemcitabine will be administered at 1250 mg/m^2

- Docetaxel will be administered at 35 mg/m^2 (in patients randomized to this docetaxel dosing regimen)
- Paclitaxel will be administered at 80 mg/m^2 as a 1 hour infusion

Please note, the other chemotherapy agents (pemetrexed and docetaxel 75 mg/m^2 [60 mg/m^2 in Asian patients]) will not be administered on this day.

In addition, the following procedures will be carried out for all patients randomized to receive single agent cytotoxic chemotherapy (pemetrexed, gemcitabine, docetaxel, or paclitaxel):

- Hematology (CBC and differential)
- AE monitoring

9.3.2.3 Cycle X Day 15 (± 1 Day)

If selected as the comparator option, docetaxel and paclitaxel will be administered at the clinic intravenously on Day 15 of each 21-day cycle:

- Docetaxel will be administered at 35 mg/m^2 (in patients randomized to this docetaxel dosing regimen)
- Paclitaxel will be administered at 80 mg/m^2 as a 1 hour infusion

Please note, the other chemotherapy agents (pemetrexed, gemcitabine, and docetaxel 75 mg/m^2 [60 mg/m^2 in Asian patients]) will not be administered on this day.

In addition, the following procedures will be carried out for all patients randomized to receive single-agent cytotoxic chemotherapy (pemetrexed, gemcitabine, docetaxel, or paclitaxel):

- Hematology (CBC and differential)
- AE monitoring

9.4 End-of-Treatment Visit (All Patients)

The following procedures will be carried out for all patients 28 (± 7) days after the last dose of study treatment (initial study treatment or cross-over treatment, whichever comes last):

- Physical examination
- Weight
- ECOG performance status
- Vital signs (blood pressure, pulse, and temperature)
- Concomitant medications and procedures
- Contraceptive counseling
- Serum pregnancy test for women of childbearing potential

- Local hematology (CBC and differential) and fasting serum chemistry (including fasting glucose)
- Tumor scans (using the same methodology as was used at screening) unless it has been < 2 weeks since last scan or disease progression was noted on the last scan. In addition, an MRI may be used in place of a CT at end-of-treatment scan if required per local authorities. For patients with clinical progression, radiographic assessment should be performed to document evidence of radiographic progression.
- Optional tumor biopsy (requires additional consent)
- Blood sampling for biomarker/EGFR mutational testing and exploratory research
- AE monitoring (until 28 days after last dose of study treatment; then only ongoing SAEs will be followed until resolution or stabilization); after the 28-day specified window, only treatment-related SAEs should be reported
- Collection and review of patient diary (patients randomized to rociletinib only)
- 12-lead ECG (in triplicate, 10-second tracings > 2 minutes apart)
- QoL questionnaires (EORTC QLQ-C30 and EORTC QLQ-LC13) and the EQ-5D
- Survival status
- Subsequent therapies for NSCLC

9.5 Follow-up (All Patients)

The following procedures will be carried out for all patients every 2 months for survival and subsequent therapy (unless otherwise specified) following the End-of-Treatment Visit:

- Survival status – this may be done during routine clinic visits or by telephone contact
- Subsequent therapies for NSCLC will be documented during routine clinic visits or by telephone contact
- For patients who discontinue treatment prior to progression, tumor scans should be assessed approximately every 6 weeks (± 1 week) until progression

9.6 Methods of Data Collection

9.6.1 Safety Evaluations

9.6.1.1 Adverse Events Assessment

The investigator has the responsibility for assessing the safety of the patients and for compliance with the protocol to ensure study integrity. Patients will be monitored for AEs from the time the first dose of rociletinib or chemotherapy is administered through to 28 days after the last dose of protocol-specified treatment. Study procedure-related AEs that occur after signing of the ICF but before administration of study treatment will also be collected. Any ongoing SAEs will be followed until resolution or stabilization. AEs and laboratory abnormalities will be graded according to the NCI CTCAE grading system (Version 4.03)[14] and recorded on the eCRF.

Complete details for monitoring AEs, including the definition of drug-related AEs, are provided in Section 10.

9.6.1.2 Clinical Laboratory Investigations

Local laboratories will be used for hematology and chemistry and must be reviewed by the investigator before starting each new treatment cycle. Additional tests may be carried out at the investigator's discretion. The panels of laboratory tests to be done are shown below:

Hematology: Hemoglobin, hematocrit, CBC and differential (with ANC), and platelet count as per the schedule of assessments at screening, during treatment (Day 1 of each cycle; and Days 8 and 15 of each cycle in patients randomized to single agent cytotoxic chemotherapy), and at the End-of-Treatment Visit. Hematology results must be reviewed by the investigator before the start of treatment.

Patients known to require concomitant therapy with anticoagulant therapy such as warfarin should have coagulation markers monitored at screening and during the study.

Clinical chemistry: C-peptide, total protein, albumin, creatinine, BUN or urea, total bilirubin, alkaline phosphatase, ALT, AST, fasting glucose, sodium, potassium, magnesium, chloride, CO_2, calcium, phosphorus, and total cholesterol, as per the schedule of assessments at screening, during treatment (Day 1 of each cycle), and at the End-of-Treatment Visit. HbA1c will be measured at screening and Day 1 of every other cycle (Cycles 3, 5, 7, etc.) while the patient is on study.

For patients randomized to rociletinib or crossed over to rociletinib only: Fasting glucose must be measured following an 8 hour fast (no food or liquid other than water) at screening, C1D1, C1D4, C1D8, C1D15, C2D1, C2D15, XO-C1D1, XO-C1D4, XO-C1D8, XO-C1D15, XO-C2D1, XO-C2D15, and every Cycle *N* D1 thereafter, and at the End-of-Treatment Visit, also if clinically indicated on study. Fasting glucose is measured as part of the clinical chemistry panel (see above) on all Cycles Day 1 visits, and measured individually C1D4, C1D8, C1D15, C2D15, XO-C1D4, XO-C1D8, XO-C1D15, and XO-C2D15. Serum levels of AAG will be determined on PK sampling days.

Urinalysis: On freshly voided clean sample by dipstick for protein, glucose, blood, pH, and ketones as per the schedule of assessments. If dipstick findings are abnormal, then a microscopic evaluation will be done to assess the abnormal findings. Urinalysis will be carried out at screening only.

Serum beta human chorionic gonadotropin (β-hCG) pregnancy test: Performed on women of childbearing potential ≤ 3 days before randomization, ≤ 3 days before XO-C1D1 (as applicable), and at the End–of-Treatment Visit. A urine pregnancy test will be performed on C1D1 and XO-C1D1 (as applicable) to confirm that the patient is not pregnant before dosing. Both values should be entered in the eCRF. A negative result must be confirmed by a physician before the first dose of study treatment can be administered.

Laboratory reports will be reviewed by the investigator or delegated physician who will then comment on out-of-range values and assess their clinical significance. Clinically significant

abnormalities and associated panel results, as well as results of any additional tests carried out as follow-up to the abnormalities, will be documented on the eCRF as an AE.

9.6.1.3 Vital Signs

Vital signs will include blood pressure, pulse, and body temperature. All vital signs will be obtained after the patient has been resting for at least 5 minutes. Vital signs will be carried out at screening, at Day 1 of each Cycle (predose), and the End-of-Treatment Visit.

9.6.1.4 12-lead Electrocardiograms

Serial 12-lead ECGs will be taken at screening and at predose on Day 1 of each cycle (comparator arm); at screening, predose on C1D1, predose and 2 hours postdose on Cycle 1 Day 15, and predose on Day 1 of each subsequent cycle (rociletinib arm and cross over); at the End-of-Treatment Visit; and as clinically indicated. ECGs must be done in triplicate, 10-second tracings > 2 minutes apart.

ECGs should be carried out after the patient has been resting for at least 5 minutes. The 12-lead ECGs collected will be analyzed and interpreted locally for patient care decisions; however, tracings will be collected centrally for independent evaluation. Details on recording ECGs and preparation for central interpretation will be included in the Investigator's File.

9.6.1.5 Body Weight and Height

Height will be measured during the screening visit only. Weight will be measured at all clinic visits (the patient should be in light indoor clothes).

9.6.1.6 Physical Examinations

Physical examinations will include an assessment of all the major body systems. Complete physical examinations will be carried out at screening and at all clinic visits.

9.6.1.7 ECOG Performance Status

ECOG performance status (Appendix B) will be assessed at screening, Day 1 of each cycle, and at the End-of-Treatment Visit. ECOG performance status should be assessed by the same study personnel at each visit, if possible. Care will be taken to accurately score performance status, especially during screening for study eligibility purposes. Additional consideration should be given to borderline ECOG performance status to avoid enrolling patients with significant impairment.

9.6.2 Efficacy Evaluations

9.6.2.1 Tumor Assessments

Tumor assessments should consist of clinical examination and appropriate imaging techniques (preferably by CT scans of the chest and abdomen with appropriate slice thickness per RECIST Version 1.1). Scans of the pelvis (CT or MRI) are required if there is prior evidence of local disease or if clinically indicated (symptomatic patients). MRI scans may be carried out in

patients unable to undergo CT scan or if requested by local regulatory authorities. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study. An MRI may be used in place of a CT at end-of-treatment scan if required per local authorities.

Tumor assessments will be carried out at screening and every 6 weeks ± 1 week from the time of randomization thereafter (Day 1 of Cycles 3, 5, 7, etc.) until tumor progression, including at the End-of-Treatment Visit if disease progression has not been documented previously. For patients with clinical progression, radiographic assessment should be performed to document evidence of radiographic progression. Tumor scans do not need to be repeated at end of treatment if < 2 weeks since the last scan or the patient had disease progression at the last scan. Scans will be evaluated locally for patient treatment decisions. Scans will also be collected and stored with a central vendor and quality control performed; central reading of scans will not be done unless requested by the sponsor. Tumor response will be interpreted using RECIST Version 1.1 (Appendix A).[11]

If a treatment cycle is delayed, the efficacy assessments should still follow the 6-weekly calendar schedule from the time of randomization.

Patients who discontinue rociletinib or chemotherapy without progression should continue to be scanned every 6 weeks (± 1 week) per protocol until disease progression occurs. Exceptions to this requirement based on local institutional or regulatory requests must be agreed in advance with the sponsor. In these patients, a scan should be performed at the End-of-Treatment Visit. In this circumstance the end-of-treatment scan could be an MRI scan.

Patients who continue rociletinib treatment post-progression or patients who crossover to rociletinib should continue to be scanned according to the protocol (ie, every 6 ± 1 weeks) until they discontinue from the study.

Brain imaging (CT/MRI) is required at baseline. Patients with brain lesions at screening should have the brain lesions followed throughout the study at the scheduled time points.

9.6.3 Pharmacokinetic Evaluations

Blood samples will be drawn for POPPK analysis at 21 ± 3 day intervals for the first 6 months (Day 1 of Cycles 2 to 7 inclusive) in all patients treated with rociletinib (ie, only in patients randomized to receive rociletinib or those who cross over to receive rociletinib following treatment with single agent cytotoxic chemotherapy). The sample can be taken predose (for example, if the study visit is early in the day) or postdose (if the visit is late in the morning or in the afternoon). The blood draw time relative to the last dosing time will be recorded at each PK sample occasion for each patient.

Serum samples for AAG analysis will be collected on the same day as PK samples.

Central laboratories will be used for bioanalysis of plasma rociletinib and 3 metabolites levels and AAG measurement. Please refer to the Laboratory Manual for details on collection and processing of blood PK and AAG samples.

9.6.4 Pharmacogenomic Assessment

For patients randomized to the rociletinib treatment arm or who cross over to rociletinib after progression on chemotherapy, and who provide additional consent, a pharmacogenomic blood sample will be collected from each patient on C1D1 or XO-C1D1 in order to detect genetic polymorphisms in CYP isoenzymes and to explore the possible correlation between potential polymorphisms and drug exposure.

9.6.5 Biomarker Assessments – FFPE Tumor Tissue

If available, archival FFPE tumor tissue derived from the primary tumor, or an accessible local/distal metastatic lesion, will be obtained within 60 days before start of treatment. If archival tumor tissue is not available, a biopsy should be obtained during the screening period. Blood samples (ctDNA analysis; see Section 9.6.6 below) should be collected immediately before the biopsy procedure if possible; otherwise, the screening blood sample can be collected 7 days after the biopsy. To ensure adequate viable tumor tissue is obtained for mutational testing and diagnostic kit development, image-guided biopsies should be achieved with 18- to 20-gauge cutting needles to provide 1 to 3 cores measuring 1 to 1.5 cm in length. Tumor samples will be processed locally to yield FFPE tissue blocks. Entire FFPE blocks should be submitted when possible. Blocks will be returned upon request if required for legal or medical treatment purposes.

If sufficient tissue is available from the baseline tumor biopsy, samples will be tested for other molecular alterations, that may modulate response or resistance to EGFR-targeted therapy including but not limited to EGFR gene amplification, MET gene amplification, PIK3CA mutations, and expression of other growth factor receptors and their ligands.

Following disease progression, patients who provide additional consent will undergo a tumor biopsy before subsequent line therapy is initiated. This tissue will be analyzed for molecular alterations that modulate resistance to the study-assigned therapy.

Sample handling instructions will be provided in a separate Laboratory Manual.

9.6.6 Pharmacodynamic Evaluations - ctDNA

Whole blood will be collected from all patients at screening, at Day 1 of each cycle, and at the End-of-Treatment Visit for detection and quantification of cell-free ctDNA biomarkers of response or resistance to therapy, including but not limited to EGFR mutations, MET gene amplification, PIK3CA mutations, and alterations in other components of the EGFR signaling pathway. Blood samples will be processed locally to yield plasma (ctDNA fraction) and buffy coats (genomic DNA fraction). Genomic DNA extracted from the buffy coat may be compared to tumor DNA so that molecular alterations unique to the tumor that may modulate response or resistance to study-assigned therapy can be unambiguously identified.

Samples may be used for the development of a blood-based diagnostic test.

Please refer to the Laboratory Manual for details on collecting and processing of blood pharmacodynamics samples.

Analysis may be performed on a subset of patients if it becomes clear that the analysis will have limited scientific value in some patients (eg, because of a very low titer of ctDNA), or if there are not enough serially collected samples from individual patients to allow for adequate biomarker evaluation.

9.6.7 Quality-of-Life Assessments

Patient reported outcomes will be measured using the EORTC QLQ-C30, EORTC QLQ-LC13,[12] and EQ-5D, which will be collected at screening, predose on C1D1, then every 2 cycles ± 1 week for the first 6 cycles. After Cycle 7, questionnaires will be collected every 3 cycles ± 1 week and at the end of treatment.

9.6.8 Patient Diary

Patient diary cards will be provided to patients randomized to rociletinib treatment at clinic visits. Patients will use the diary cards to note the date, time, and dose of rociletinib administration whilst at home. Diary cards should be returned at each visit and reviewed by study personnel for completeness and accuracy versus study drug returned.

10 ADVERSE EVENT MANAGEMENT

10.1 Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a patient administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational medicinal product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction, or the significant worsening of the indication under investigation that is not recorded elsewhere on the eCRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening are not considered AEs.

It is the responsibility of the investigator to document all AEs that occur during the study. AEs should be elicited by asking the patient a nonleading question (eg, “Have you experienced any new or changed symptoms since we last asked/since your last visit?”). AEs will be reported on the AE eCRF. Symptoms reported spontaneously by the patient during the physical examination will also be documented on the AE eCRF (not on the physical examination eCRF, which is reserved for physical signs or findings).

10.2 Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that occurs at any dose (including after informed consent is given and before dosing) that:

- Results in death. Death may occur as a result of the underlying disease process. Nevertheless, any event resulting in death during the reporting period must be treated as an SAE and reported as such. All deaths occurring within 28 days of the last administration of study treatment should be reported as SAEs.
- Is life-threatening (patient is at immediate risk of death from the event as it occurred)
- Requires in-patient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or seizures that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

10.3 Definition of an Adverse Event of Special Interest

An adverse event of special interest (AESI [serious or nonserious]) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (eg, health authorities or ethics committees) might also be warranted.

Details on the sponsor's currently agreed list of AESIs for rociletinib can be found in the current rociletinib Investigator's Brochure. These AESIs are to be reported to the sponsor expeditiously (see Section 10.9 for reporting instructions).

10.4 Events or Outcomes Not Qualifying as Serious Adverse Events

The following are not considered SAEs:

- Pre-planned or elective hospitalization including social and/or convenience situations (eg, respite care)
- Overdose of either Clovis study drug/chemotherapy comparators or concomitant medication unless the event meets SAE criteria (eg, hospitalization). However, the event should still be captured as a non-serious AE on the appropriate eCRF page. In addition, if there are other signs or symptoms which satisfy criteria for SAEs associated with the overdose, they should be reported as SAEs.
- Events of progression of the patient's underlying cancer as well as events clearly related to progression of the patient's cancer (signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal during the study or within the safety reporting period. If the event has a fatal outcome during the study or within the safety reporting period, then the event of Progression of Disease must be recorded as an AE and as an SAE with CTCAE Grade 5 (fatal outcome) indicated.
- Diagnosis of progression of disease or hospitalization due to signs and symptoms of disease progression alone should not be reported as SAEs

10.5 Clinical Laboratory Assessments as Adverse Events and Serious Adverse Events

It is the responsibility of the investigator to assess the clinical significance of all abnormal values as defined by the list of reference ranges from the local laboratory. In some cases, significant changes in laboratory values within the normal range will require similar judgment.

An abnormal laboratory value that is not already associated with an AE is to be recorded as an AE only if any one of the following criteria is met:

- An action on the study drug is made as a result of the abnormality
- Intervention for management of the abnormality is required

- At the discretion of the investigator should the abnormality be deemed clinically significant

10.6 Pregnancy or Drug Exposure during Pregnancy

If a patient becomes pregnant during the study the investigator is to stop dosing with study drug(s) immediately.

A pregnancy is not considered to be an AE or SAE; however, it must be reported to the sponsor using the Pregnancy Report Form within the same timelines as an SAE (Section 10.9). **This applies to female patients as well as female partners of male patients.**

A pregnancy should be followed through to outcome, whenever possible. Once the outcome of the pregnancy is known, the Pregnancy Outcome Report Form should be completed and reported to the sponsor.

AEs or SAEs that occur during pregnancy will be assessed and processed according to the AE or SAE processes using the appropriate AE or SAE forms.

10.7 Recording of Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

Any AE from the time the first dose of rociletinib or chemotherapy is administered through to 28 days after the last dose, will be recorded on the AE eCRF. In addition, study procedure-related AEs that occur after signing of the ICF and before the first dose of rociletinib or chemotherapy will also be captured on the AE eCRF. Any other AE that occurs prior to the first dose of study drug should be recorded on the Medical History eCRF. In order to avoid vague, ambiguous, or colloquial expressions, the AE should be recorded in standard medical terminology rather than the patient's own words. Whenever possible, the investigator should combine signs and symptoms that constitute a single disease entity or syndrome. For example, fever, headache, and nasal discharge may be reported as coryza, if that is a reasonable diagnosis.

The existence of an AE may be concluded from a spontaneous report from the patient; from the physical examination; or from special tests such as the ECG, laboratory assessments, or other study-specified procedure (source of AE).

Each AE is to be evaluated for duration, severity, seriousness, and causal relationship to the investigational drug. The action taken and the outcome must also be recorded.

SAEs that occur during the study or within 28 days after receiving the last dose of study treatment, and all AESIs, whether or not related to study drug, must be immediately reported to the sponsor/designated safety contact **within 24 hours** of knowledge of the event (Section 10.9). After the 28-day specified window, only SAEs considered to be treatment-related should be reported. This should be done by faxing or emailing the completed SAE/AESI report to the Sponsor/designee contact provided on the SAE/AESI report form. Information on the follow-up of AEs, SAEs, and AESIs is provided in Section 10.8. SAEs that are not considered treatment-related should be reported per local institutional or regulatory policy and practices, using the SAE form until alternative therapy has started.

10.7.1 Intensity of Adverse Events

The severity of the AE will be graded according to the NCI CTCAE Version 4.03 grading scale.[14] For AEs not covered by NCI CTCAE, the severity will be characterized as mild, moderate, severe, or life-threatening according to the following definitions:

- Mild events are usually transient and do not interfere with the patient's daily activities
- Moderate events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities
- Severe events interrupt the patient's usual daily activities and hospitalization (or prolongation of hospitalization) may be required
- Life-threatening events require urgent intervention to prevent death

10.7.2 Causal Relationship of Adverse Events to Investigational Medicinal Products

Medical judgment should be used to determine the cause of the AE considering all relevant factors such as, but not limited to, the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to the study medication, dechallenge or rechallenge.

Not Related

- An AE that is clearly due to extraneous causes (eg, concurrent disease, concomitant medications, disease under study, etc.)
- It does not follow a reasonable temporal sequence from administration of study drug
- It does not follow a known pattern of response to study drug
- It does not reappear or worsen when study drug is restarted
- An alternative explanation is likely but not clearly identifiable

Related

- An AE that is difficult to assign to alternative causes
- It follows a strong or reasonable temporal sequence from administration of study drug
- It could not be reasonably explained by the patient's clinical state, concurrent disease, or other concomitant therapy administered to the patient
- It follows a known response pattern to study drug
- It is confirmed with a positive rechallenge or supporting laboratory data

10.7.3 Outcome and Action Taken

The investigator will record the action taken and outcome for each AE according to the following criteria:

Action Taken with Study Drug

- None
- Dose reduced/delayed
- Drug temporarily interrupted
- Drug permanently discontinued
- Other (specify)

Outcome

- Recovered
- Recovered with sequelae
- Improved
- Ongoing
- Death
- Lost to follow-up

10.8 Follow-up of Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

All AEs (including SAEs and AESIs) occurring during the study are to be followed up in accordance with good medical practice until resolved; judged no longer clinically significant; or, if a chronic condition, until fully characterized until 28 days after the last dose of study treatment. All SAEs and AESIs must be followed until resolution or stabilization.

10.9 Regulatory Aspects of Serious Adverse Event Reporting and Adverse Events of Special Interest

All SAEs, AESIs, and pregnancy, regardless of relationship to study drug, must be reported to the sponsor/designated safety contact within 24 hours of knowledge of the event, according to the procedures below. It is important that the Investigator provides an assessment of relationship of the SAE to study treatment at the time of the initial report. The Clinical Trial Serious Adverse Event/ Adverse Event of Special Interest (SAE/AESI) Report Form must be used for reporting SAEs.

While not considered an SAE, pregnancy occurring in a female patient or in the female partner of a male patient must also be reported to the sponsor/designated safety contact as soon as the event is known by the clinical site. If the pregnancy occurs in a female patient, study drug should

be stopped immediately. Notification to the sponsor/designated safety contact should take place via facsimile or email utilizing the Pregnancy Report Form.

Further details on SAE/pregnancy reporting can be found in the Investigator's File.

Clovis or its designee is responsible for submitting reports of AEs associated with the use of the drug that are both serious and unexpected to the U.S. Food and Drug Administration (FDA), according to 21 Code of Federal Regulations (CFR) 312.32; to the Japanese Pharmaceuticals and Medical Devices Agency (PMDA); to the European regulatory authorities according to the European Commission Clinical Trials Directive (2001/20/EC); and to other regulatory authorities, according to national law and/or local regulations. All investigators participating in ongoing clinical studies with the study medication will receive copies of these reports for prompt submission to their IRB or IEC. In accordance with the European Commission Clinical Trials Directive (2001/20/EC), Clovis or its designee will notify the relevant ethics committees in concerned member states of applicable suspected unexpected serious adverse reactions (SUSARs) as individual notifications or through periodic line listings.

Clovis or its designee will submit all safety updates and periodic reports to the regulatory authorities as required by applicable regulatory requirements.

11 STATISTICAL METHODS

11.1 Analysis Populations

The following analysis populations are defined for the study:

- **Intent-to-treat (ITT) population:** all randomized patients
- **Safety population:** all patients who have received at least 1 dose of rociletinib or single-agent cytotoxic chemotherapy

11.2 Statistical Methods

11.2.1 General Considerations

Quantitative variables will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) and/or frequency and percentages for medically relevant categories. Categorical variables will be presented using frequencies and percentages.

Kaplan-Meier methodology will be used to summarize time to event variables.

All data will be used to their maximum possible extent but without any imputations for missing data.

All statistical analyses will be conducted with the statistical analysis software (SAS®) System.

11.2.2 Patient Disposition

The frequency and percentage of patients in each analysis population and stratification subgroups will be presented. The primary reason for discontinuation of study treatment will be summarized.

11.2.3 Baseline Characteristics

Baseline characteristics and demographic data will be summarized for the safety population.

11.2.4 Efficacy Analyses

The efficacy endpoints will be evaluated using RECIST Version 1.1.[11]

The primary and key secondary endpoints will be tested among the centrally confirmed T790M+ and all randomized patients, using an ordered step-down multiple comparisons procedure. InvPFS in the T790M+ subgroup will be tested first at a one-sided 0.025 significance level. If invPFS in the T790M+ subgroup is statistically significant then invPFS in all randomized patients will be tested at a one-sided 0.025 significance level. The remaining key secondary efficacy analyses will also be tested using this step-down approach in the order presented below. Once statistical significance is not achieved for one test, the statistical significance will not be declared for all subsequent analyses in the ordered step-down procedure.

11.2.4.1 Primary Endpoint: Progression-free Survival

The primary endpoint of the study is PFS according to RECIST Version 1.1 as determined by investigator assessment.

PFS will be calculated as 1+ the number of days from the date of randomization to documented radiographic progression as determined by the investigator, or death due to any cause, whichever occurs first. Patients without a documented event of radiographic progression will be censored on the date of their last adequate tumor assessment (ie, radiological assessment) or date of randomization if no tumor assessments have been performed. For patients who continue treatment post-progression, the first date of progression will be used for the analysis of PFS.

Kaplan-Meier methodology will be used to summarize PFS. The stratified and unstratified log-rank tests and the HR will be used for comparing the PFS distributions among the rociletinib and single-agent cytotoxic chemotherapy treated patients. The stratification factors of brain metastases and territory will be used for analysis.

A PFS sensitivity analysis based on an Independent Radiographic Review (IRR, irrPFS) will be performed. The irrPFS is defined as the time from randomization to disease progression according to RECIST v1.1 as assessed by IRR, or death due to any cause, whichever occurs first.

11.2.4.2 Secondary Efficacy Endpoints

OBJECTIVE RESPONSE RATE

The ORR is the best overall response recorded from randomization until disease progression or recurrence as assessed by the investigator.

The ORR will be summarized with frequencies and percentages. The frequency and percentages of patients with a best overall response of CR, PR, stable disease (SD), or progressive disease (PD) will be summarized.

DURATION OF RESPONSE

The DR for CR and PR will be measured from the date that any of these best responses is first recorded until the first date that PD is objectively documented. DR will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) as well as categorically. For patients who continue treatment post-progression, the first date of progression will be used for the analysis.

OVERALL SURVIVAL

OS will be calculated as 1+ the number of days from randomization to death due to any cause. Patients without a documented date of death will be censored on the date the patient was last known to be alive.

POPULATION PK ANALYSES

Sparse blood sampling for POPPK analyses will be conducted in all patients treated with rociletinib. A specific POPPK data analysis plan will be developed and will outline the detailed approach to data handling, model development and diagnostics, individual model parameter estimation, exploration of covariate effects, and final model evaluation techniques.

11.2.4.3 Exploratory Endpoints

DISEASE CONTROL RATE

The DCR is defined as the percentage of patients who have achieved a CR, PR, or SD lasting at least 12 weeks. The frequency and percentages of patients with a best overall response of CR, PR, or SD lasting at least 12 weeks, SD lasting less than 12 weeks, or PD will be summarized.

TIME-TO-TREATMENT FAILURE

The time-to-treatment failure will be computed as 1+ the number of days from the first dose of study drug to the last dose of study drug and will be presented with summary statistics.

OS, ORR, PFS, DR, AND DCR IN PATIENTS WHO CROSS OVER TO RECEIVE ROCILETINIB

OS, ORR, PFS, DR, and DCR in patients who cross over from single-agent cytotoxic chemotherapy to receive rociletinib will be summarized descriptively.

CHANGE FROM BASELINE IN PROS USING THE EORTC QLQ-C30, EORTC QLQ-LC13 AND THE EQ-5D PREFERENCE-BASED HEALTH INSTRUMENT

QoL will be measured using the PROs of the EORTC QLQ-C30, EORTC QLQ-LC13[12] and EQ-5D.[13]

The EORTC questionnaires will be scored using the published scoring algorithms provided by the EORTC. For each item or scale, a linear transformation will be applied to standardize the raw score to a range from 0 to 100. A high scale score represents a higher response level. Thus, a **high score for a functional scale** represents a *high/healthy level of functioning*, a **high score for the global health status/QoL** represents a *high QoL*, but a **high score for a symptom scale/item** represents a *high level of symptomatology/problems*.

The baseline QoL measurement will be defined as the last value prior to or on the day of the first dose of study treatment. The on-treatment period will be defined as the day after the first dose of study treatment to 28 days after the last dose of study treatment. QoL measurements collected during the on-treatment period will be included in the summary tables.

Evaluation of Symptoms

An improvement in symptoms will be defined as a $\geq$ 10 point decrease from baseline. A worsening in symptoms will be defined as a $\geq$ 10 point increase from baseline. Patients with neither an increase nor a decrease will be considered stable. The frequency and percentage of patients categorized as an increase, stable, or decrease will be presented.

Time to Deterioration

The time to a worsening in symptoms will be computed as 1+ the number of days from the date of randomization to the first instance of a ≥ 10 point increase from baseline in symptoms.

Longitudinal Analysis

The summary of QoL data will include descriptive statistics (N, mean, standard deviation, minimum, median, and maximum) of the mean and/or percent change from baseline during the on-treatment period. Summaries using descriptive statistics of the change from baseline to each scheduled visit during the on-treatment period will be presented. Graphical presentations may be used to present the mean changes over time.

EQ-5D Health Status

Analyses of changes and/or percent changes from baseline will be analyzed for each scheduled post-baseline visit and for the final visit for the EQ-5D instrument and the EQ-VAS. If more than one measurement exists for a patient on a particular day, then an arithmetic average will be calculated. This average will be considered to be that patient's measurement for that day. Post-baseline measurements more than 28 days after the last dose of protocol-specified treatment will not be included. Patients that do not have both a baseline measurement and at least one post-baseline measurement will not be included.

At a given visit, the change and/or percent change from baseline will be compared between the randomized treatment groups using an analysis of covariance (ANCOVA), with the treatment as a categorical factor and baseline measurement for the parameter as a continuous covariate.

Change from Baseline in Mutant EGFR Levels in ctDNA

The change from baseline in tissue and blood biomarkers associated with the EGFR signaling pathway will be summarized with descriptive statistics, and the t-test will be used to compare the mean changes between rociletinib and the comparator at each scheduled visit. Both the time from randomization to the first observed increase in plasma mutant EGFR levels and the time from first observed increase in plasma mutant EGFR levels to disease progression will be compared between arms and summarized using Kaplan-Meier methodology.

Comparison of Blood and Tissue Results for T790M

The relationship between T790M detected in tumor compared with that detected in blood will be explored. This will involve determining the sensitivity, specificity, and positive and negative predictive values of blood with respect to tumor assuming that EGFR mutational status in tumor is a true reflection of tumor biology. Additionally, an analysis of clinical endpoints based on the results of EGFR mutation plasma test may be performed.

Analyses may be performed on a subset of patients if it becomes clear that the analysis will have limited scientific value in some patients (eg, because of a very low titer of ctDNA), or if there are not enough serially collected samples to allow for adequate biomarker evaluation.

BIOMARKERS ASSOCIATED WITH RESPONSE OR RESISTANCE TO ROCILETINIB

Blood may be tested for biomarkers of response or resistance to EGFR-targeted therapy. Analysis may be performed on a subset of patients if it becomes clear that the analysis will have limited scientific value in some or if there are not enough serially collected samples from individual patients to allow for adequate biomarker evaluation.

11.2.5 Safety Analyses

The safety analyses will be performed using the safety population (all patients who have received at least 1 dose of rociletinib or single-agent cytotoxic chemotherapy).

11.2.5.1 Extent of Exposure

The number of cycles of treatment will be summarized by treatment group.

11.2.5.2 Adverse Events

AE coding will be performed using MedDRA. The severity of the toxicities will be graded according to the NCI CTCAE whenever possible. Treatment-emergent AEs are defined as AEs with an onset date on or after the date of first dose of study treatment until the date of the last dose plus 28 days. AEs will be considered treatment-emergent if all or part of the date of onset of the AE is missing and it cannot be determined if the AE meets the definition for treatment-emergent.

The number and percentage of patients who experienced treatment-emergent AEs for each SOC and PT will be presented by treatment group. Multiple instances of the treatment-emergent AEs in each SOC and multiple occurrences of the same PT are counted only once per patient. The number and percentage of patients with at least one treatment-emergent AE will also be summarized by treatment group.

Separate tables will present the following by treatment group and study phase:

- All treatment-emergent AEs
- Treatment-emergent AEs by CTCAE grade
- Grade 3 or greater treatment-emergent AEs
- Treatment-related, treatment-emergent AEs
- Serious treatment-emergent AEs
- Treatment-emergent AEs with an outcome of death
- Treatment-emergent AEs leading to discontinuation of study treatment
- Treatment-emergent AEs resulting in interruption, reduction, or delay of study treatment

The incidence of treatment-emergent AEs will be summarized by relationship to treatment using "treatment-related" and "not treatment-related" categories. If a patient experiences multiple occurrences of the same AE with different relationship categories, the patient will be counted once as a relationship category of treatment-related.

If a patient experiences multiple occurrences of the same AE with different intensity toxicity grades, the patient will be counted once for the maximum (most severe) toxicity grade. AEs with a missing intensity will be presented in the summary table with a toxicity grade of "Missing". For each toxicity grade, the number and percentage of patients with at least 1 treatment-emergent AE of the given grade will be summarized.

Non-treatment-emergent AEs (pre- and post-treatment) will be presented in the data listings.

11.2.5.3 Clinical Laboratory Evaluations

Clinical laboratory evaluations include the continuous variables for hematology, serum chemistry, and urinalysis. Laboratory values will be presented in Systeme International units. The baseline laboratory value will be defined as the last value prior to or on the day of the first dose of study treatment. The on-treatment period will be defined as the day after the first dose of study treatment to 28 days after the last dose of study treatment. Laboratory values collected during the on-treatment period will be included in the summary tables.

The summary of laboratory data will include descriptive statistics (N, mean, standard deviation, minimum, median, and maximum) of the maximum, minimum, and last value during the treatment period by treatment group. Summaries using descriptive statistics of the change from baseline to the maximum, minimum, and last value during the on-treatment period will also be given by treatment group. Separate listings will be produced for clinically significant laboratory abnormalities (ie, those that meet Grade 3 or 4 criteria according to CTCAE) by treatment group.

11.2.5.4 Vital Signs Measurements

The baseline vital signs measurement will be defined as the last value prior to or on the day of the first dose of study treatment. The on-treatment period will be defined as the day after the first dose to 28 days after the last dose of study treatment. Vital signs measurements collected during the on-treatment period will be included in the summary tables. The vital signs measurements collected after the on-treatment period will only be presented in the data listings.

The summary of vital signs data will include descriptive statistics (N, mean, standard deviation, minimum, median, and maximum) of the maximum, minimum, and last value during the on-treatment period by treatment group. Summaries using descriptive statistics of the change from baseline to the maximum, minimum, and last value during the on-treatment period will also be given by treatment group.

11.2.5.5 12-lead Electrocardiograms

ECG intervals will be stratified into categories indicative of potential clinical significance. Each patient's maximum QT and QT_C intervals from the pre-treatment visit and treatment period visits will be classified as ≤ 450 msec, > 450 to ≤ 480 msec, > 480 to ≤ 500 msec, and > 500 msec. For each patient's maximum change from the pre-treatment ECG visit for QT and QT_C, intervals will be classified into < 30 msec, ≥ 30 to < 60 msec, and ≥ 60 msec. The number and percentage of patients in each classified category will be presented by treatment group. Additional endpoints will include abnormal T waves and U waves and other ECG intervals and diagnostic parameters.

Descriptive statistics will be used to summarize other ECG parameters of PR, QRS, QT, and RR interval, and the corresponding changes from pre-treatment ECG visit at each time point. Plots of the mean QT/QT_C over time will be provided.

11.2.5.6 Other Safety Measurements

Body weight and ECOG performance status will be summarized with descriptive statistics (N, mean, standard deviation, minimum, median, and maximum). Concomitant medications/procedures will be tabulated and summarized.

11.3 Sample Size Considerations

Up to 600 patients will be randomized in a 1:1 ratio to receive treatment with rociletinib or single-agent cytotoxic chemotherapy.

The primary objective of this study is to estimate the difference in PFS between rociletinib and single-agent cytotoxic chemotherapy. The median PFS for cytotoxic chemotherapy in this patient population is expected to be approximately 4 months[15] while the median PFS in all rociletinib patients (both T790M+ and negative) is expected to be at least 6 months.

A step-down procedure will be used where PFS will first be evaluated in the T790M+ subgroup followed by all randomized patients.

The total sample size for the study is based on the minimum anticipated treatment effect of 4 months versus 6 months median PFS in all patients. A total of 600 patients should result in about 400 events of progression which provides 90% power to detect a HR of 0.70 at a one-sided 0.025 significance level.

The targeted number of T790M+ patients in this study is between 250 and 275 patients. A sample size of 250 T790M+ patients should result in about 170 events of progression which provides 90% power to detect a HR of 0.60 at a one-sided 0.025 significance level.

In the event that the frequency of T790M+ patients in this trial is lower than expected, enrollment will continue until 250 T790M+ patients have been enrolled.

11.4 Interim Analysis

A data monitoring committee consisting of both Clovis personnel and the primary study investigators will meet no less than twice a year to review the safety and efficacy data to ensure that a favorable risk/benefit ratio is maintained throughout the study.

No formal stopping rules for efficacy will be implemented.

12 PATIENT DISPOSITION

12.1 Patient Discontinuations

To the extent possible, end-of-treatment procedures should be carried out on all patients who receive rociletinib or single-agent cytotoxic chemotherapy. The End-of-Treatment Visit should occur 28 (± 7) days following the last dose of study treatment. After stopping protocol-specified treatment, all patients will remain in the study and will be followed for safety (until 28 days after last dose for all AEs or until resolution for study treatment related SAEs) and for survival status and subsequent therapy assessment (approximately every 2 months from the End-of-Treatment Visit until death or sponsor decision, whichever comes first). Patients who discontinue treatment prior to progression should continue to have scans every 6 ± 1 weeks until progression.

A patient must be discontinued from protocol-prescribed therapy if any of the following apply:

- Consent withdrawal at the patient's own request or at the request of their legally authorized representative
- Radiographic progression of patient's underlying disease per RECIST Version 1.1, except as described in Section 5.1.3. If clinical progression is diagnosed then confirmation with a CT scan will be required before patient withdrawal.
- Any event, adverse or otherwise, that, in the opinion of the investigator, would pose an unacceptable safety risk to the patient
- An intercurrent illness that, in the opinion of the investigator, would affect assessments of the clinical status to a significant degree
- A positive pregnancy test at any time during the study
- Noncompliance as described in Section 7.7
- Investigator decision

In addition, the sponsor may discontinue the trial early for any of the reasons noted in Section 13.6.

The sponsor (or designee) should be notified of all study terminations as soon as possible. The date and reason for cessation of study treatment must be documented in the eCRF and source documents.

13 STUDY ADMINISTRATION

13.1 Regulatory and Ethical Considerations

This study will be conducted in compliance with the protocol; Good Clinical Practices (GCPs) including International Conference on Harmonization (ICH) Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines; FDA regulatory requirements; and in accordance with the ethical principles of the Declaration of Helsinki.

13.1.1 Regulatory Authority Approvals

The sponsor or designee will submit the study protocol plus all relevant study documents to concerned regulatory agencies for approval before the study start. No patient will be admitted to the study until appropriate regulatory approval of the study protocol has been received.

Each investigator must complete a Form FDA 1572 or equivalent and provide the completed form according to written instructions to the sponsor (or designee). Each investigator must submit to the sponsor (or designee) financial disclosure information according to national law and/or local regulations.

US-generated data will be handled in accordance with the Health Information Portability and Accountability Act (HIPAA). The trial will be registered at www.clinicaltrials.gov using the Protocol Registration System.

13.1.2 Independent Ethics Committee/Institutional Review Board

This protocol and any material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the investigator to an IEC/IRB. This also applies to protocol amendments.

Clovis will supply relevant data for the investigator to submit the study protocol and additional study documents to the IEC/IRB. The principal investigator will submit the study protocol for review and approval by an IEC/IRB, according to national law and/or local regulations, and will provide the IEC/IRB with all appropriate materials.

Verification of the IEC's/IRB's unconditional approval of the study protocol and the written ICF will be transmitted to Clovis. This approval must refer to the study by exact study protocol title and number, identify the documents reviewed, and state the date of the review.

No patient will be admitted to the study until appropriate IEC/IRB approval of the study protocol has been received, the investigator has obtained the signed and dated ICF, and the sponsor is notified.

The principal investigator will submit appropriate reports on the progress of the study to the IEC/IRB at least annually in accordance with applicable national law and/or local regulations and in agreement with the policy established by the IEC/IRB and sponsor.

The IEC/IRB must be informed by the principal investigator of all subsequent study protocol amendments and of SAEs or SUSARs occurring during the study that are likely to affect the safety of the patients or the conduct of the study.

13.2 Confidentiality of Information

The investigator must assure that patients' anonymity is strictly maintained and that their identities are protected from unauthorized parties. Only patient initials and an identification code (ie, not names) should be recorded on any form submitted to the sponsor and the IEC/IRB. The investigator must keep logs on screened and enrolled patients. In addition, the investigator must have a list where the identity of all treated patients can be found.

The investigator agrees that all information received from Clovis, including, but not limited to, the Investigator's Brochure, this protocol, eCRFs, the protocol-specified treatment, and any other study information, remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study center to any third party or otherwise into the public domain.

13.3 Patient Informed Consent

All information about the clinical study, including the patient information and the ICF, is prepared and used for the protection of the human rights of the patient according to ICH GCP guidelines and the Declaration of Helsinki.

It is the responsibility of the investigator to obtain signed ICFs from each patient participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures.

The ICF, prepared by the Investigator with the assistance of the sponsor, must be approved along with the study protocol by the IEC/IRB and be acceptable to the sponsor.

The patient must be provided with the patient information and ICF consistent with the study protocol version used and approved by the relevant IEC/IRB. The ICF must be in a language fully comprehensible to the prospective patient. Patients (and/or relatives, guardians, or legal representatives, if necessary) must be given sufficient time and opportunity to inquire about the details of the study and to discuss and decide on their participation in the study with the investigator concerned. The patient and the person explaining about the study and with whom they discuss the informed consent will sign and date the ICF. A copy of the signed ICF will be retained by the patient and the original will be filed in the Investigator File unless otherwise agreed.

13.4 Study Monitoring

A monitor will contact and visit the investigator at the study center before the entry of the first patient as necessary during the study until after the last patient has completed. A monitor will also perform a study closure visit.

In accordance with ICH GCP guidelines, the investigator must ensure provision of sufficient time, reasonable space, and adequate qualified personnel for the monitoring visits. The visits are for the purpose of verifying adherence to the study protocol and the completeness, consistency, and accuracy of data entered on the eCRF and other documents.

The investigator will make all source data (ie, the various study records, the eCRFs, laboratory test reports, other patient records, drug accountability forms, and other pertinent data) available for the monitor and allow access to them throughout the entire study period. Monitoring is done by comparing the relevant site records of the patients with the entries on the eCRF (ie, source data verification). It is the monitor's responsibility to verify the adherence to the study protocol and the completeness, consistency, and accuracy of the data recorded on the eCRFs.

Drug accountability will be performed as described in Section 7.5. The Investigator Site File will be reviewed to ensure all regulatory documents (eg, IRB/IEC approvals, approved ICFs, SAE reporting to IRB/IEC, etc.) are present.

By agreeing to participate in the study, the investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of the monitoring visits are resolved. Contact information for the study monitor is located in the Investigator File. Representatives from Clovis may also contact and visit the investigators and monitor data during the study.

13.5 Case Report Form

The data will be collected using an electronic data capture (EDC) system by remote data entry on eCRFs. Sites will receive training on the EDC system. All users will be supplied with unique login credentials.

Before study start, the investigator will prepare a list showing the signature and handwritten initials of all individuals authorized to make or change entries on eCRFs. This "study center personnel and delegation list" must be kept current throughout the study.

For each patient enrolled, an eCRF must be completed and reviewed by the principal investigator or co-investigator within a reasonable time period (< 2 weeks) after data collection. This also applies to records for those patients who fail to complete the study. If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

All laboratory data and investigator observations on the results and any other clinically significant test results must be documented on eCRFs.

Full information regarding EDC and completing eCRFs is included in the Investigator File. All questions or comments related to electronic capture should be directed to the assigned monitor.

13.6 Study Termination and Site Closure

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures. In terminating the study, Clovis and the investigator will assure that adequate consideration is given to the protection of the patients' interests.

Clovis reserves the right to discontinue the study at any time for medical or administrative reasons. When feasible, a 30-day written notification will be given.

The entire study will be stopped if:

- The protocol-specified treatment is considered too toxic to continue the study
- Evidence has emerged that, in the opinion of the sponsor or the investigator(s), makes the continuation of the study unnecessary or unethical
- The stated objectives of the study are achieved
- The sponsor discontinues the development of oral rociletinib

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded on the eCRF. All reasons for discontinuation of treatment must be documented. In terminating the study, the investigator will ensure that adequate consideration is given to the protection of the patients' interests.

13.7 Modification of the Study Protocol

Protocol amendments, except when necessary to eliminate an immediate hazard to patients, must be made only with the prior approval of Clovis. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent document. The IEC/IRB must be informed of all amendments and give approval before their implementation. The sponsor will submit any study protocol amendments to the concerned regulatory authorities for approval and keep the investigator(s) updated as detailed in the ICH GCP guidelines.

13.8 Retention of Study Documents

The study site will maintain a study file, which should contain, at minimum, the Investigator's Brochure, the protocol and any amendments, drug accountability records, correspondence with the IEC/IRB and Clovis, and other study-related documents.

The investigator agrees to keep records and those documents that include (but are not limited to) the identification of all participating patients, medical records, study-specific source documents, source worksheets, all original signed and dated ICFs, copies of all eCRFs, query responses, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and Clovis or its designees.

The investigator shall retain records required to be maintained for a period of 5 years following the date a marketing application in an ICH region is approved for the drug for the indication for which it is being investigated or, if no application is to be filed or if the application is not approved for such indication, until at least 5 years after the investigation is discontinued. However, these documents should be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by Clovis. In addition, the investigator must make provision for the patients' medical records to be kept for the same period of time.

No data should be destroyed without the agreement of Clovis. Should the investigator wish to assign the study records to another party or move them to another location, Clovis must be notified in writing of the new responsible person and/or the new location. Clovis will inform the Investigator, in writing, when the trial-related records are no longer needed.

Patients' medical records and other original data will be archived in accordance with the archiving regulations or facilities of the investigational site.

13.9 Clinical Study Report

A clinical study report will be prepared under the responsibility and supervision of Clovis and signed by the sponsor's chief medical officer, thereby indicating their agreement with the analyses, results, and conclusions of the clinical study report.

13.10 Study Publication

All data generated from this study are the property of Clovis and shall be held in strict confidence along with all information furnished by Clovis. Independent analysis and/or publication of these data by the investigator(s) or any member of their staff are not permitted without the prior written consent of Clovis. Written permission to the investigator will be contingent on the review by Clovis of the statistical analysis and manuscript, and will provide for nondisclosure of Clovis confidential or proprietary information. In all cases, the parties agree to submit all manuscripts or abstracts to all other parties 30 days before submission. This will enable all parties to protect proprietary information and to provide comments based on information that may not yet be available to other parties.

13.11 Quality Assurance Audits

An audit visit to clinical centers may be conducted by a quality control auditor appointed by Clovis. The purpose of an audit, which is independent of and separate from routine monitoring or quality control functions, is to evaluate trial conduct and compliance with the protocol, standard operating procedures (SOPs), ICH GCPs, and the applicable regulatory requirements. The investigator and the sponsor may also be subject to an inspection by FDA, European Regulatory authorities, or other applicable regulatory authorities at any time. The auditor and regulatory authorities will require authority from the investigator to have direct access to the patients' medical records. It is important that the investigator(s) and their staff cooperate with the auditor or regulatory authorities during this audit or inspection.

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15 APPENDICES

Appendix A. Response Evaluation Criteria in Solid Tumors

Appendix B. Eastern Cooperative Oncology Group Performance Status Scale

Appendix C. Study CO-1686-020 Extension Phase

Appendix A

Response Evaluation Criteria in Solid Tumors

The RECIST guidelines (Version 1.1) are described in Eisenhauer (2009)[11] and at http://www.eortc.be/Recist/Default.htm. A short summary is given below.

Measurable Disease:
Tumor lesions: measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter [LD] to be recorded) with the following:

1. A minimum size of 10 mm by CT scan (CT scan thickness no greater than 5 mm)
2. A minimum size of 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable)
3. A minimum size of 20 mm by chest X-ray

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: to be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be not greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Nonmeasurable Disease:

All other lesions (or sites of disease), including small lesions (LD < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly nonmeasurable lesions, are considered nonmeasurable disease. Lesions considered truly nonmeasurable include leptomeningeal disease, ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitic involvement of skin and lung, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

Bone Lesions

Bone lesions, cystic lesion, and lesions previously treated with local therapy require particular comment. Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic–blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are nonmeasurable.

Cystic Lesions

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) because they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred as target lesions.

Lesions with Prior Local Treatment

Tumor lesions situated in a previous irradiated area or in an area subjected to other locoregional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

Target Lesions

All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the LD) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the LD for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target Lesions

RECIST criteria require unequivocal quantification of the changes in tumor size for adequate interpretation of the sum of target lesions. Consequently, when the boundaries of the primary are difficult to delineate, this tumor should not be considered a target lesion.

Guidelines for Evaluation of Measurable Disease

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

Evaluation of Target Lesions

Complete Response	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
Stable Disease	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.
Progressive Disease	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.

Evaluation of Non-target Lesions

Complete Response	Disappearance of all non-target lesions and normalization of tumor marker level.
Stable Disease/Incomplete Response	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
Progressive Disease	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

If tumor markers are initially above the institutional ULN, they must normalize for a patient to be considered a complete responder.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Time Point Response

A response assessment will occur at the protocol-specified time points. The tables below provide a summary of the overall response status calculation at each time point for patients who have measureable and non-measureable disease (non-target disease only).

Time Point Response: Patients with Target (+/– Non-target) Disease			
Target Lesions	**Non-target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not evaluated	No	PR
SD	Non-PD or not evaluated	No	SD
Not Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

NE = Not evaluable

Evaluation of Best Overall Response When Confirmation of CR and PR Required		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes this disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response, which is most likely to occur in the case of PD; eg, if only 2 of 3 baseline target lesions are assessed and result in a > 20% increase in the sum, then the patient would be assessed as a PD regardless of the missing lesion.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having symptomatic deterioration. Every effort should be made to document the objective progression, even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspiration/biopsy) prior to confirming the complete response status.

Confirmatory Measurement/Duration of Response

Confirmation

CT scans are required every 6 ± 1 weeks. If an initial CR or PR is noted, confirmatory scans must be performed 4 ± 1 week later. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of no less than 4 ± 1 weeks.

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started).

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

Duration of Stable Disease

SD is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Appendix B

Eastern Cooperative Oncology Group Performance Status Scale

ECOG Performance Status	
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work or 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 C

Study CO-1686-020 Extension Phase

OBJECTIVE OF THE EXTENSION PHASE

The purpose of the Extension Phase is to allow patients to continue on study but to avoid unnecessary collection of data that will no longer be analyzed or required for regulatory purposes, whilst maintaining an appropriate level of safety monitoring.

In addition, this amendment also introduces the availability of NAT2 testing for patients, an indirect indicator of the likelihood of developing hyperglycaemia and QTc prolongation. The availability and disclosure of this information to the patients' treating physician will not affect the monitoring and associated treatment guidelines for these adverse events.

INTRODUCTION

Additional information on efficacy/safety aspects

The most current clinical and non-clinical updates, in particular those pertaining to efficacy and safety data, are provided in the current Investigator's Brochure, in which integrated summaries of efficacy and safety data are presented.

Additional information relating to Hyperglycemia and QTc prolongation

The polymorphic enzyme NAT2 mediates the N-acetylation of M502 to form M544 and also plays a role in the elimination of M460. NAT2 genotype polymorphism was assessed for the group of patients who received rociletinib at 500 mg BID, 625 mg BID, 750 mg BID, and 1000 mg BID and who gave additional informed consent for genomic testing. The NAT2 genotype polymorphism testing was performed using an assay based on polymerase chain reaction (PCR) followed by mass spectrometry to identify single nucleotide polymorphisms in NAT2. Based on NAT2 genotype results, patients were classified as having "low", "intermediate", and "rapid" acetylator phenotype.[29] Acetylator status is currently available for 635 patients. Additional testing will be completed as additional samples are received.

Adverse event and laboratory data based on NAT2 phenotype are summarized in Appendix C, Table 1, Appendix C, Table 2 , and Appendix C, Table 3. Analyses are presented by acetylator status for all doses combined, since the combined-dose findings were consistent with the findings within each dose group.

Appendix C, Table 1 demonstrates that Grade 3 events are less common in patients who are classified as "rapid" acetylators. As expected, the relationship is most clear for hyperglycemia and QT-prolongation, while other AESIs appear to be less closely associated with acetylator status. Appendix C, Table 2 shows that hyperglycemia appears to be less frequent and less severe in rapid acetylators. Appendix C, Table 3 shows that QTcF prolongation on ECG appears to be less frequent and less severe in rapid acetylators.

Appendix C, Table 1: Grade 3 or Greater Treatment-emergent Adverse Events by Acetylator Status

	Overall (N = 635)		
	Slow (n=300)	**Intermediate (n=259)**	**Rapid (n=76)**
Overall	243 (81%)	194 (75%)	48 (63%)
Hyperglycemia (CT)	131 (44%)	66 (26%)	13 (17%)
QTc prolongation (CT)	44 (15%)	19 (7%)	1 (1%)
Malignant neoplasm progression	39 (13%)	39 (15%)	8 (11%)
Cataracts (CT)	12 (4%)	9 (4%)	7 (9%)
Pneumonitis (CT)	3 (1%)	4 (2%)	0
Diarrhea	13 (4%)	16 (6%)	1 (1%)

Abbreviation: CT=combined terms.

Appendix C, Table 2: Hyperglycemia Lab-shift by Acetylator Status

	Overall (N = 635)		
	Slow (n = 300)	**Intermediate (n = 259)**	**Rapid (n = 76)**
Subjects with any post-baseline glucose values > 250 mg/dL	121 (40%)	65 (25%)	17 (22%)
Subjects with 2 or more post-baseline glucose values > 250 mg/dL	51 (17%)	36 (14%)	7 (9%)
Subjects with any post-baseline glucose values > 500 mg/dL	11 (4%)	7 (3%)	1 (1%)
Subjects with 2 or more post-baseline glucose values > 500 mg/dL	3 (1%)	0 (0.0)	0 (0.0)

Appendix C, Table 3: QTcF Changes on ECG by Acetylator Status

	Overall (N = 635)		
	Slow (n = 300)	**Intermediate (n = 259)**	**Rapid (n = 76)**
QTcF Post-baseline ≥ 450 msec	198 (66%)	131 (51%)	34 (45%)
QTcF Post-baseline ≥ 481 msec	92 (31%)	44 (17%)	7 (9%)
QTcF Post-baseline ≥ 501 msec	59 (31%)	22 (9%)	1 (1%)
Two of more within 3 days ≥ 501 msec	19 (6%)	10 (4%)	0 (0.0)
QTcF Change from Baseline > 30 msec	246 (82%)	171 (66%)	47 (62%)
QTcF Change from Baseline > 60 msec	141 (47%)	57 (22%)	9 (12%)
Abbreviation: ECG=electrocardiogram.			

For those patients ongoing on rociletinib trials, informed consent and testing for NAT2 polymorphism status will be offered and the results will be shared with the treating physician. It will be up to the patient in consultation with the treating physician to decide continued participation in the trial in light of the acetylator status results or whether alternative treatment options should be sought.

Regardless of acetylator status, monitoring should be the same for all patients receiving rociletinib whilst on treatment.

STUDY DESIGN

Treatment Regimen and Duration of Therapy

All patients will sign an informed consent which explains the rationale for closing the rociletinib (CO-1686) clinical development program for NSCLC and the option for ongoing patients to continue receiving study treatment, should they decide to do so and/or if in the opinion of their treating physician they continue to receive clinical benefit.

Patients may continue to receive rociletinib if the PI and patient deem it is appropriate for the patient though the availability and suitability of alternative treatment options should be considered by the treating physician and discussed with the patient. Rociletinib will be administered daily on a 21-day cycle. Dosing will be delayed or decreased according to protocol-specified toxicity criteria (Section 7.4). Each dose should continue to be taken with 8 oz. (240 mL) of water and with a meal or within 30 minutes after a meal two times per day. Tablets should be swallowed whole.

Treatment may continue until disease progression or intolerable toxicity. Please note, patients on rociletinib may opt to continue to receive treatment with rociletinib following radiographic progression as outlined in the NCCN guidelines for treatment of NSCLC with EGFR TKIs if patient provides additional consent, the investigator feels it is in the patient's best interest and with sponsor approval. Similarly patients may opt to crossover to rociletinib following progression on single agent cytotoxic chemotherapy if eligibility criteria are met per Section 6.4. It is important that before deciding to continue treatment with rociletinib post progression in either of the two stated scenarios, additional treatment options are explored and discussed with the patient by the treating physician. In general, eligible patients may include those with asymptomatic systemic progression or locally symptomatic progression, such as brain metastases amenable to local treatment, with concomitant asymptomatic systemic progression or continued systemic disease control. This must be discussed with the sponsor and will be reviewed on a case-by-case basis.

If a patient continues treatment post-progression, all Extension Phase study assessments should continue per protocol and data should be captured in the eCRF. The patient should be discontinued from treatment once it is clear that no further clinical benefit can be achieved.

Both the hyperglycemia and QTc management guidelines (Section 7.4) should be followed during this extension phase and any modifications/deviations from these guidances should be discussed and agreed upon with the sponsor prior to implementation.

Once study treatment has been discontinued and the End of Treatment visit has been completed, study participation will cease. Investigational centers will interpret tumor scans locally for the purpose of making treatment decisions and for final tumor response evaluation. The study will close once all patients have either completed participation, have transferred to a locally approved treatment access program (eg, a named patient program) in accordance with relevant local regulations or the sponsor decides to close the study.

PATIENT ELIGIBILITY AND WITHDRAWAL CRITERIA

Eligibility and Number of Patients

This amendment applies to patients who remain on either rociletinib or comparator chemotherapy on the CO-1686-020 study. No additional patients will be enrolled.

Withdrawal Criteria

The patient has the right to stop treatment or to withdraw from the study at any time.

Patients will continue to receive treatment until one of the following cessation criteria applies:

- Consent withdrawal at the patient's own request or at the request of their legally authorized representative.
- Progression of patient's underlying disease.
  - Post-progression treatment is permitted, at the discretion of the Investigator and with the approval of the sponsor.
- Intercurrent illness that prevents administration of treatment
- Any event, adverse or otherwise, that, in the opinion of the investigator, would pose an unacceptable safety risk to the patient.
- Major noncompliance that may affect patient safety (Reference Section 7.7).
- Pregnancy.
- Investigator decision.

In addition, the sponsor may discontinue the trial early for any of the reasons noted in Section 13.6 of the protocol.

The date and reason for cessation of treatment will be documented. Patients with ongoing SAEs will be followed until either resolution or stabilization has been determined.

STUDY PROCEDURES

Schedule of Assessments

The procedures and assessments to be performed are outlined in the Schedule of Assessments presented in Appendix C, Table 4; Appendix C, Table 5; and Appendix C, Table 6. Procedures are synchronized with administration day of treatment unless indicated. The revised evaluations should commence immediately after the patient is consented, maintaining previous treatment cycle and day sequence.

Appendix C, Table 4: Schedule of Assessments for Patients Randomized to Rociletinib

Procedure	Prior to beginning Amendment 4 Evaluations	Day 1 of each cycle	End-of-Treatment Visit (28 ± 7 days after last dose)
Informed Consent	X		
Physical Examination including vision check		X	X
Vital Signs[a] and Weight		X	X
Concomitant Medications and Procedures		X	X
Contraceptive Counseling[b]			X
Pregnancy Test[c]			X
Local hematology[d]		X	X
Local fasting Serum Chemistry[e]		X	X
Adverse events(including SAEs and AESI)[f]		X	X
Rociletinib dispensing/ administration		X	
Patient diary[g]		X	X
ECG Assessments using central ECG machine[h]		X	X
Tumor Scans[i]	To be done per institution standard of care or 6 ± 1 weeks during treatment ; scans are not required at the End of Treatment Visit		
PGx blood sample (Optional Sampling)[j]		X[j]	

[a] = Vital signs (blood pressure, pulse, and temperature) taken predose on drug administration days.
[b] = Patients are to continue using effective contraception for 6 months after last dose of CO-1686 and report any pregnancies during this period.
[c] = Serum ß-hCG to be evaluated by local lab will be performed only on women of childbearing potential.
[d] = Hematology evaluation should include reticulocytes ~~Includes hemoglobin, hematocrit, CBC, and differential (with ANC), and platelet count~~.Blood will be analyzed at a local laboratory and must be reviewed by the investigator before starting each new cycle of administration. Additional tests may be performed at the investigator's discretion
[e] = Glucose must be measured following an 8 hour fast (no food or liquid other than water). Hemoglobin A1c will be measured on Day 1 of every other cycle while the patient is on study. Samples should be analyzed by local laboratory.
[f] = Patients will be monitored for AEs/SAEs/AESI from the time the first dose of CO-1686 is administered through 28 days after the last dose.
[g]= Patient diaries should be collected and reviewed for compliance at each visit. No diary will be dispensed at end of treatment.
[h]=12-lead ECG (in triplicate, 10-sec tracings > 2 min apart) prior to dosing up to and including Cycle 12, at a minimum. For patients who are ongoing at this time and for whom QT has been < 470 ms (average of the triplicate value) throughout the study, ECG monitoring may be subsequently taken every 3rd cycle thereafter. ECGs will be performed and interpreted locally for patient care decisions; however, tracings should be submitted to the central lab for independent evaluation.
[i]=Tumor scans will no longer be required to be submitted to a central reviewer; Disease progression to continue to be assessed locally by the Investigator. If a patient discontinues treatment before progression or is continuing treatment post progression (approval from Sponsor is required), then the decision to conduct additional scans and the frequency of those scans to monitor disease progression will be the responsibility of the treating physician
[j]= Only one sample is needed and may be collected at any visit to enable NAT2 analysis.

Appendix C, Table 5: Schedule of Assessments for Patients Randomized to Single Agent Cytotoxic Chemotherapy

Procedure	Prior to beginning Amendment 4 Evaluations	Day 1 of each cycle	Day 8 of each cycle	Day 15 of each cycle	End-of-Treatment Visit (28 ± 7 days after last dose)
Informed Consent	X				
Physical Examination including vision check		X			X
Vital Signs[a] and Weight		X			X
Concomitant Medications and Procedures		X			X
Contraceptive Counseling[b]					X
Pregnancy Test[c]					X
Local hematology CBC and differential[d]		X	X	X	X
Local fasting Serum Chemistry[e]		X			X
Adverse events (SAEs)[f]		X	X	X	X
Chemotherapy administration[g]		X	X[g]	X[g]	
ECG Assessments using central ECG machineg[h]		X			X
Tumor Scans[i]	To be done per institution standard of care or every 6 ± 1 weeks during treatment; scans are not required at the End of Treatment Visit				

[a] = Vital signs (blood pressure, pulse, and temperature) taken predose on drug administration days.
[b] = Patients are to continue using effective contraception for 6 months after last dose of chemotherapy and report any pregnancies during this period.
[c] = Serum ß-hCG to be evaluated by local lab will be performed only on women of childbearing potential.
[d] = Includes hemoglobin, hematocrit, CBC, and differential (with ANC), and platelet count. Blood will be analyzed at a local laboratory and must be reviewed by the investigator before starting each new cycle of administration. Additional tests may be performed at the investigator's discretion
[e] = Glucose must be measured following an 8 hour fast (no food or liquid other than water). Hemoglobin A1c will be measured on Day 1 of every other cycle while the patient is on study. Samples should be analyzed by local laboratory.
[f] = Patients will be monitored for AEs/SAEs from the time the first dose of chemotherapy is administered through 28 days after the last dose.
[g]=All chemotherapy agents will be administered on Day 1 of each 21-day cycle. In addition, gemcitabine, docetaxel at the 35 mg/m^2 dose, and paclitaxel will be administered on Day 8 of each 21-day cycle; and docetaxel at the 35 mg/m^2 dose and paclitaxel will also be administered on Day 15 of each 21-day cycle. This does not apply to pemetrexed and docetaxel at the 75 mg/m^2 dose, which will only be administered on Day 1 of each 21-day cycle
[h]=12-lead ECG (in triplicate, 10-sec tracings > 2 min apart) prior to dosing up to and including Cycle 12, at a minimum. For patients who are ongoing at this time and for whom QT has been < 470 ms (average of the triplicate value) throughout the study, ECG monitoring may be subsequently taken every 3rd cycle thereafter. ECGs will be performed and interpreted locally for patient care decisions; however, tracings should be submitted to the central lab for independent evaluation.
[i]=Tumor scans will no longer be required to be submitted to a central reviewer; Disease progression to continue to be assessed locally by the Investigator. Frequency of the scans to monitor disease progression will be the responsibility of the treating physicians.

Appendix C, Table 6: Schedule of Assessments for Patients who Cross Over to Rociletinib after Chemotherapy

	Consent	Screening		Treatment Period (Daily dosing)							Post-treatment Period
Procedure[a]	**Before Any Screening Procedures**	**Day –35 to Day –1**	**Day –14 to Day –1**	**XO-Cycle 1 Day 1 (XO-C1D1)**[a, b]	**XO-Cycle 1 Day 4 ± 1 Day**	**XO-Cycle 1 Day 8 ± 1 Day**	**XO-Cycle 1 Day 15 ± 1 Day**	**XO-Cycle 2 Day 1 (21 ± 3 days after C1D1)**	**XO-Cycle 2 Day 15 ± 1 day**	**XO-Cycle 3+, Day 1 (every 21 ± 3 days)**	**End-of-Treatment Visit (28 ± 7 days after last dose)**
Protocol Amendment 4 Crossover informed Consent	X										
Physical examination, including vision check			X	X				X		X	X
Vital signs[c], height (screening only), weight, ~~ECOG PS~~			X (including height)	X				X		X	X
Previous/concomitant medications and procedures		X		X				X		X	X
Contraceptive counseling[d]		X									X
Local pregnancy test[e]			X	X							X
Local hematology, ~~CBC and differential~~[f]			X	X				X		X	X
Local fasting serum chemistry[g]			X	X	Fasting glucose only	Fasting glucose only	Fasting glucose only	X	Fasting glucose only	X	X
Tumor scans[h]		X		To be done per institution standard of care or every 6 ± 1 weeks during treatment, from XO-C1D1; End of Treatment scans are not required							
Adverse events (including SAEs and AESI)[i]		X	X	X				X		X	X
Rociletinib dispensing/administration				X				X		X	
Patient diary[j]				X				X		X	X

ECG[k]		X		X			X	X		X	X
PGx blood sample[l] (Optional **ONE** time Sampling)		X	X	X				X		X	

[a] Unless specified, procedure is completed ± 1 day of scheduled time point and is synchronized with administration day of rociletinib (XO-C1D1).

[b] Procedures required on XO-C1D1 may be omitted if completed ≤ 3 days earlier during the screening period. The EOT Visit may be performed earlier in patients requiring immediate treatment with another systemic anti-cancer therapy upon prior approval of the sponsor

[c] Vital signs (blood pressure, pulse, and temperature, and ECOG PS) taken predose on XO-C1D1, and predose at every subsequent visit. All vital signs will be obtained after the patient has been resting for at least 5 minutes. Height is only required once at screening.

[d] Fertile male patients and female patients of childbearing potential are to continue using effective contraception for 6 months after the last dose of rociletinib and report any pregnancies during this period.

[e] Serum β-hCG (evaluated by local laboratories) will be performed only on women of childbearing potential ≤ 3 days before XO-C1D1. An additional urine pregnancy test must be performed locally and results obtained prior to dosing on XO-C1D1 to confirm that the patient is not pregnant before dosing.

[f] Hematology evaluation should include reticulocytes ≤ 14 days before XO-C1D1. Blood will be analyzed at a local laboratory and must be reviewed by the investigator before start of each new cycle of rociletinib administration. Additional tests may be performed at the investigator's discretion.

[g] Fasting glucose required on XO-Cycle 1 Day 4 ± 1 day, XO-Cycle 1 Day 8 ± 1 day, XO-Cycle 1 Day 15 ± 1 day, and XO-Cycle 2 Day 15 ± 1 day and on Day 1 of each subsequent cycle Following an 8 hour fast (no food or liquid other than water). HbA1c will be measured ≤ 14 days before XO-C1D1 and on Day 1 of every other treatment cycle (XO-Cycles 3, 5, 7, etc.). Samples will be analyzed by a local laboratory.

[h] Tumor scans obtained at progression on/after comparator arm treatment should be used as XO-screening scans. Other studies (MRI, X-ray) may be performed. Tumor scans will then be performed according the institutional standard of care or every 6 weeks ± 1 week from the time of crossover (Day 1 of XO-Cycles 3, 5, 7, etc.) until tumor progression. Disease progression to continue to be assessed locally by the Investigator. If a patient discontinues treatment before progression or is continuing treatment post progression (with approval from Sponsor), then the decision to conduct additional scans and the frequency of those scans to monitor disease progression will be the responsibility of the treating physician

[i] Patients will be monitored for AEs/SAEs/AESIs from the time the first dose of CO-1686 is administered through 28 days after the last dose.

[j] Patient diaries should be collected and reviewed for compliance at each visit. No diary will be dispensed at end of treatment.

[k] 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart) prior to dosing up to and including Cycle 12, at a minimum. For patients who are ongoing at this time and for whom QT has been < 470 ms (average of the triplicate values) throughout the study, ECG monitoring may be subsequently taken every 3rd cycle thereafter. ECGs will be performed and interpreted locally for patient care decisions; however, tracings should be submitted to the central lab for independent evaluation.

[l] Only one sample is needed and may be collected at any visit to enable NAT2 analysis.

Patients Randomized to Rociletinib

Day 1 of Each Cycle (see also Appendix C, Table 4)

Patients will be instructed to **refrain** from taking their dose of oral CO-1686 at home on the day of their clinic visit (Day 1 of the cycle) because the dose will be taken during the clinic visit. The following procedures will be completed:

- Physical examination
  - Including a vision check as part of a standard physical exam
- Weight
- Vital signs (blood pressure, pulse, and temperature)
- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart) prior to dosing, up to and including Cycle 12, at a minimum. For patients who are ongoing at this time and for whom QT has been < 470 ms (average of the triplicate values) throughout the study, ECG monitoring may be subsequently taken every 3rd cycle thereafter. ECGs will be performed and interpreted locally for patient care decisions; however, tracings should be submitted to the central lab for independent evaluation. ECGs can be collected at any time pre-dose on the day of the scheduled collection.
- Local Fasting serum chemistry (including fasting glucose). HbA1c will be measured every other cycle (Day 1 of Cycle 3, 5, 7 etc).
- Local Hematology (including reticulocyte count)
- Concomitant medication and procedures
- AE monitoring (until 28 days after last dose of protocol specified treatment; then only ongoing SAEs assessed as related to the study drug, and AESIs regardless of causality , are followed until resolution or stabilization)
- Collection and review of patient diary and CO-1686 drug return. CO-1686 tablets will be dispensed to the patient; patient diary will be provided to the patient
- Tumor assessments will be performed per institution standard of care or every 6 ± 1 weeks after dosing until disease (tumor or clinical) progression. Disease progression to continue to be assessed locally by the Investigator. If a patient discontinues treatment before progression or is continuing treatment post progression (with approval from Sponsor), then the decision to conduct additional scans and the frequency of those scans to monitor disease progression will be the responsibility of the treating physician.
- (Optional) PGx Blood Sample
  - Patient may consent for optional PGx sample collection if not previously collected already, and have the sample collected for NAT2 analysis
  - Sample should only be collected at a single visit

Patients Randomized to Single Agent Cytotoxic Chemotherapy

Day 1 of Each Cycle (see also Appendix C, Table 5)

- All chemotherapy agents will be administered to the patients at the clinic intravenously on Day 1 of each 21-day cycle:
  - Pemetrexed will be administered at 500 mg/m^2
  - Gemcitabine will be administered at 1250 mg/m^2
  - Docetaxel will be administered either at 75 mg/m^2 (60 mg/m^2 for patients residing in East-Asian territories) or at 35 mg/m^2
  - Paclitaxel will be administered at 80 mg/m^2 as a 1 hour infusion
- Physical examination
  - Including a vision check as part of a standard physical exam
- Weight
- Vital signs (blood pressure, pulse, and temperature)
- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart) prior to dosing, up to and including Cycle 12, at a minimum. For patients who are ongoing at this time and for whom QT has been < 470 ms (average of the triplicate values) throughout the study, ECG monitoring may be subsequently taken every 3rd cycle thereafter. ECGs will be performed and interpreted locally for patient care decisions; however, tracings should be submitted to the central lab for independent evaluation. ECGs can be collected at any time pre-dose on the day of the scheduled collection.
- Local fasting serum chemistry (including fasting glucose). HbA1c will be measured every other cycle (Day 1 of Cycle 3, 5, 7 etc).
- Local hematology (including reticulocyte count)
- Concomitant medication and procedures
- AE monitoring (including SAEs)
- Tumor assessments will be performed per institution standard of care or every 6 ± 1 weeks after dosing until disease (tumor or clinical) progression. Disease progression to continue to be assessed locally by the Investigator and the frequency of those scans to monitor disease progression will be the responsibility of the treating physician.

Cycle X Day 8 (± 1 Day)

If selected as the comparator option, gemcitabine, docetaxel, and paclitaxel will be administered at the clinic intravenously on Day 8 of each 21-day cycle:

- Gemcitabine will be administered at 1250 mg/m^2
- Docetaxel will be administered at 35 mg/m^2 (in patients randomized to this docetaxel dosing regimen)
- Paclitaxel will be administered at 80 mg/m^2 as a 1 hour infusion

Please note, the other chemotherapy agents (pemetrexed and docetaxel 75 mg/m^2 [60 mg/m^2 in Asian patients]) will not be administered on this day.

In addition, the following procedures will be carried out for all patients randomized to receive single agent cytotoxic chemotherapy (pemetrexed, gemcitabine, docetaxel, or paclitaxel):

- Hematology (CBC and differential)
- AE monitoring (including SAEs)

Cycle X Day 15 (± 1 Day)

If selected as the comparator option, docetaxel and paclitaxel will be administered at the clinic intravenously on Day 15 of each 21-day cycle:

- Docetaxel will be administered at 35 mg/m^2 (in patients randomized to this docetaxel dosing regimen)
- Paclitaxel will be administered at 80 mg/m^2 as a 1 hour infusion

Please note, the other chemotherapy agents (pemetrexed, gemcitabine, and docetaxel 75 mg/m^2 [60 mg/m^2 in patients residing in East-Asian territories]) will not be administered on this day.

In addition, the following procedures will be carried out for all patients randomized to receive single-agent cytotoxic chemotherapy (pemetrexed, gemcitabine, docetaxel, or paclitaxel):

- Hematology (CBC and differential)
- AE monitoring (including SAEs)

Patients who Cross Over to Rociletinib after Chemotherapy

Screening Assessments (See also Appendix C, Table 6)

The following baseline assessments will be established prior to the first dose of oral rociletinib and ≤ 35 days following radiographic progression on single-agent cytotoxic chemotherapy. Patients will be required to sign a cross over ICF before screening procedures begin.

To be performed **≤ 35 days prior to XO-C1D1**:

- Informed Consent
- Prior and concomitant medications and procedures
- Contraceptive counseling
- Study procedure-related AEs

- 12-lead ECG (in triplicate, 10-second tracings > 2 min apart) will be performed and interpreted locally for patient care decisions; however, tracings should be submitted to the central lab for independent evaluation.
- Tumor scans will be performed per institution standard of care: scans used to determine radiographic progression on single agent cytotoxic chemotherapy will be used as baseline scans in cross over.

To be performed **≤ 14 days prior to XO-C1D1**:

- Physical examination by body system
  - Including a vision check as part of a standard physical exam
- Height and weight
- Vital signs (blood pressure, pulse, and temperature)
- Local hematology (including reticulocyte count)
- Local fasting serum chemistry (including fasting glucose). HbA1c will be measured every other cycle (Day 1 of Cycle 3, 5, 7 etc).
- Study procedure-related AEs

To be performed **≤ 3 days prior to XO-C1D1**:

- Serum pregnancy test (by local laboratory) ≤ 3 days prior to randomization for women of childbearing potential

Cross Over Cycle 1 Day 1 (XO-C1D1)

Patients will be required to take their first dose of rociletinib at the clinic with 8 oz (240 mL) of water and with a meal or within 30 minutes after a meal. The following procedures will be carried out pre- and postdose.

Predose Assessments	**Postdose Assessments**
Physical examination, including vision check Weight Vital signs (blood pressure, pulse, and temperature) Urine pregnancy test (with negative result) Concomitant medications and procedures Local hematology (including reticulocytes) Local fasting serum chemistry (includes glucose, HbA1c will be measured every other cycle (Day 1 of Cycle 3, 5, 7 etc). Rociletinib tablets will be dispensed to the patient Patient diary dispensed 12-lead ECG (in triplicate, 10-second tracings > 2 minutes apart) will be performed and interpreted locally for patient care decisions; however, tracings should be submitted to the central lab for independent evaluation. ECGs can be collected at any time pre-dose on the day of the scheduled collection.	AEs/SAEs/AESI experienced by the patient since dosing will be documented Concomitant medications administered since dosing will be recorded

Enough rociletinib tablets (and diary cards) will be dispensed to the patient for daily dosing until the next study clinic visit.

Cross Over Cycle 1 Days 4, 8 and 15 (± 1 Day)

The following procedures will be carried out:

- Local Fasting glucose
- **(Day 15 only)** 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart). ECGs will be performed and interpreted locally for patient care decisions; however, tracings should be submitted to the central lab for independent evaluation. ECGs can be collected at any time pre-dose on the day of the scheduled collection

Cross Over Cycle 2 Day 1 and every 21 ± 3 Days Thereafter

The following procedures will be carried out at 21 ± 3 day intervals:

- Physical examination
  - Including a vision check as part of a standard physical exam
- Weight
- Vital signs (blood pressure, pulse, and temperature)
- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart) prior to dosing, up to and including Cycle 12, at a minimum. For patients who are ongoing at this time and for whom QT has been < 470 ms (average of the triplicate values) throughout the study, ECG monitoring may be subsequently taken every 3rd cycle thereafter. ECGs will be performed and interpreted locally for patient care decisions; however, tracings should be submitted to the central lab for independent evaluation. ECGs can be collected at any time pre-dose on the day of the scheduled collection
- Local hematology (including reticulocyte count)
- Local fasting serum chemistry (includes fasting glucose). HbA1c will be measured every other cycle (Day 1 of Cycles 3, 5, 7, etc.) after initiating rociletinib treatment.
- Concomitant medication and procedures since last visit
- AE monitoring (until 28 days after last dose of protocol specified treatment; then only ongoing SAEs assessed as related to the study drug, and AESIs regardless of causality , are followed until resolution or stabilization.
- Collection and review of patient diary and CO-1686 drug return. CO-1686 tablets will be dispensed to the patient; patient diary will be provided to the patient
- Tumor assessments will be performed per institution standard of care or every 6 ± 1 weeks after dosing until disease (tumor or clinical) progression. Disease progression to continue to be assessed locally by the Investigator. If a patient discontinues treatment before progression or is continuing treatment post progression (with approval from Sponsor), then the decision to conduct additional scans and the frequency of those scans to monitor disease progression will be the responsibility of the treating physician.

Cross Over Cycle 2 Day 15

The following procedures will be carried out:

- Local Fasting glucose

End of Treatment Visit (All Patients)

The following procedures will be performed for all patients 28 days (±7 days) after the last dose of study treatment (initial study treatment or cross-over treatment, whichever comes last):

- Physical examination
  - Including a vision check as part of a standard physical exam
- Weight
- Vital signs (blood pressure, pulse, and temperature)
- Concomitant medications and procedures since last visit
- 12-lead ECG (in triplicate, 10-sec tracings > 2 min apart) will be performed and interpreted locally for patient care decisions; however, tracings should be submitted to the central lab for independent evaluation.
- Local Hematology (including reticulocyte count)
- Local fasting serum chemistry (including fasting glucose)
- Serum pregnancy test for women of childbearing potential
- Contraceptive counseling (Both fertile male and female patients)
- AE monitoring (until 28 days after last dose of study treatment; then only ongoing serious adverse events (SAEs) are followed until resolution or stabilization)
- Collection and review of patient diary (patient randomized to rociletinib only)