A Phase 1b/2 study of the safety and efficacy of rociletinib (CO-1686) administered in combination with MPDL3280A in patients with activating EGFR mutation-positive (EGFRm) advanced or metastatic non-small cell lung cancer (NSCLC)

Protocol Number:	CO-1686-032
Investigational Product:	Rociletinib, MPDL3280A
IND Number:	[redacted]
EUDRA CT Number	[redacted]
Development Phase:	Phase 1b/2
Indication Studied:	Locally advanced or metastatic NSCLC with mutant epidermal growth factor receptor (EGFR)
Sponsor Name and Address:	Clovis Oncology, Inc. 2525 28th Street 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 ICH GCP Guidelines. Essential study documents will be archived in accordance with applicable regulations.
Protocol Date:	26 May 2015
[redacted]	[redacted]

CONFIDENTIALITY STATEMENT

Protocol Approval Signature Page

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[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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SYNOPSIS

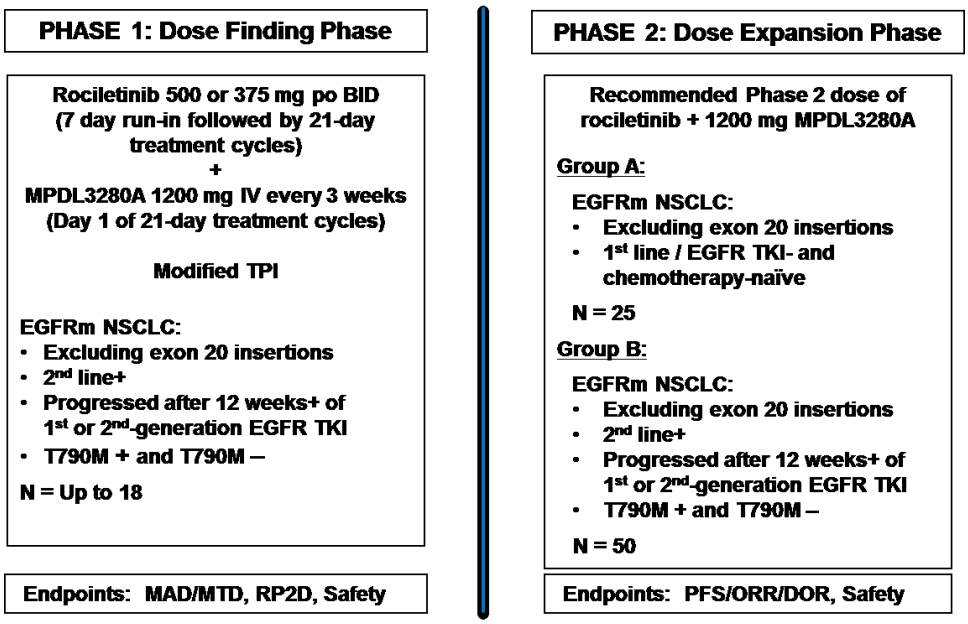
Protocol Number	CO-1686-032
Title	A Phase 1b/2 study of the safety and efficacy of rociletinib (CO-1686) administered in combination with MPDL3280A in patients with activating EGFR mutation-positive (EGFRm) advanced or metastatic non-small cell lung cancer (NSCLC)
Phase	1b/2
Introduction	Rociletinib is a novel, potent, covalent (irreversible) small molecule, tyrosine kinase inhibitor (TKI) that selectively targets mutant forms of the epidermal growth factor receptor (EGFR). 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 (eg, L858R, del19), and rociletinib has minimal inhibitory activity towards the wild-type EGFR at clinically relevant doses. Clovis Oncology, Inc. (Clovis or Sponsor) is developing rociletinib as a therapeutic to be administered orally (PO) to patients with EGFRm NSCLC. The recommended Phase 2 doses (RP2Ds) of rociletinib, 500 mg and 625 mg, twice daily (BID), were determined in Study CO-1686-008, a study conducted in patients with EGFRm advanced or metastatic NSCLC who had prior treatment with an EGFR inhibitor. Overall responses based on Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) were observed across a range of doses with rociletinib. Among NSCLC patients with the T790M mutation (T790M+) treated at the 500 mg or 625 mg BID, the overall response rate (ORR) was 67%.[1] Responses to rociletinib are rapid, frequently occurring within less than 12 weeks. The median progression-free survival (PFS) for subjects receiving rociletinib monotherapy at 500 mg or 625 mg in the context of acquired resistance has been reported as 10.4 months.[1] Responses to rociletinib have also been observed in patients without the T790M mutation (T790M–).[1] The most common rociletinib-related toxicity observed is hyperglycemia, which is generally managed with oral anti-hyperglycemic therapy. Adverse events (AEs) typical of wild-type (WT) EGFR inhibition (the combination of rash and chronic diarrhea) have not been observed with rociletinib. MPDL3280A is a human IgG1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. MPDL3280A was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and consequently, eliminates detectable Fc-effector function and depletion of cells expressing PD-L1. MPDL3280A targets human PD-L1 and inhibits its interaction with its receptor, PD-1. MPDL3280A also blocks the binding of PD-L1 to B7.1, an interaction that is reported to provide additional inhibitory signals to T cells.[2] In Phase 1 studies of MPDL3280A, the maximum tolerated dose (MTD) was not reached, and no dose-limiting toxicity (DLT) was reported. The most commonly observed AEs have been rash and diarrhea. The RP2D of intravenous (IV) single-agent MPDL3280A has been identified as 1200 mg every 3 weeks. Data for 53 patients with NSCLC (including squamous and non-squamous histologies) treated with MPDL3280A have been presented. A 23% ORR was reported.[3] The response rate in subjects with PD-L1 expression in infiltrating immune cells was 46%. Tumor responses

	occurred as early as the first assessment. PFS in this group was remarkable, with a 45% PFS at a 24-week landmark assessment. The most common AEs in this group were fatigue and decreased appetite. PD-L1 was found to be down regulated in the presence of erlotinib in EGFRm NSCLC tumors but not in those with WT EGFR, suggesting that PD-L1 expression is dependent on EGFR signaling conferred by activating EGFR mutations. Furthermore, recent data indicate that PD-L1 is overexpressed in EGFR-TKI-resistant cell lines, suggesting that PD-L1 upregulation could contribute to acquired resistance to EGFR TKIs. Based on these data, dual therapies of EGFR TKIs and anti-PD-L1 antibodies, targeted at overcoming acquired resistance in EGFRm NSCLC, may provide significant benefit to these patients with a high unmet medical need. In addition, the combination of therapies may prevent the commonly acquired mechanisms of resistance to occur. In this study, the safety and efficacy of rociletinib in combination with MPDL3280A will be investigated in patients with EGFRm NSCLC.
Planned Number of Patients	Phase 1: Approximately 18 patients. Phase 2: Up to 75 patients.
Planned Number of Sites	Up to 14 sites in the United States, France and Spain.
Study Objectives	**Primary Objectives:** **Phase 1:** • To determine the safety and tolerability, DLTs, MTD or maximum administered dose (MAD) and RP2D of the combination of rociletinib and MPDL3280A; • To assess the pharmacokinetic (PK) profile of rociletinib (and its metabolites) and MPDL3280A when given in combination. **Phase 2:** • To determine the efficacy of the combination of rociletinib and MPDL3280A based on ORR per RECIST v1.1 (Appendix A) in the following groups of patients: ▪ **Group A:** Patients with EGFRm advanced or metastatic NSCLC who have not previously received an EGFR TKI or chemotherapy; ▪ **Group B:** Patients with EGFRm advanced or metastatic NSCLC who have progressed on a prior EGFR TKI. **Secondary Objectives:** **Phase 1:** • To determine preliminary efficacy and pharmacodynamics of the combination of rociletinib and MPDL3280A in enrolled patients. **Phase 2:** • To determine the efficacy of the combination of rociletinib and MPDL3280A based on ORR per modified RECIST incorporating immune-related response criteria (irRC; Appendix B) in Groups A and B;

	• To assess the activity of the combination of rociletinib and MPDL3280A based upon duration of response (DOR) and PFS; • To assess the pharmacodynamic relationship between biomarkers and clinical activity, and/or resistance to study drug.
Study Endpoints	**Primary Endpoints:** **Phase 1:** • Treatment-emergent AEs; • DLTs; • PK parameters for rociletinib (and its metabolites) and MPDL3280A. **Phase 2:** • ORR according to RECIST v1.1 (Appendix A) as determined by Investigator assessment. **Secondary Endpoints:** • ORR according to modified RECIST incorporating irRC (Appendix B); • DOR, DCR, and PFS according to RECIST v1.1 as determined by Investigator assessment; • DOR, DCR, and PFS according to modified RECIST incorporating irRC (Appendix B); • Overall survival (OS); • Change from baseline in mutant EGFR levels in circulating tumor DNA (ctDNA) obtained from plasma; **Exploratory Endpoints:** • Positive and negative percent agreement between blood and tissue results for T790M and EGFR activating mutations. • Incidence of anti-therapeutic antibody (ATA) response to MPDL3280A and potential correlation with PK, pharmacodynamics, safety and efficacy parameters; • Identification of biomarkers associated with response or resistance to rociletinib and/or MPDL3280A; • Changes in expression of immune-related markers (including, but not limited to, granzyme B or other exploratory markers) in archival and/or fresh tumor tissue prior to and after MPDL3280A and rociletinib treatment; • Markers of RAS-RAF-MEK signaling cascade (including, but not limited to, EGFR) in archival and/or fresh tissue; • PD-L1 status by immunohistochemistry (IHC) or quantitative polymerase chain reaction (PCR) in archival and/or fresh tissue.

Study Design

This is a Phase 1b/2 multicenter, open-label, non-randomized study in patients with EGFRm advanced or metastatic NSCLC to be conducted in two phases: a Dose Finding Phase (Phase 1) and a Dose Expansion Phase (Phase 2). A schematic of the study is presented below.



Phase 1: The Dose Finding Phase will be conducted with patients who have progressed after at least 12 weeks of treatment with a prior first- or second-generation EGFR TKI (ie, erlotinib, gefitinib, afatanib), regardless of T790M mutation status. The Dose Finding Phase will be used to determine the MTD or MAD and RP2D of the combination of rociletinib and MPDL3280A, and to evaluate the safety, tolerability, and PK profile of the combination treatment.

Specific doses of rociletinib will be administered in combination with a fixed dose of MPDL3280A. Combination doses of rociletinib with MPDL3280A will be defined for each Dosing Cohort enrolled during the Dose Finding Phase, and currently two potential Dosing Cohorts are planned (see table below). The first Dosing Cohort will be 500 mg BID rociletinib and 1200 mg MPDL3280A on Day 1 of each 21-day cycle. At minimum, 3 patients will be enrolled into this first cohort. If this combination dose is determined to be safe and tolerable, no further dose modifications for either drug will be made. Based on emerging safety and evaluable PK and/or pharmacodynamics data, additional doses or schedules of rociletinib may be evaluated.

Cohort	Rociletinib Dose	MPDL3280A Dose
1	500 mg PO BID	1200 mg IV every 3 weeks Day 1 of each 21-day cycle
2	375 mg PO BID	

BID, twice daily; IV, intravenous; PO, oral.

The Dose Finding Phase will include a 7-day Run-in-Period of rociletinib monotherapy at the specified dose of the Dosing Cohort prior to the initiation of combination treatment. Patients who experience an adverse event that requires a reduction or delay of more than 48 hours in

	the dosing of rociletinib during the Run-in-Period will not go on to receive the combination of rociletinib and MPDL3280A, but will remain on study to receive rociletinib monotherapy; an additional patient will be enrolled as a replacement for inclusion in the same Dosing Cohort. For the Dose Finding Phase, Cycle 1 will begin with the initiation of combination treatment following a successful Run-in-Period and will be the period of safety and DLT evaluation for each Dosing Cohort (see Section 3.2 for further details on DLT evaluation and Dosing Cohort decision-making). Thereafter, treatment and monitoring of patients will be conducted in 21-day treatment cycles. The RP2D for the combination of rociletinib and MPDL3280A will be determined based on cumulative data from all cohorts. A safety expansion cohort of up to 6 patients may be enrolled to further examine the tolerability of a dose combination of interest or the tolerability of combination dosing without a rociletinib monotherapy Run-in-Period. **Phase 2:** The Dose Expansion Phase will be conducted in EGFR TKI treatment-naïve and chemotherapy-naïve patients (Phase 2 Group A) and in the same population of patients as in Phase 1 (Phase 2 Group B) (see schematic above). The Dose Expansion Phase will be used to assess the RP2D of the combination of rociletinib and MPDL3280A for preliminary efficacy and pharmacodynamics effects, in addition to safety and tolerability in these patient populations. For the Dose Expansion Phase, there will not be a Run-in-Period; treatment will begin with both rociletinib and MPDL3280A on C1D1, and treatment and monitoring of patients will be conducted in consecutive 21-day treatment cycles. **Safety Monitoring:** Throughout the study, oversight will be provided by the Clinical Safety Committee (CSC), comprised of all Principal Investigators and the Sponsor's Medical Monitor and Drug Safety representative. The CSC will: • Review and confirm all DLTs; • Determine all cohort dose-escalation and de-escalation decisions during the Dose Finding Phase; • Determine the MTD or MAD and RP2D to take into the Dose Expansion Phase; • Review safety evaluation of all patients.

Inclusion Criteria	All patients must meet all of the following inclusion criteria: 1. Signed and dated informed consent, approved by the Independent Ethics Committee (IEC) or Institutional Review Board (IRB), obtained prior to the performance of any study-specific procedures or assessments and ability to understand and comply with protocol requirements and instructions; <u>Baseline Characteristics</u> 2. Males and females ≥18 years of age; 3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; 4. Adequate hematological and biological function, based on the following laboratory values: • Bone Marrow Function: ▪ Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L; ▪ Lymphocyte count ≥ 0.5 x 10^9/L; ▪ Platelets > 100.0 × 10^9/L (without transfusion within 2 weeks prior to receipt of study drug); ▪ Hemoglobin ≥ 9 g/dL (or 5.6 mmol/L) (patients may be transfused and/or receive erythropoietin stimulating agents to meet this criterion per institutional guidelines). • Hepatic Function: ▪ Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × upper limit of normal (ULN); if liver metastases, ≤ 5 × ULN; ▪ Bilirubin ≤ 2.0 × 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: ▪ Serum creatinine ≤ 1.5 × ULN or creatinine clearance ≥ 50 mL/min. • Electrolytes: ▪ Potassium and magnesium within normal range, patients may receive supplements to meet this requirement. • Coagulation status: ▪ International normalized ratio (INR) and activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN; ▪ This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose. 5. Ability to swallow and retain orally administered study drug; <u>EGFRm NSCLC Disease Characteristics</u> 6. Histologically or cytologically documented metastatic or unresectable, locally advanced or metastatic NSCLC, with prior histopathological reports showing evidence of one or more activating EGFR mutation (eg, G719X, exon 19 deletion, L858R, L861Q), except for exon 20 insertion; 7. Measurable disease as defined by RECIST v1.1 (Appendix A): • Previously irradiated lesions should not be counted as target lesions;

Inclusion Criteria (continued)	• Lesions that are intended to be used to collect tissue samples for biopsy should not be counted as target lesions. 8. Biopsy of tumor tissue for central evaluation within 60 days prior to the first day of study treatment (Run-in-Period Day 1 for Phase 1; C1D1 for Phase 2); 9. For Phase 1 and Phase 2 Group B, patients must have progressed after at least 12 weeks of treatment with a 1st or 2nd generation EGFR TKI (eg, erlotinib, gefitinib, afatinib) for advanced or metastatic NSCLC. A minimum of a 3 day washout period is required for previous EGFR TKIs. • Previous chemotherapy for NSCLC is allowed for patients enrolled in Phase 1 and Phase 2 Group B 10. For Phase 2 Group A, patients must be EGFR TKI treatment-naïve and chemotherapy-naïve 11. Anticipated life expectancy of at least 3 months; <u>Medical/Surgical History</u> 12. A minimum of 14 days must have elapsed since any palliative radiotherapy; 13. A minimum of 14 days must have elapsed from last invasive surgery, and wound healing has occurred; 14. Any ongoing potentially reversible treatment-related toxicities must be resolved to Grade ≤ 1 EXCEPT alopecia or (with agreement from the Medical Monitor) the expected EGFR TKI toxicities of rash or diarrhea that are stable with intervention; 15. No planned major surgery while on study; <u>Concomitant Medications or Procedures</u> 16. Women of childbearing potential must have a negative serum pregnancy test within 7 days prior to the first dose of study treatment and agree to use highly effective contraception as defined in the full protocol, during the study and for 90 days following the last dose of MPDL3280A or rociletinib; 17. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception as described in the full protocol for at least 14 days prior to administration of the first dose of study treatment, during the study, and for 90 days following the last dose of MPDL3280A or rociletinib.

Exclusion Criteria	Any of the following criteria will exclude patients from study participation: EGFRm NSCLC Disease Characteristics 1. Documented evidence of an exon 20 insertion mutation in the EGFR gene; 2. Symptomatic, untreated or unstable central nervous system or leptomeningeal metastases. (Patients with treated and stable brain metastases [confirmed by 2 scans at least 4 weeks apart], with no evidence of cavitation or hemorrhage in the brain lesion are eligible provided that they are asymptomatic and do not require corticosteroids); Medical/Surgical History 3. Previous treatment with rociletinib or MPDL3280A, or other 3rd generation EGFR TKI (eg, AZD-9291, HM61713), or PD-1 axis-targeted therapy (eg, anti-PD-1 or anti-PD-L1); 4. Prior treatment with CD137 agonists or other immune checkpoint blockade therapies, including anti-CTLA-4 therapeutic antibodies; 5. Uncontrolled pleural effusion, pericardial effusion or ascites requiring recurrent drainage procedures (once monthly or more frequently); 6. Uncontrolled hypercalcemia (> 1.5 mmol/L ionized calcium or Ca > 12 mg/dL or corrected calcium > ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab: • Patients who are receiving bisphosphonate therapy or denosumab specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemina are eligible; • Patients who are receiving denosumab prior to enrollment must be willing and eligible to receive a bisphosphonate instead while on study. 7. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric humanized antibodies or fusion proteins; 8. Known hypersensitivity to Chinese hamster ovary cell products or any component of the MPDL3280A or rociletinib formulations; 9. History of prior allogeneic hematopoietic stem cell transplantation or prior solid organ transplantation; 10. History of autoimmune disease (*please review* Appendix E): • Patients with a history of Type 1 diabetes on a stable anti-hyperglycemic regimen; autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone; vitiligo; or alopecia are eligible for this study. 11. Positive test for human immunodeficiency virus (HIV); 12. Patients with active hepatitis B virus (HBV) (defined by a positive hepatitis B surface antigen [HBsAg] test at screening): • Patients with past or resolved HBV infection (defined by a negative HBsAg test and a positive anti-hepatitis B core antigen [anti-HBc] antibody test) are eligible. HBV DNA must be obtained in these patients prior to first day of study treatment.

Exclusion Criteria (continued)	13. Patients with active hepatitis C virus (HCV): • Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV ribonucleic acid (RNA). 14. Active tuberculosis; 15. Signs or symptoms of infection within 2 weeks prior to first day of study treatment; 16. Received therapeutic oral or IV antibiotics within 2 weeks prior to first day of study treatment: • Patients receiving prophylactic antibiotics (eg, to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible. 17. Administration of a live, attenuated vaccine within 4 weeks before first day of study treatment or anticipation that such a live attenuated vaccine will be required during the study: • Influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live, attenuated influenza vaccine (eg, FluMist®) within 4 weeks prior to first day of study treatment or at any time during the study. 18. Class II to IV heart failure as defined by the New York Heart Association functional classification system (Appendix G) • Patients with a known left ventricular ejection fraction (LVEF) < 40% will be excluded; • Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF < 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate, to be eligible. 19. Patients who have experienced untreated and/or uncontrolled cardiovascular conditions and/or have symptomatic cardiac dysfunction (unstable angina, congestive heart failure, myocardial infarction within the previous 3 months; coronary angioplasty, or stenting or bypass grafting within the past 6 months; cardiac ventricular arrhythmias requiring medication; any history of 2nd or 3rd degree atrioventricular conduction defects); 20. Any of the following cardiac abnormalities or history: • Clinically significant abnormal 12-lead electrocardiogram (ECG) or QT interval corrected using Fridericia's method (QT_CF) > 450 ms; • Inability to measure QT interval on ECG; • Personal or family history of long QT syndrome; • Implantable pacemaker or implantable cardioverter defibrillator; • Resting bradycardia < 55 beats/min. 21. History of idiopathic pulmonary fibrosis, organizing pneumonia (eg, bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computerized tomography (CT) scan: • History of radiation pneumonitis in the radiation field (fibrosis) is permitted. 22. Females who are pregnant or breast feeding; 23. Presence of active gastrointestinal (GI) disease (including GI bleeding or ulceration) or other condition that could affect GI absorption (eg, malabsorption syndrome, history of biliary tract disease);

Exclusion Criteria (continued)	24. Uncontrolled medical, psychological, familial, sociological, or geographical conditions that interfere with the patient's safety, ability to provide informed consent, or ability to comply with the protocol; 25. Malignancies other than NSCLC within 5 years prior to enrollment, with the exception of those with a negligible risk of metastasis or death (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer, or ductal carcinoma in situ); <u>Previous and Concomitant Medications</u> 26. Patients who are currently receiving treatment with any medications that have the potential to prolong the QT interval if that treatment cannot be either discontinued or switched to a different medication prior to first day of study treatment. The wash out period for the medication should be at least 5 times the medication's half-life (see http://crediblemeds.org/ for a list of QT-prolonging medications); 27. Treatment with systemic immunostimulatory agents (including but not limited to interferon [IFN], interleukin [IL]-2) within 6 weeks or five half-lives of the drug, whichever is shorter, prior to first day of study treatment; 28. Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and antitumor necrosis factor [anti-TNF] agents) within 2 weeks prior to first day of study treatment: • The use of inhaled corticosteroids and mineralocorticoids (eg, fludrocortisone) is allowed.
Study Treatment	Rociletinib is provided as 250 mg or 125 mg tablets. During the Dose Finding Phase (Phase 1), dosing with rociletinib at the cohort-assigned dose will begin on the first day of the 7-day Run-in-Period of rociletinib monotherapy. During the Dose Expansion Phase (Phase 2), dosing with rociletinib at the RP2D for the combination will begin on C1D1. Patients will self-administer rociletinib orally BID at the cohort-assigned dose, unless dose reduction is required for adverse event management. Patients should take rociletinib as directed by the treating physician. Patients will be instructed to take each dose of rociletinib with 8 oz. (240 mL) of water and with a meal or within 30 minutes after a meal. Tablets should be swallowed whole. MPDL3280A is provided in single-use, 20-cc USP/Ph. Eur. Type 1 glass vials as a colorless-to-slightly yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20 mL (1200 mg) of MPDL3280A solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume. Dosing with MPDL3280A at a fixed dose of 1200 mg will begin on C1D1 (for Phase 1, C1D1 follows the Run-in-Period of rociletinib monotherapy) and Day 1 of each 21-day cycle thereafter. Administration of MPDL3280A will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. Dose modification guidelines for rociletinib and MPDL3280A are described in Section 5.7.

Concomitant Medications	Concomitant therapy includes any prescription or over-the-counter medications or preparations used by a patient from 28 days prior to the first dose of study treatment through 28 days after the last dose of study treatment, or the date of administration of subsequent anticancer therapy, whichever is earlier. All concomitant medications should be reported to the Investigator and recorded. Guidelines for use of concomitant medications are detailed in Section 7.
Withdrawal Criteria	A patient must be discontinued from all study treatment if any of the following apply: • Consent withdrawal at the patient's own request or at the request of their legally authorized representative; • Clinical disease progression where the Investigator believes that the patient will not continue to benefit from study treatment (*Note:* patients will be permitted to continue study treatment after a radiographic progression [Appendix A and Appendix B] if the benefit-risk ratio is judged to be favorable and continued treatment is approved by the Medical Monitor); • 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 and requires discontinuation of therapy; • A positive pregnancy test at any time during the study; • Non-compliance as described in Section 5.5; • Investigator decision. In addition, the Sponsor may discontinue the study early for any of the reasons noted in Section 12.6.
Study Procedures	The Screening Period will be 28 days prior to the first dose of study treatment. Some assessments are required to be performed within shorter windows (eg, 7 or 14 days) prior to the first dose of study treatment (see Table 1). A mandatory baseline biopsy will be collected within 60 days prior to first dose of study treatment. The Treatment Period will consist of 21-day treatment cycles. In Phase 1 only, there will be an additional 7-day Run-in-Period of rociletinib monotherapy. Clinic visits are scheduled on Day 1 of each cycle and more frequently during Cycle 1 (see Table 1). Tumor assessments will be conducted for the duration that the patient is on study treatment (Section 8.4.3.1). In addition, patients will provide blood samples for PK and pharmacodynamics/biomarker assessments at protocol-defined time points (see Table 2). During a Follow-up Period, patients will be followed for adverse events through 28 days after last dose of study treatment, or until initiation of subsequent anticancer therapy, whichever is earlier. Patients will also be contacted approximately every 3 months for collection of data on subsequent anticancer treatment and survival. In addition, the patient will be asked to return 120 days after the last dose of MPDL3280A to collect samples for pharmacokinetic (PK) and anti-therapeutic antibody (ATA) samples (see Table 2). See the Table 1 for detailed study procedures.

PK	Please refer to Table 2 for a detailed PK sampling schedule. On scheduled PK sampling days, patients should be instructed to not self-administer study drug at home, but to bring rociletinib to the clinic along with breakfast. After a predose PK blood draw, patients will eat breakfast and take the morning dose of rociletinib within 30 minutes after starting their meal. On days of MPDL3280A infusions, patients will be administered IV MPDL3280A approximately 2 hours after the morning rociletinib dose. Times of the meals and administrations of study drugs in the clinic should be recorded. Additional unscheduled PK blood samples will be collected at the time of fresh tumor biopsy and may also be collected when a patient experiences an adverse event for which the Investigator would like to have PK data to help understand the safety observation.
Pharmacody-namics	Please refer to Table 2 for a detailed pharmacodynamic blood sampling schedule. A mandatory fresh tumor tissue biopsy specimen will be collected within 60 days prior to the first day of study treatment for all patients. In addition, an optional fresh tumor biopsy may be collected at time of permanent treatment discontinuation due to disease progression (at the time the Investigator believes the patient is no longer deriving clinical benefit from study treatment, if treatment beyond radiographic disease progression is approved). The baseline tissue biopsy specimen from screening will be used for a retrospective confirmation of EGFR mutation status by a central laboratory. The baseline biopsy as well as the optional tissue biopsy collected at progression will also be used to investigate mechanisms of response, primary resistance, and acquired resistance to rociletinib and MPDL3280A. Blood samples will be collected for pharmacogenomic and pharmacodynamics analyses. The pharmacogenomic blood sample will be collected predose on C1D1 for genomic deoxyribonucleic acid (DNA) purification. The DNA sample may be evaluated by next generation sequencing (NGS), and molecular alterations in germline and tumor DNA may be compared so that molecular alterations unique to the tumor that may modulate response or resistance to EGFR targeted therapy can be unambiguously identified. Pharmacodynamic blood samples will be collected and processed as described in Table 2 and Section 8.4.5.
Statistical Procedures	Statistical methods are described in Section 10.

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Table 1: Study CO-1686-032 Schedule of Assessments

Procedure[A]	Screening Period	Rociletinib 7-day Run-In- Period (Phase 1 only)	Treatment Period				End of Treatment[C]	Follow Up
			Cycle 1 combination therapy (21-day cycle)			Cycle 2+ combination therapy (21-day cycle)		
	Day -28 to Day 0	Day 1[B]	Day 1[B]	Day 4	Days 8 and 15 ±2 days	Day 1 ±3 days		
Informed consent	X							
Documentation of EGFR mutational status[D]	X							
Medical/oncology history[E]	X							
Physical examination	Complete[F,G]	Limited[H]	Complete[G]	Limited[H]	Limited[H]	Limited[H]	Complete[G]	
ECOG performance status[I]	X[F]	X	X			X	X	
Vital signs[J]	X[F]	X	X	X	X	X	X	
Hematology (including reticulocytes)[K]	X[F]	X	X		X	X	X	
Coagulation tests [L]	X[F]							
Urinalysis[M]	X							
Fasting serum chemistry[N]	X[F]	X	X			X	X	
Fasting blood glucose[O]				X	X			
Serum pregnancy test[P]	X						X	
Hemoglobin A1c	X					Odd cycles		
TSH, free T_3 and free T_4[Q]	X					X	X	
HIV/HBV/HCV serology[R]	X							
ECHO/MUGA[S]	X							
12-lead ECG[T]	X[F]	X	X	X	X	X	X	
Pulmonary function test[U]	X							

Procedure[A]	Screening Period	Rociletinib 7-day Run-In- Period (Phase 1 only)	Treatment Period				End of Treatment[C]	Follow Up
			Cycle 1 combination therapy (21-day cycle)			Cycle 2+ combination therapy (21-day cycle)		
	Day -28 to Day 0	Day 1[B]	Day 1[B]	Day 4	Days 8 and 15 ±2 days	Day 1 ±3 days		
Tumor biopsy[V]	X						X[C,V]	
Tumor assessments[W]	X					X	X[C,W]	
Pharmacogenomic blood sample (predose)		X	X (Phase 2 only)					
Rociletinib PK sampling[X]		X	X		Days 8-9	X (see Table 2)	X[C,X]	
MPDL3280A PK sampling[X]			X			X (see Table 2)	X[C,X]	X
ATA testing[X]			X			X (see Table 2)	X[C,X]	X
TBNK blood sample[X]	X[F]		X		X		X[C,X]	
Pharmacodynamic blood sample[X]	X		X		Day 8	X (see Table 2)	X[C,X]	
Dispense rociletinib/ drug accountability/diary[Y]		X	X			X		
Rociletinib in-clinic administration[Y]		X	X		Day 8	X		
MPDL3280A administration[Z]			X			X		
Adverse events[AA]	X	X	X	X	X	X	X	
Concomitant medications[BB]	X	X	X	X	X	X	X	
Survival assessment/ subsequent therapies[CC]							X	X

ATA, anti-therapeutic antibody; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; MUGA, multigated acquisition (scan); PK, pharmacokinetic; TBNK, T, B, and natural killer; TSH, thyroid-stimulating hormone.

A	Unless otherwise specified: Clinic visits for the specified assessments in Cycle 2+ should be completed ± 3 days of the scheduled time point relative to C1D1. Assessments are to be performed prior to administration of study treatment, when applicable. All results must be reviewed by the Investigator prior to administration of study treatment. Perform assessments as scheduled on C1D4 (ie, no window) and assessments for C1D8 and C1D15 within ± 2 days of the scheduled time points.
B	Procedures required on Day 1 of Run-in-Period (Phase 1) or C1D1 (Phase 2) may be omitted if completed ≤ 3 days earlier during the Screening Period.
C	Patients will be asked to return to the clinic 28 days (+7 days) after the last dose of study treatment, or before the patient initiates another anticancer agent, if sooner, for assessment of patient safety. Collect optional tumor biopsy and blood samples for PK, pharmacodynamic, TBNK, and ATA analyses scheduled for the EOT Visit as close as possible to the date of the decision to discontinue treatment (ie, not necessary to wait until EOT Visit for sample collection). Tumor assessment scans do not need to be repeated if radiographic disease progression has been documented previously or the last scans were performed < 2 weeks before the last dose of study treatment or the patient had disease progression at the last scan. All AEs (including SAEs and protocol-defined events of special interest), regardless of attribution, will be recorded until 28 days after the last dose of study treatment or until initiation of another anticancer therapy, whichever occurs first. Ongoing AEs considered related to study treatment and all SAEs will be followed until the event has resolved to baseline grade, the event is assessed by the Investigator as stable, new anticancer treatment is initiated, the patient is lost to follow up, the patient withdraws consent, or it is determined that the study treatment or participation is not the cause of the AE.
D	For patients being considered for enrollment in the study, screening assessments will not begin until patient tumor EGFR mutation status is determined through local assessments.
E	Record patient's medical history, including smoking status, medical conditions, and oncology history, including date of cancer diagnosis, prior cancer treatment, and any surgical procedures.
F	Perform procedure within 14 days prior to first day of study treatment.
G	Includes height (at screening only), weight (the patient should be in light indoor clothes; no shoes), and the evaluation of head, eyes, ears, nose and throat (HEENT) and cardiovascular, dematologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems.
H	Includes weight (the patient should be in light indoor clothes; no shoes), an assessment of all baseline abnormalities and recording of associated changes, questioning of the patient about any skin or vision changes, and any other symptom-directed examination.
I	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.
J	After the patient has been resting for at least 5 minutes, measure body temperature, heart rate, respiratory rate, and blood pressure. For the first infusion of MPDL3280A, measure vital signs within 60 minutes before, every 15 (± 5) minutes during the infusion, and 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before the infusion, during the infusion if clinically indicated or if symptoms occurred in the prior infusion, and 1 hour (± 10 minutes) after the infusion.
K	Includes hemoglobin, hematocrit, WBC and differential (with ANC), reticulocyte count, and platelet count. Hematology results must be reviewed by the Investigator before administration of rociletinib and/or MPDL3280A.
L	Includes prothrombin time, international normalized ratio (INR), and activated partial thromboplastin time (aPTT). Patients known to require concomitant therapy with anticoagulants such as warfarin should also have INR monitored throughout the study.
M	Collect a freshly voided, clean sample and analyze by 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.
N	Includes total protein, albumin, creatinine, blood urea nitrogen (BUN) or urea, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol, **fasting** glucose, sodium, potassium, magnesium, chloride, calcium, phosphorus and uric acid. Fasting glucose must be measured after an 8-hour fast (no food or liquid other than water).
O	Fasting glucose must be measured after an 8-hour fast (no food or liquid other than water).
P	Perform for females of childbearing potential ≤ 7days before first day of study treatment and at the EOT Visit. If the serum pregnancy test results are not available on the first day of study treatment, a urine pregnancy test can be performed on the first day of study treatment. A negative result must be confirmed by a physician before the first dose of study treatment.

Q	TSH, free T3, and free T4 will be tested at screening, and thereafter, TSH will be tested every 3 months or as clinically indicated.
R	***For patients who have positive serology for anti-HBc**: HBV DNA must be collected prior to administration of MPDL3280A in patients who have positive serology for anti-HBc.
S	***For patients with known history of (or suspected current potential for) pericardial effusions:*** baseline and as clinically indicated.
T	12-lead ECG performed in triplicate 10-sec tracings > 2 min apart in patient at rest for at least 5 minutes. The average of triplicates should be recorded. Data will also be transmitted for central review.
U	Conduct at baseline and as clinically indicated. Pulmonary function tests must include an assessment of diffusing capacity of lung for carbon monoxide (DL_{CO}).
V	Collect a mandatory biopsy of either primary or metastatic tumor tissue within 60 days prior to the first day of study treatment. Corresponding blood samples (see Table 2) should be obtained before the tumor specimen collection. If a biopsy was performed outside of the protocol within 60 days prior to administration of study drug, and no intervening treatment was given, a repeat biopsy is not required if an adequate tumor tissue specimen from the recent biopsy can be provided to the Sponsor during the Screening Period. The optional tumor biopsy (requires separate consent) will be collected from patients who permanently discontinue study treatment because of disease progression (or patient is considered by the Investigator to no longer benefit from study treatment, if treatment is continued beyond a radiographic progression); the biopsy should be collected as close as possible to the date of the decision to discontinue treatment (ie, not necessary to wait until EOT Visit for sample collection).
W	Obtain baseline tumor assessments (clinical examination and scans) within 28 days before first day of study treatment. Scans will include the pelvis, chest, and abdomen (preferably CT scans with ≤ 5 mm slice thickness). Brain imaging is required at baseline and must be repeated at follow-up tumor assessments for patients with brain lesions. Other studies (magnetic resonance imaging [MRI] and X-ray) may be performed if required. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the study. Tumor assessments during the Treatment Period will occur every 2 cycles (6 weeks ±1 week) through Cycle 6 (ie, at the end of Cycles 2, 4, and 6); every 3 cycles (9 weeks ± 1 week) after Cycle 6 (ie, at the end of Cycles 9, 12, etc); and at the EOT Visit. The frequency of tumor assessments may be further reduced after 2 years with approval of the Medical Monitor. Tumor assessments at the EOT Visit are not required if radiographic disease progression has been documented previously or the last tumor assessments were performed < 2 weeks before the last dose of study treatment. If an initial CR or PR is noted, confirmatory scans must be performed 4 to 6 weeks later.
X	Collect blood samples for PK, pharmacodynamic, TBNK, and ATA analyses according to the schedule and instructions in Table 2. On scheduled PK sampling days, instruct patients to not administer study drug at home, but to bring rociletinib to the clinic along with breakfast. After a predose PK blood draw, patients will eat breakfast and take the morning dose of rociletinib within 30 minutes after starting their meal. On days of MPDL3280A infusions, patients will be administered IV MPDL3280A approximately 2 hours after the morning rociletinib dose. Times of the PK blood draws, meals, and administrations of study drugs in the clinic should be recorded. Note: At the EOT Visit, collect samples as close as possible to the date of the decision to discontinue treatment (ie, not necessary to wait until EOT Visit for sample collection). During the Follow-up Period, patients will be asked to return 120 days after the last dose of MPDL3280A for collection of MPDL3280A PK and ATA samples. Samples for MPDL3280A PK and ATA and TBNK will only be collected in patients who have at least one dose of MPDL3280A (ie, not applicable to patients who remain on rociletinib monotherapy because they are ineligible for combination therapy [see Section 5.7.2]).
Y	Dispense a sufficient number of rociletinib tablets to last until the next visit and provide a medication diary. Extra study drug may be dispensed if there is a reasonable possibility that the patient's next visit may be delayed (eg, because of inclement weather or distance of patient's home from study center). Instruct patient on how to take study drug and to record the time and date they take each study drug dose in the diary and return all unused study drug at each study visit. Collect and review medication diary, collect unused tablets, and assess compliance at each subsequent visit. In-clinic administration of rociletinib is required on days that predose or postdose blood samples are collected (see Table 2).
Z	Administer MPDL3280A as an IV infusion at a fixed dose of 1200 mg IV starting at C1D1 and every 3 weeks thereafter (one infusion per 21-days). The initial dose of MPDL3280A will be delivered over 60 (± 15) minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 30 (± 10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes.
AA	Monitor patients for AEs from the time of signed informed consent (study procedure-related events included) through 28 days after the last dose of study treatment, or subsequent anticancer therapy if sooner (see Section 9 for details).
BB	Record concomitant medications from 28 days prior to the first dose of study treatment through 28 days after the last dose of study treatment, or subsequent anticancer therapy, whichever is earlier. See Section 7 for details.
CC	Collect survival follow-up information, including all subsequent anticancer therapy, via telephone calls, patient medical records, and/or clinic visits 12 weeks (± 1 week) until death, loss to follow up, or study termination by the Sponsor.

Table 2: Clinical Sample Collection (PK, ATA, TBNK, Pharmacodynamic)[a]

Study Visit		Rociletinib PK	MPDL3280A PK	MPDL3280A ATA	TBNK and/or pharmacodynamic
Screening		–	–	–	Both [b]
Run In	Day 1	Predose [c] (***Phase 1 only***)	–	–	–
Cycle 1[d]	Day 1[e]	Predose [c]	Predose [c] 30 (± 10) min (after end of infusion) [e]	Predose [c]	Both [b] (Predose)
	Day 8	Predose [c] 0.5, 1, 1.5, 2.5, 4, and 6 hours post-morning dose (***Phase 1 only***) [e]	–	–	Both [b] (Predose)
	Day 9 (Phase 1 only)	Predose [c] (24-hrs after D8 morning dose)	–	–	–
	Day 15	–	–	–	TBNK
Cycle 2-4 [d]	Day 1	Predose [c]	Predose [c]	Predose [c]	Pharmacodynamic
Cycle 5	Day 1	–	–	–	Pharmacodynamic
Cycle 6 [d]	Day 1	Predose [c]	Predose [c]	Predose [c]	Pharmacodynamic
Cycle 8 [d]	Day 1	Predose [c]	Predose [c]	Predose [c]	Pharmacodynamic
Cycle 9	Day 1	–	–	–	Pharmacodynamic
Every 8 cycles after C8 (Cycles 16, 24, *etc*) [d]	Day 1	Predose [c]	Predose [c]	Predose [c]	Pharmacodynamic
EOT Visit		X	X	X	Both [b]
120 days (± 30 days) after last dose of MDPL3280A	At visit	–	X	X	–
At time of fresh biopsy	–	X	X	X	Both [b]

ATA, anti-therapeutic antibody; EOT, End of Treatment; PK, pharmacokinetics; TBNK, T, B, and natural killer cells.

[a] Please refer to the Laboratory Manual for details on sample handling and processing.
[b] The pharmacodynamics collection should occur after the TBNK collection and is always predose/pre-infusion.
[c] Predose refers to the morning dose of rociletinib.
[d] Collection of the actual time(s) of dose administration is essential for both rociletinib and MPDL3280A.
[e] MPDL3280A dose administration should start approximately 2 hours after the morning rociletinib dose, which is to occur within 30 minutes after the start of the morning meal.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	anti-hepatitis B core antigen
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATA	anti-therapeutic antibody
AUC	area under the curve
AUC_{0-24}	area under the curve from time zero to 24 hours
BID	twice daily
BSA	body surface area
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CK	creatine kinase
C_{max}	maximum concentration
CR	complete response
CRO	contract research organization
CSC	Clinical Safety Committee
CT	computed tomography
ctDNA	circulating tumor DNA
CTCAE	Common Terminology Criteria for Adverse Events (Version 4.03)
CXDX	Cycle X Day X
CYP	cytochrome P450
DCR	disease control rate
DL_{CO}	diffusing capacity of lung for carbon monoxide
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
DVT	deep venous thrombosis
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EGFRm	epidermal growth factor receptor mutation-positive
EOT	End of Treatment
EURTAC	European Tarceva™ versus Chemotherapy Study
FBG	fasting blood glucose
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGO	ground glass opacities
GI	gastrointestinal
GLP	Good Laboratory Practice
HBr	hydrobromide

HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HEENT	head, eyes, ears, nose and throat
HIPAA	Health Information Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IFN	interferon
IHC	immunohistochemistry
IL	interleukin
IMP	investigational medicinal product
INR	international normalized ratio
irAE	immune-related adverse event
IRB	Institutional Review Board
irRC	immune-related response criteria
IV	intravenous
LFT	liver function test
LVEF	left ventricular ejection fraction
MAD	maximum administered dose
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
MUGA	multigated acquisition (scan)
NCI	National Cancer Institute
NGS	next generation sequencing
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
OS	overall survival
ORR	overall response rate
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	progressive disease
PE	pulmonary embolism
PET	positron emission tomography
PFS	progression free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PO	oral(ly)
PR	partial response
PRN	as needed
PT	prothrombin time
PVC	polyvinylchloride

Q	every
QOD	every other day
QD	once daily
QT_CF	QT interval corrected using Fridericia's method
RECIST	Response Evaluation Criteria in Solid Tumors, Version 1.1
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAS	statistical analysis software
SD	stable disease
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	elimination half-life
T790M	EGFR mutation in exon 20, gatekeeper mutation
T790M–	T790M mutation-negative
T790M+	T790M mutation-positive
TBNK	T-cell, B-cell, and natural killer
TKI	tyrosine kinase inhibitor
t_{max}	time to maximum concentration
TNF	tumor necrosis factor
TPI	toxicity probability interval
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States (of America)
WBC	white blood cell
WT	wild type

1 INTRODUCTION

Despite years of research and prevention strategies, lung cancer continues to be the most common cancer worldwide and the most common cause of cancer-related deaths worldwide,4 accounting for 1.8 million new cases and 1.6 million deaths in 2012. Lung cancer has a 5-year survival rate of less than 10% in patients with advanced disease.5

Activating epidermal growth factor receptor (EGFR) mutations are key drivers of non-small cell lung cancer (NSCLC) malignancy in 10% to 15% of patients of European descent and approximately 30% of patients of East Asian descent.6 The two most frequently detected EGFR mutations in NSCLC patients are in the kinase domain: L858R substitution in exon 21 and deletions in a specific amino acid motif in exon 19 (Del19). Following demonstration of improved response rates and progression-free survival (PFS) over cytotoxic chemotherapy in Phase 3 studies of erlotinib, gefitinib, and afatinib,[7,8,9,10,11] treatment of such patients with EGFR inhibitors is now standard of care.

While the toxicity profile is also improved with first-generation tyrosine kinase inhibitors (TKIs) compared to chemotherapy, significant toxicities do occur. Toxicity associated with both erlotinib and gefitinib includes skin rash and diarrhea related to inhibition of the wild-type (WT, normal) EGFR in skin and intestine, respectively.[12,13,14]

Despite the initial response, patients generally experience progression within 9 months to 14 months of starting erlotinib, gefitinib, or afatinib. After disease progression on an EGFR-TKI, patients are often treated with chemotherapy. A number of small studies report response rates of 14% to 18% and PFS of around 4 months on chemotherapy after failure of an EGFR-TKI.[15,16]

Mechanisms of resistance commonly include acquisition of secondary activating mutations while the initial activating mutation is maintained.[17] The most common cause of resistance is thought to be due to development of a second site EGFR mutation in exon 20 called T790M (the "gatekeeper" mutation), which prevents drug from binding to the receptor.[17,18,19,20] In addition, resistance may be associated with amplification of the EGFR gene or other genes that drive tumor growth such as MET gene amplification and PI3K mutations. Second-generation TKIs such as dacomitinib, neratinib, and afatinib have demonstrated limited clinical activity when the T790M mutation is present possibly because the toxicity from potent WT EGFR inhibition limits dosing such that drug concentrations required to inhibit T790M are not achieved.[21] Assessment of post-progression survival in patients treated with EGFR-TKI indicated that those with EGFR T790M mutation-positive (T790M+) tumors had a median post-progression survival of 1.9 years (95% CI, 1.6-2.6 years).[22] Thus, NSCLC patients who have failed treatment with TKIs and whose tumors express T790M mutation represent a group with fatal disease and unmet need. Furthermore, methods to prevent the acquisition of the T790M mutation are desirable.

In addition to the development of acquired mutations, evasion of immune destruction has been found to be an important mechanism of tumorigenesis and disease progression. Programmed death 1 (PD-1) protein is a T-cell coinhibitory receptor and has two known ligands, PD-L1 (B7-H1) and PD-L2 (B7-DC). PD-L1 is selectively expressed on many tumors and on cells within the tumor microenvironment. Binding of PD-L1 to its receptors suppresses T-cell migration, proliferation and secretion of cytotoxic mediators, and restricts tumor cell killing.

Potentiation of immune responses has been observed via blockade of the interaction between PD-1 and PD-L1 and has resulted in antitumor activity in both nonclinical models and early clinical studies.

Recent studies suggest that activation of PD-1 pathway may contribute to immune escape in EGFR-driven tumors. PD-L1 is overexpressed in EGFR-mutated NSCLC cell lines and resected tumors. In addition, inhibition of EGFR signaling with erlotinib resulted in down-regulation of PD-L1 expression in EGFR-mutated NSCLC cells but not in those with WT EGFR. These and other data suggest that PD-L1 expression may be dependent on EGFR signaling via activating EGFR mutations. In a recent study, overexpression of PD-L1 was demonstrated in the presence of erlotinib in EGFR-TKI-resistant H195 cells, which harbor both an activating mutation and the T790 mutation. Thus, blockade of PD1- PD-L1 signaling may help to overcome acquired resistance to EGFR-TKIs.

Rociletinib is a novel, potent, small molecule TKI that irreversibly binds and inhibits EGFR with the common activating (L858R, Del19) and T790M-resistance mutations and has minimal activity towards WT EGFR. Clovis Oncology, Inc. (Clovis or Sponsor) is developing rociletinib as a therapeutic agent to be administered orally (PO) to patients with EGFRm NSCLC who have been previously treated with an EGFR-targeted therapy and have a T790M mutation in EGFR.

The recommended Phase 2 doses (RP2Ds) of single-agent rociletinib are 500 and 625 mg twice daily (BID), as determined in the Phase 1/2 study, CO-1686-008 in patients with advanced or metastatic EGFRm NSCLC previously treated with an EGFR inhibitor. In CO-1686-008, Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) responses have been observed across a range of doses of rociletinib (500 mg BID to 1000 mg BID), and the overall response rate (ORR) among NSCLC patients with the T790M+ treated with rociletinib at 500 mg or 625 mg BID, the Phase 2 clinical doses, was approximately 67%.1 Responses to rociletinib are rapid, frequently occurring within less than 12 weeks. The median PFS in patients receiving rociletinib monotherapy at 500 mg or 625 mg in the context of acquired resistance has been reported as 10.4 months.1 Responses have also been observed in T790M negative (T790M–) patients.1 The most common rociletinib-related adverse event (AE) observed in single-agent studies has been hyperglycemia, which is generally managed with oral anti-hyperglycemic therapy. AEs typically associated with the inhibition of WT EGFR (eg, the combination of rash and chronic diarrhea) have not been observed with rociletinib.

MPDL3280A is a human IgG1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. MPDL3280A was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and consequently, eliminates detectable Fc-effector function and depletion of cells expressing PD-L1. MPDL3280A targets human PD-L1 and inhibits its interaction with its receptor, PD-1. MPDL3280A also blocks the binding of PD-L1 to B7.1, an interaction that is reported to provide additional inhibitory signals to T cells.2

The interaction of PD-L1 with PD-1 and B7.1 inactivates T cells and prevents further T cell priming, and increased PD-L1 expression on tumor cells and/or tumor-infiltrating cells is a mechanism of cancer evasion of immune surveillance.

In Phase 1 studies of MPDL3280A, the maximum tolerated dose (MTD) was not reached, and no dose-limiting toxicity (DLT) was reported. The most common observed AEs have been fatigue and decreased appetite. The RP2D of intravenous (IV) single-agent MPDL3280A has been identified as 1200 mg every 3 weeks.

Antitumor activity has been observed in single-agent studies of MPDL3280A at doses from 1 mg/kg to 20 mg/kg in multiple tumor types. Data for 53 patients with NSCLC (including squamous and non-squamous histologies) treated with MPDL3280A has been presented. A 23% ORR based on RECIST v1.1was reported.3 The response rate in patients with PD-L1 expression in infiltrating immune cells was 46%. Tumor responses occurred as early as the first assessment. PFS in this group was remarkable for a 45% PFS at a 24-week landmark assessment.3

Treatment of tumors with rociletinib often results in a pronounced reduction in tumor volume, likely resulting in the increase of tumor antigen expression, CD8+ T cell infiltration, and a decrease in immunosuppressive cytokines. However, the immune response may be limited due to increased expression of immunomodulatory proteins such as PD-1, PD-L1, and B7.1 on the surface of tumor and T cells. As such, it is anticipated that the combination of MPDL3280A to rociletinib will enhance the immune antitumor immune response via blockade of the inhibitory signaling resulting from the interactions of PD-L1 with PD-1 and B7.1.

Two independent mechanisms of action, each with promising activity in patients with NSCLC, the potential for complementarity of these mechanisms of action, and largely non-overlapping safety profiles provide strong rationale for the current study, which will examine the combination of rociletinib and MPDL3280A in patients with EGFRm NSCLC. The tolerability of the combination is expected to be acceptable given the minimal overlapping toxicity profile and the overall tolerability of the two agents in patients with previously treated advanced cancers.

1.1 Rociletinib Nonclinical Overview

Refer to the rociletinib Investigator's Brochure (IB) for detailed nonclinical data.

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

Pharmacology

Rociletinib exhibited 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.[23] In addition, the efficacy of rociletinib was examined in an $EGFR^{L858R/T790M}$ transgenic model and compared with that of afatinib. Whereas complete responses were observed in all mice treated with rociletinib, there was very limited activity in the mice treated with afatinib (please refer to IB for additional details).

Metabolism

In human liver microsomes, rociletinib was stable, with ≤ 27% turnover in 60 minutes. Rociletinib was not metabolized significantly by human recombinant cytochrome P450 (CYP) enzymes, with ≤ 10% metabolized in a 60-minute incubation. CYP2C8 mediates the oxidative metabolism of rociletinib, and CYP2D6 potentially plays a minor role at most in rociletinib metabolism. 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) (see Section 7.6 for guidance on use of concomitant medication that may affect the metabolism of rociletinib).

Safety Pharmacology and Toxicology

Safety pharmacology and toxicology studies were performed in rats and dogs with rociletinib HBr.

In repeat-dose toxicity studies in rats, primary indices of toxicity included dose-dependent clinical signs (thinning haircoat [females], squinting, pale ears or body, and hunched posture), decreased food consumption, and loss in body weight and decreased body weight gain. Squinting was observed in rats administered high-dose rociletinib and was associated with atrophy of the meibomian gland in the eyelid. 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 four tissues which was reversible and principally occurred in the high-dose group. Only minor effects were observed with rociletinib on hematopoietic tissue. All clinical observations were reversible with exception of body weight effects in male animals that received the highest dose (300 mg/kg/dose BID). All clinical pathology changes were fully reversed.

In repeat-dose toxicity studies in dogs, primary indices of toxicity included dose-related clinical signs: 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 and lack of impact on body weights or food consumption. All clinical observations were reversible, except for non-formed feces in one animal. Focal duodenal erosion in one male animal dosed at 50 mg/kg/dose BID was the only potential treatment-related effect identified histologically.

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 two *in vitro* assays and was not phototoxic when evaluated in a phototoxicity study with Long-Evans pigmented rats.

1.2 MPDL3280A Nonclinical Overview

Refer to the MPDL3280A IB for detailed nonclinical data.

The nonclinical strategy of the MPDL3820A program was to demonstrate *in vitro* and *in vivo* activity, to determine *in vivo* pharmacokinetic (PK) behavior, to demonstrate an acceptable safety profile, and to identify a Phase 1 starting dose. Comprehensive pharmacology, PK, and toxicology evaluations were performed with MPDL3280A.

The safety, PK, and toxicokinetics of MPDL3280A were investigated in mice and cynomolgus monkeys to support IV administration and to aid in projecting the appropriate starting dose in humans. Given the similar binding of MPDL3280A for cynomolgus monkey and human PD-L1, the cynomolgus monkey was selected as the primary and relevant nonclinical model for understanding the safety, PK, and toxicokinetics of MPDL3280A.

Overall, the nonclinical PK and toxicokinetics observed for MPDL3280A supported entry into clinical studies, including providing adequate safety factors for the proposed Phase 1 starting doses. The results of the toxicology program were consistent with the anticipated pharmacologic activity of downmodulating the PD-L1/PD-1 pathway; heightened immune responses and the potential to increase immune-associated inflammatory lesions were identified as possible safety risks in patients.

1.3 Clinical Experience with Rociletinib

Refer to the rociletinib IB for detailed clinical data.

Five studies are currently ongoing (CO-1686-008, CO-1686-018, CO-1686-019, CO-1686-022, CO-1686-020), and one clinical study has been completed (CO-1686-016).

Ongoing studies:

- CO-1686-008 (TIGER-X) is a Phase 1/2, open-label, safety, PK, and preliminary efficacy study of rociletinib in patients with advanced NSCLC. Phase 1 is a dose escalation phase to determine the MTD, and it is fully enrolled. Phase 2 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 it is currently enrolling;
- CO-1686-018 (TIGER-J) 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 Phase 2, single arm, open-label, safety and efficacy study of rociletinib as second-line EGFR-directed TKI therapy in patients with EGFRm NSCLC with and without the T790M mutation.

- CO-1686-022 (TIGER-1) is a Phase 2/3, randomized, open-label study of rociletinib versus erlotinib as first-line treatment for patients with EGFR-mutant, advanced NSCLC.

- CO-1686-020 (TIGER-3) is a Phase 3, randomized, open-label study of rociletinib versus single-agent chemotherapy in patients with EGFRm NSCLC after failure of at least one prior EGFR-targeted TKI and platinum-doublet chemotherapy.

Completed study:

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

1.3.1 Safety of Rociletinib from Clinical Studies

Preliminary safety data are presented for the ongoing CO-1686-008 and completed CO-1686-016 studies. As of 04 June 2014, 190 patients have received at least one dose of rociletinib: 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 NSCLC patients who received rociletinib in Study CO-1686-008.

Study CO-1686-008

Preliminary safety data are reported for 148 patients with advanced NSCLC in this study, including 57 patients who were treated with rociletinib free base at total daily doses ranging from 150 mg up to 1800 mg (once daily [QD], BID, and three times daily [TID] dosing schedules) and 91 patients who were treated with rociletinib HBr at total daily doses ranging from 1000 mg to 2000 mg (500 mg BID, 625 mg BID, 750 mg BID and 1000 mg BID). Rociletinib HBr is being studied in ongoing clinical studies and will be used in this study (Section 5.1).

Dose-Limiting Toxicities: 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 rociletinib 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 6.1.2.

Serious Adverse Events (SAEs) and Deaths: A total of 43 patients experienced at least one SAE, and among these, 17 patients (11.5%) had an SAE assessed as related to study drug. The most commonly reported treatment-related SAE was hyperglycemia (reported by 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. Treatment-related SAEs are summarized in Table 3.

There were 11 deaths on study, including the 28-day post-treatment period after the last dose of rociletinib. Eight deaths were reported as due to progression of NSCLC, one death due to pulmonary embolism, one death due to pneumonia, and one death of unknown cause. A causal relationship with rociletinib could not be ruled out for the death of unknown cause; all other deaths were reported as unrelated to study drug.

Table 3: Treatment-Related Serious Adverse Events Reported by 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%)

BID, twice daily; ECG, electrocardiogram; FB, rociletinib free base; HBr, rociletinib hydrobromide; N, number of patients; SAE, serious adverse event.

Treatment-Related Adverse Events (AEs): The most frequently reported treatment-related AEs (all grades, ≥ 20% of patients) were hyperglycemia (33%; including Medical Dictionary for Regulatory Activities [MedDRA] Preferred Terms blood glucose elevated, glucose tolerance impaired, and hyperglycemia), nausea (28%), and fatigue (20%). Treatment-related AEs reported by at least 5% of patients are summarized in Table 4. The majority of AEs were mild or moderate in severity.

Other Treatment-Related Adverse Events of Interest

Rash and Diarrhea: Rociletinib selectively inhibits mutant EGFR, and as expected, the syndrome of dose-related WT-driven rash and diarrhea has not been observed in clinical studies of rociletinib. All reported events of diarrhea were either Grade 1 or Grade 2.

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

Pneumonitis: There have been two AEs of pneumonitis, and one SAE of pneumonitis, all assessed by the Investigator as related to rociletinib. Patients recovered after steroid therapy.

QT Prolongation: Rociletinib exposure is associated with QT 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 prolongation during treatment with rociletinib. Typically, the abnormality is evident by Day 15 of therapy, and the increase remains stable with continued dosing. QT interval corrected using Fridericia's method (QT_CF) intervals longer than 500 msec have been observed in 10 patients (7.6%).

Table 4: Treatment-Related Adverse Events Reported by 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 treatment-emergentAE							
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%)

BID, twice daily; FB, rociletinib free base; HBr, rociletinib hydrobromide; N, number of patients.

1.3.2 Activity of Rociletinib from Clinical Studies

Preliminary activity data for rociletinib are available from the Phase 1/2 CO-1686-008 study.

Although the primary objectives of the first phase of Study CO-1686-008 were to evaluate the safety, toxicity, and PK profile of rociletinib, there is robust preliminary evidence of activity for rociletinib across therapeutic doses of rociletinib (rociletinib free base 900 mg BID, and rociletinib HBr 500 mg BID to 1000 mg BID) for T790M+ patients previously treated with one or more lines of an EGFR TKI. As of 04 June 2014, 22 of 40 patients (55%) had a Response Evaluation Criteria in Solid Tumors (RECIST) partial response (PR), and the disease control rate (DCR) was approximately 92%.

1.3.3 Pharmacokinetics of Rociletinib

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 HBr increased with ascending single doses (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 3-12 hours postdose with a mean increase of 172% at 12 hours postdose (-22% to +400%) and a mean increase of 77% in AUC_{0-24} (+10% to 146%), with no change in elimination 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.

Data for repeat doses are available from six healthy subjects who were dosed in the fed state with 500 mg BID rociletinib for 4 days. PK profiles of rociletinib following morning and evening dosings were similar, with low intra-subject variability (Day 1 and Day 4 comparison). There was no accumulation of rociletinib.

Study CO-1686-008: Ongoing Phase 1/2 Study

In the Phase 1/2 patient study (CO-1686-008), PK after rociletinib HBr administration were available from a total of 51 patients. (Rociletinib HBr showed increased absorption and thus higher exposure than rociletinib free base.) For rociletinib HBr, the median t_{max} was 1.5 to 3.25 hours, and $t_{1/2}$ ranged from 1.7 to 4.7 hours. After rociletinib HBr administration, exposure (measured as C_{max} and AUC_{0-24}) increased approximately dose-proportionally from 500 mg to 1000 mg BID.

1.4 Clinical Experience with MPDL3280A

Refer to the MPDL3280A IB for detailed clinical data.

1.4.1 Safety of MPDL3280A from Clinical Studies

The presented safety data for MPDL3280A have been derived from the treatment of patients in Study PCD4989g. In this study, patients are receiving MPDL3280A monotherapy. No DLTs have been observed at any dose level and no MTD was established.

As of 10 May 2014, in the PCD4989g study, 412 patients have been treated with MPDL3280A. The PCD4989g study consisted of patients with NSCLC, renal cell carcinoma, melanoma, and urothelial bladder cancer (88, 69, 45, and 79 patients, respectively), as well as other tumor types.

The majority of AEs reported were Grade 1 or 2 in maximum severity (based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 [NCI CTCAE v4.03].[24] The most frequently observed AEs (occurring in ≥ 10% of treated patients) included fatigue, nausea, decreased appetite, pyrexia, dyspnea, diarrhea, constipation, cough, headache, back pain, vomiting, anemia, arthralgia, rash, insomnia, asthenia, abdominal pain, chills, and pruritus.

Given the mechanism of action of MPDL3280A, events associated with inflammation and/or immune-mediated AEs are being closely monitored during the MPDL3280A clinical program. Potential immune-related events that have been reported include dermatologic, hepatic, endocrine, and respiratory events (eg, pneumonitis); hepatitis/elevated liver function tests (LFTs); and influenza-like illness.

Dyspnea, cough, fatigue, hypoxia, pneumonitis and pulmonary infiltrates have been associated with the administration of MPDL3280A and have primarily been observed in patients with underlying NSCLC. Mild to moderate events of pneumonitis have been reported with MPDL3280A.

1.4.2 Pharmacokinetics of MPDL3280A

On the basis of available preliminary PK data (0.03−20 mg/kg), MPDL3280A appeared to show linear PK at doses ≥ 1 mg/kg. For the 1-mg/kg and 20-mg/kg dose groups, the mean apparent CL and the mean Vss had a range of 3.20 to 4.44 mL/day/kg and 48.1 to 65.7 mL/kg, respectively, which is consistent with the expected profile of an IgG1 antibody in humans.

1.5 Rationale for Study

Targeted approaches in cancer therapy aim to inhibit molecular pathways or mutant proteins that are critical for driving growth or survival of the tumor. Pharmacologic inhibition of the EGFR pathway with EGFR TKIs has proven successful in inducing regression of tumors whose transformation is driven by receptors or mutations that activate this dominant pathway. However, even when highly effective at reducing tumor burden, targeted therapies invariably drive emergence of resistance, limiting the duration of response (DOR). Rociletinib is a novel, irreversible, small molecule TKI that selectively targets mutant forms of EGFR including the T790M “gatekeeper” mutation as well as common activating mutations (eg, L858R and del 19), while sparing the WT EGFR.

Immunotherapy attempts to harness the host immune system to recognize and kill the transformed cells. Because the immune response is dynamic, it has the potential to match the cancer's ability to mutate and evolve, increasing the odds of generating durable responses. Thus, combining tumor-targeted therapies with agents that enhance antitumor immunity represents an increasingly attractive treatment paradigm for cancer. Antibodies targeting T-cell immune checkpoint inhibitors such as PD-L1 and PD-1 have demonstrated the capacity to generate durable responses in patients with multiple cancer types.[25,26] Nonclinical studies have shown that the combination of targeted therapies and blockade of PD-1 can lead to durable complete tumor responses that are not achieved by either approach alone.[27] The increase in tumor cell death induced by combination treatment can be reasonably expected to result in more effective release and presentation of a greater diversity of tumor antigens, thus potentiating the antitumor immune response.

PD-L1 was found to be down regulated in the presence of erlotinib in EGFRm NSCLC tumors but not in those with WT EGFR, suggesting that PD-L1 expression is dependent on EGFR signaling conferred by activating EGFR mutations. Furthermore, recent data indicate that PD-L1 is overexpressed in EGFR-TKI resistant cell lines, suggesting that PD-L1 upregulation could contribute to acquired resistance to EGFR TKIs. Based on these data, dual therapies of EGFR TKIs and anti-PD-L1 antibodies, targeted at overcoming acquired resistance in EGFRm NSCLC may provide significant benefit to these patients with a high unmet medical need. In addition, the combination of therapies may prevent the commonly acquired mechanisms of resistance to occur.

In this study, the safety and efficacy of rociletinib in combination with MPDL3280A will be investigated in patients with EGFRm NSCLC. The study will be conducted in 2 phases, a Dose Finding Phase (Phase 1) to determine the optimal dose for the combination of rociletinib against a fixed dose of MPDL3280A, and a Dose Expansion Phase (Phase 2) in two separate cohorts to evaluate preliminary efficacy of the combination of rociletinib and MPDL3280A in EGFRm NSCLC patients who are EGFR TKI treatment-naïve and chemotherapy-naïve or who have progressed on a prior EGFR TKI.

MPDL3280A will be administered at a fixed dose of 1200 mg IV every 21 days. The fixed dosage (equivalent to an average body weight-based dose of 15 mg/kg) is informed by available clinical activity, safety, and PK data. Antitumor activity has been observed across doses from 1 mg/kg to 20 mg/kg. The MTD of MPDL3280A was not reached, and no DLTs have been observed at any dose in Study PCD4989g. Available preliminary PK data (0.03-20 mg/kg) from Study PCD4989g suggest that for doses ≥ 1 mg/kg, overall MPDL3280A exhibits a PK profile that is both linear and consistent with typical IgG1 antibodies. Detectable anti-therapeutic antibodies (ATAs) were observed in patients at all dose levels but were associated with changes in PK for some patients in only the lower dose cohorts (0.3, 1, and 3 mg/kg). Patients dosed at the 10, 15, and 20 mg/kg dose levels have maintained target trough levels of drug despite the detection of ATAs.

Simulations do not suggest any clinically meaningful differences in exposure following a fixed dose or a dose adjusted for weight. On the basis of this analysis, a fixed dose of 1200 mg has been selected (equivalent to an average body weight-based dose of 15 mg/kg).

The starting dose for rociletinib in this study is 500 mg PO BID. This is the lower of two clinically active doses that were expanded in Phase 1 and Phase 2 studies of rociletinib monotherapy in EGFRm NSCLC patients. It has been found to have comparable activity to the 625 mg BID dose, with a more favorable overall safety profile. Section 3.2 provides detailed information regarding the planned doses for each dose escalation cohort and dose escalation guidelines for the study.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objectives

The following are the primary objectives for Phase 1 and Phase 2:

Phase 1

- To determine the safety and tolerability, MTD or maximum administered dose (MAD), and RP2D of the combination of rociletinib and MPDL3280A;
- To assess the PK profile of rociletinib (and its metabolites) and MPDL3280A when given in combination.

Phase 2

- To determine the efficacy of the combination of rociletinib and MPDL3280A based on overall response rate per RECIST v1.1 (Appendix A) in the following groups of patients:
  - **Group A**: Patients with EGFRm advanced or metastatic NSCLC who have not previously received an EGFR TKI or chemotherapy.
  - **Group B:** Patients with EGFRm advanced or metastatic NSCLC who have progressed on a prior EGFR TKI.

2.1.2 Secondary Objectives

The following are the secondary objectives for Phase 1 and Phase 2:

Phase 1

- To determine preliminary efficacy and pharmacodynamics of the combination of rociletinib and MPDL3280A in enrolled patients.

Phase 2

- To determine the efficacy of the combination of rociletinib and MPDL3280A based on ORR per modified RECIST incorporating immune related response criteria (irRC; Appendix B) in Groups A and B;
- To assess the activity of the combination of rociletinib and MPDL3280A based upon DOR and PFS;
- To assess the pharmacodynamic relationship between biomarkers and clinical activity, and/or resistance to study drug.

2.2 Endpoints

2.2.1 Primary Endpoints

The following are the primary endpoints for Phase 1 and Phase 2:

Phase 1

- Treatment-emergent AEs;
- DLTs;
- PK parameters for rociletinib (and its metabolites) and MPDL3280A.

Phase 2

- ORR according to RECIST v1.1 (Appendix A) as determined by Investigator assessment.

2.2.2 Secondary Endpoints

The following are the secondary endpoints for this study:

- ORR according to modified RECIST incorporating irRC (Appendix B);
- Duration of response, DCR, and PFS according to RECIST v1.1 (Appendix A) as determined by Investigator assessment;
- Duration of response, DCR, and PFS according to modified RECIST incorporating irRC (Appendix B);
- Overall survival (OS);
- Change from baseline in mutant EGFR levels in circulating tumor DNA (ctDNA) obtained from plasma.

2.2.3 Exploratory Endpoints

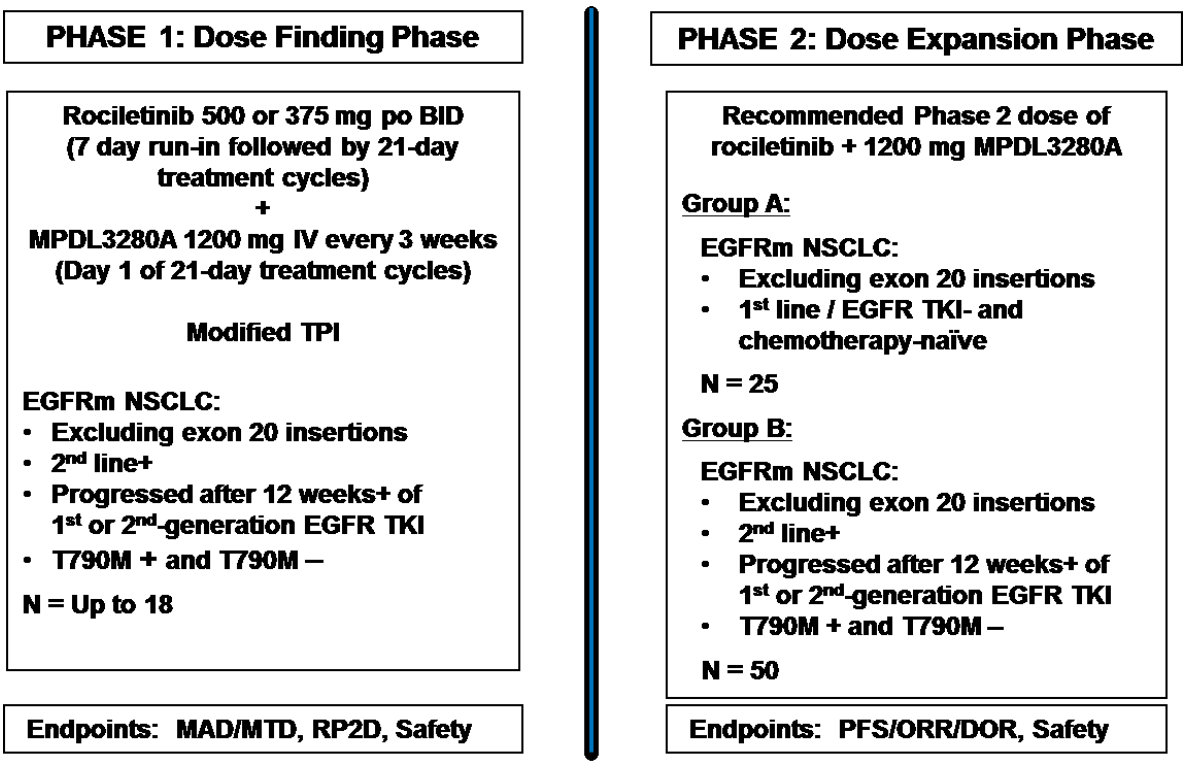
The following are the exploratory endpoints for this study:

- Positive and negative percent agreement between blood and tissue results for T790M and EGFR activating mutations;
- Incidence of ATA response to MPDL3280A and potential correlation with PK, pharmacodynamics, safety and efficacy parameters;
- Identification of biomarkers associated with response or resistance to rociletinib and/or MPDL3280A;
- Changes in expression of immune-related markers (including but not limited to granzyme B or other exploratory markers) in archival and/or fresh tumor tissue prior to and after MPDL3280A and rociletinib treatment;
- Markers of RAS-RAF-MEK signaling cascade (including but not limited to EGFR) in archival and/or fresh tissue;
- PD-L1 status by immunohistochemistry (IHC) or quantitative polymerase chain reaction (PCR) in archival and/or fresh tissue.

3 STUDY DESIGN

This is a multicenter, open-label, non-randomized study in patients with EGFRm advanced or metastatic NSCLC to be conducted in two phases: a Dose Finding Phase (Phase 1) and a Dose Expansion Phase (Phase 2). A schematic of the study design is presented in Figure 1.

Figure 1: Study Schematic



BID, twice daily; DOR, duration of response; EGFRm, epidermal growth factor receptor mutatant; MAD, maximum administered dose; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; ORR, overall response rate; PFS, progression-free survival; T790M–, T790M mutation-negative; T790M+, T790M mutation-positive; TKI, tyrosine kinase inhibitor; TPI, toxicity probability interval.

3.1 Clinical Safety Committee

Throughout the study, oversight will be provided by the Clinical Safety Committee (CSC), comprised of all Principal Investigators, the Sponsor's Medical Monitor and the Sponsor's drug safety representative. The CSC will:

- Review and confirm all DLTs;
- Determine all cohort dose-escalation and de-escalation decisions (assignment of Dosing Cohorts) during the Dose Finding Phase (Phase 1);
- Determine the MAD or MTD and RP2D to extend into the Expansion Phase (Phase 2), based on available safety, tolerability, and PK data;
- Review safety data for all patients during Phase 1 and Phase 2.

3.2 Dose Finding Phase (Phase 1)

The Dose Finding Phase will be conducted with patients who have progressed after at least 12 weeks of treatment with a prior first- or second-generation EGFR TKI (ie, erlotinib, gefitinib, afatanib), regardless of T790M mutation status. The Dose Finding Phase will be used to determine the MTD or MAD and RP2D of the combination of rociletinib and MPDL3280A, and to evaluate the safety, tolerability, and PK profile of the combination treatment. The Dose Finding Phase will include a 7-day Run-in-Period of rociletinib monotherapy prior to the initiation of combination treatment. Patients will receive daily oral BID doses of rociletinib at the Dosing Cohort-defined dose level (Section 3.2.2). Patients who experience an AE that requires a reduction or more than 48-hour delay in dose of rociletinib during the Run-in-Period will not go on to receive the combination of rociletinib and MPDL3280A, but will remain on study to receive rociletinib monotherapy; an additional patient will be enrolled as a replacement for inclusion in the same Dosing Cohort.

For the Dose Finding Phase, Cycle 1 will begin with the initiation of combination treatment following a successful completion of the Run-in-Period and will be used for the determination of DLTs. Patients will continue to receive daily oral BID doses of rociletinib (at the Dosing Cohort-defined dose level) and IV doses of MPDL3280A on Day 1 of each cycle, in consecutive 21-day cycles. Thereafter, treatment and monitoring of patients will be conducted in 21-day treatment cycles. Patients will be evaluated regularly for safety, PK, efficacy and pharmacodynamics according to the Schedule of Assessments (see Table 1). For further details on the planned assessments and analyses of safety, PK, efficacy and pharmacodynamics, please refer to Sections 8.4.2-8.4.5.

3.2.1 Dose-Limiting Toxicity

Determination of DLTs will be made during the first 21 days of combination treatment with rociletinib and MPDL3280A (ie, during Cycle 1 after the rociletinib Run-in-Period) in the Dose Finding Phase. A DLT is defined as a clinically significant AE or laboratory abnormality assessed as at least related to the study drug (rociletinib and/or MPDL3280A), unrelated to disease progression, and that meets any of the following criteria:

Cytopenia:

- Grade 4 neutropenia persisting for more than 7 days;
- Febrile neutropenia, defined as an absolute neutrophil count (ANC) < 1000/mm^3 and a single temperature of > 38.3ºC (101ºF);
- Grade 4 thrombocytopenia persisting for more than 7 days or thrombocytopenia with clinically significant bleeding (ie, bleeding that requires blood or platelet transfusion or other medical intervention, or that may cause disability or death, such as cerebral hemorrhage).

Organ Toxicity:

- Grade ≥ 3 symptomatic hepatic toxicities lasting for > 48 hours, or Grade ≥ 3 asymptomatic hepatic toxicities lasting for > 7 days with the following exception:

- For patients with Grade 2 Alkaline phosphatase (ALP) abnormality at baseline, an increase to > 8 × the upper limit of normal (ULN) lasting > 48 hours (if symptomatic) or > 7 days (if asymptomatic) will be considered a DLT.

- Grade ≥ 3 nonhematologic, nonhepatic organ toxicity, with the following exceptions:

  DLT Toxicity Exceptions

  - Grade 3 nausea, vomiting, or diarrhea that resolves to Grade ≤ 1 within 7 days after starting appropriate supportive therapy (see Section 6.2.2);
  - Grade ≥ 3 asymptomatic or mildly symptomatic rash that can be adequately managed with supportive care (see Section 6.2.4) or symptomatic rash that resolves to become asymptomatic and/or Grade ≤ 2 within 7 days of appropriate supportive therapy;
  - Grade ≥ 3 fatigue that resolves to Grade ≤ 2 within 7 days;
  - Grade 3 arthralgia that can be adequately managed with supportive care or that resolves to Grade ≤ 2 within 7 days;
  - Grade 3 autoimmune thyroiditis or other endocrine abnormality that can be managed by endocrine therapy and that would not necessitate initiation of systemic corticosteroids;
  - Grade 3 fever (in the absence of any clinically significant source of fever) that resolves to Grade ≤ 2 within 7 days with supportive care;
  - Grade 3 laboratory abnormality that is asymptomatic and deemed by the Investigator to be not clinically significant;
  - Grade ≥ 3 hyperglycemia lasting ≤ 7 days. Grade > 3 hyperglycemia will be considered a DLT only if it lasts for more than 7 days despite optimized anti-hyperglycemic treatment (eg, oral anti-hyperglycemic therapy);
  - Grade ≥ 3 elevation of serum creatine kinase (CK) level that is asymptomatic (ie, not accompanied by signs, symptoms, or other laboratory abnormalities associated with rhabdomyolysis or myocardial injury) that is deemed by the Investigator to be clinically insignificant and that returns to Grade ≤ 2 within 7 days.

3.2.2 Assignment of Dosing Cohorts

Specific doses of rociletinib will be administered in combination with a fixed dose of MPDL3280A. Combination doses of rociletinib with MPDL3280A will be defined for each Dosing Cohort enrolled during the Dose Finding Phase, and currently two potential Dosing Cohorts are planned (see Table 5). The first Dosing Cohort will be 500 mg BID rociletinib and 1200 mg MPDL3280A on Day 1 of each 21-day cycle. At minimum, 3 patients will be enrolled into this cohort. If this combination dose is determined to be safe and tolerable, no further dose modifications for either drug will be made. Based on emerging safety and evaluable PK and/or pharmacodynamics data, the CSC may evaluate additional doses or schedules of rociletinib.

Table 5: Phase 1 Dosing Cohorts

Cohort	Rociletinib Dose	MPDL3280A Dose
1	500 mg PO BID	1200 mg IV every 3 weeks Day 1 of each 21-day cycle
-1	375 mg PO BID	

BID, twice daily; IV, intravenous; PO, oral.

A modified toxicity probability interval (mTPI) method (Appendix H) will be used to guide decisions on assignment of patients to different Dosing Cohorts. Compared with the 3+3 design, the mTPI method reduces the risk of exposing patients to doses above the MTD, which is defined as the acceptable daily oral dose with estimated probability of toxicity closest to 33%. The mTPI design is a model-based approach that has a pre-specified decision matrix that recommends escalating, reducing or maintaining the same dose or stopping dose escalation, based on the number of DLTs observed in the dose level under evaluation. Consequently, patients enrolled into the trial can be allocated to appropriate doses without conducting additional computations.

At each dose level, after the first evaluable 3 patients have completed Cycle 1, the CSC will meet to evaluate the Dosing Cohort data and to make a decision on the next step for Dosing Cohort assignment (increase dose, decrease dose, maintain same dose, or stop), which will be guided by the mTPI decision table (Appendix H). A patient will be deemed evaluable for safety and DLT determination if they have received at least 75% of the planned total dose of each drug within Cycle 1. Patients who receive <75% of the planned total dose of either rociletinib or MPDL3280A for reasons other than study drug-related AEs will not be included in the evaluation of the Dosing Cohort and will be replaced. If the dose is maintained, up to an additional 6 patients may be enrolled at the same dose, and the next safety evaluation will take place after all patients have completed Cycle 1. The CSC may decide to meet at any time to evaluate a Dosing Cohort if a safety signal arises or other data become available to justify re-evaluation of the Dosing Cohort before it is fully enrolled.

The enrollment/evaluation process will continue until at least 6 patients have been treated at any single dose level or enrollment of the maximum sample size of 18 patients for the Phase 1 portion of this study has been achieved.

3.2.3 Recommended Phase 2 Dose

The RP2D will be determined by the CSC based on cumulative data from all Dosing Cohorts in the Dose Finding Phase. A Safety Expansion Cohort of up to 6 patients may be enrolled to further examine the tolerability of a dose combination of interest or the tolerability of the combination dosing without a rociletinib Run-in-Period.

3.3 Dose Expansion Phase (Phase 2)

The Dose Expansion Phase will be conducted in two patient cohorts (see also Figure 1):

Group A: EGFR TKI treatment-naïve and chemotherapy-naïve patients.

Group B: Patients who have progressed after at least 12 weeks of treatment with a prior first- or second-generation EGFR TKI (ie, erlotinib, gefitinib, afatanib), regardless of T790M mutation status.

The Dose Expansion Phase will be used to assess the RP2D of the combination of rociletinib and MPDL3280A for preliminary efficacy and pharmacodynamics effects, in addition to safety and tolerability, in these patient populations. For the Dose Expansion Phase, there will not be a Run-in-Period; rather, treatment will begin with both rociletinib and MPDL3280A on Cycle 1 Day 1 (C1D1). Patients will receive daily oral BID doses of rociletinib (RP2D) and IV doses of MPDL3280A on Day 1 of each cycle, in consecutive 21-day cycles. Patients will be evaluated regularly for safety and efficacy according to the Schedule of Assessments (see Table 1). For further details on the planned assessments and analyses of safety, PK, efficacy and pharmacodynamics, please refer to Sections 8.4.2-8.4.5.

3.4 Study Conduct and Duration of Patient Follow-Up

The study will comprise a Screening Period, and Treatment Period, and a Follow-up Period as outlined in Table 6. Please refer to Section 8 for additional details.

Table 6: Study Schematic (CO-1686-032)

<table>
<tr><td rowspan="3">SCREENING PERIOD</td><td colspan="3">Sign ICF</td></tr>
<tr><td colspan="3">Screening Assessments</td></tr>
<tr><td colspan="3">Up to 28 days before 1st dose of study drug (biopsy within 60 days prior)</td></tr>
<tr><td colspan="4">Enrollment</td></tr>
<tr><td rowspan="5">TREATMENT PERIOD
Oral rociletinib BID + IV MPDL3280A every 21days</td><td rowspan="5">Study assessments every 21 days. Additional ECG and glucose monitoring during Cycle 1 (Day 4, Day 8, and Day 15). Tumor assessments every 2 cycles through Cycle 6 (end of Cycles 2, 4, and 6); every 3 cycles after Cycle 6 (end of Cycles 9, 12, etc.); and at the EOT Visit. The frequency of tumor assessments may be reduced after 2 years with approval of Medical Monitor.</td><td rowspan="4">Cycle 1</td><td>Day 1</td></tr>
<tr><td>Day 4</td></tr>
<tr><td>Day 8</td></tr>
<tr><td>Day15</td></tr>
<tr><td>Cycle 2 +</td><td>Day 1</td></tr>
<tr><td colspan="4">↓</td></tr>
<tr><td></td><td>Disease Progression

(Optional post-progression tumor biopsy)</td><td colspan="2">Rociletinib and/or MPDL3280A treatment post-progression (Sponsor approval) with continued assessments per protocol</td></tr>
<tr><td colspan="4">↓</td></tr>
<tr><td rowspan="6">END OF STUDY PERIOD</td><td colspan="3">Treatment discontinuation</td></tr>
<tr><td colspan="3">Follow-up Safety Assessment</td></tr>
<tr><td colspan="3">28 days after last dose of study drug (rociletinib or MPDL3280A)</td></tr>
<tr><td colspan="3">PK/ATA blood samples 120 days after last dose of MPDL3280A (see Table 2)</td></tr>
<tr><td colspan="3">Follow-up for subsequent anticancer therapies and survival</td></tr>
<tr><td colspan="3">Every 12 weeks</td></tr>
</table>

ATA, anti-therapeutic antibody; BID, twice-daily; ICF, informed consent form; IV, intravenous; PK, pharmacokinetics

4 STUDY POPULATION

4.1 Number of Patients and Sites

The total enrollment planned for this study is approximately 93 patients (18 patients in Phase 1, and up to 75 patients in Phase 2). There will be approximately 14 investigative sites in the United States (US), France, and Spain.

4.2 Inclusion Criteria

All patients must meet all of the following inclusion criteria:

1. Signed and dated informed consent, approved by the Independent Ethics Committee (IEC) or Institutional Review Board (IRB), obtained prior to the performance of any study-specific procedures or assessments and ability to understand and comply with protocol requirements and instructions;

Baseline Characteristics

2. Males and females ≥ 18 years of age;
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1;
4. Adequate hematological and biological function, based on the following laboratory values:

- Bone Marrow Function
  - ANC ≥ 1.5×10^9/L;
  - Lymphocyte count ≥ 0.5×10^9/L;
  - Platelets > 100.0×10^9/L (without transfusion within 2 weeks prior to receipt of study drug);
  - Hemoglobin ≥ 9 g/dL (or 5.6 mmol/L) (patients may be transfused and/or receive erythropoietin stimulating agents to meet this criterion per institutional guidelines).
- Hepatic Function
  - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × upper limit of normal (ULN); if liver metastases, ≤ 5 × ULN;
  - Bilirubin ≤ 2.0 × 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
  - Serum creatinine ≤ 1.5 × ULN or creatinine clearance ≥ 50 mL/min.

- Electrolytes
  - Potassium and magnesium within normal range, patients may receive supplements to meet this requirement.
- Coagulation status
  - International normalized ratio (INR) and activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN;
  - This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose.

5. Ability to swallow and retain orally administered study drug;

EGFRm NSCLC Disease Characteristics

6. Histologically or cytologically documented metastatic or unresectable, locally advanced or metastatic NSCLC, with prior histopathological reports showing evidence of one or more activating EGFR mutation (eg, G719X, exon 19 deletion, L858R, L861Q), except for exon 20 insertion;
7. Measurable disease as defined by RECIST v1.1 (Appendix A):
   - Previously irradiated lesions should not be counted as target lesions;
   - Lesions that are intended to be used to collect tissue samples for biopsy should not be counted as target lesions.
8. Biopsy of tumor tissue for central evaluation within 60 days prior to the first day of study treatment (Run-in-Period Day 1 for Phase 1; C1D1 for Phase 2);
9. For Phase 1 and Phase 2 Group B, patients must have progressed after at least 12 weeks of treatment with a 1st or 2nd generation EGFR TKI (eg, erlotinib, gefitinib, afatinib) for advanced or metastatic NSCLC. A minimum of a 3-day washout period is required for previous EGFR TKIs.
   - Previous chemotherapy for NSCLC is allowed for patients enrolled in Phase 1 and Phase 2 Group B.
10. For Phase 2 Group A, patients must be EGFR TKI treatment-naïve and chemotherapy-naïve;
11. Anticipated life expectancy of at least 3 months;

Medical/Surgical History

12. A minimum of 14 days must have elapsed since any palliative radiotherapy;
13. A minimum of 14 days must have elapsed from last invasive surgery, and wound healing has occurred;
14. Any ongoing potentially reversible treatment-related toxicities must be resolved to Grade ≤ 1 EXCEPT alopecia or (with agreement from the Medical Monitor) the expected EGFR TKI toxicities of rash or diarrhea that are stable with intervention;
15. No planned major surgery while on study;

Concomitant Medications or Procedures

16. Women of childbearing potential must have a negative serum pregnancy test within 7 days prior to the first dose of study treatment and agree to use highly effective contraception as defined in the full protocol, during the study and for 90 days following the last dose of MPDL3280A or rociletinib;
17. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception as described in the full protocol for at least 14 days prior to administration of the first dose of study treatment, during the study, and for 90 days following the last dose of MPDL3280A or rociletinib.

4.3 Exclusion Criteria

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

EGFRm NSCLC Disease Characteristics

1. Documented evidence of an exon 20 insertion mutation in the EGFR gene;
2. Symptomatic, untreated or unstable central nervous system or leptomeningeal metastases. (Patients with treated and stable brain metastases [confirmed by 2 scans at least 4 weeks apart], with no evidence of cavitation or hemorrhage in the brain lesion are eligible provided that they are asymptomatic and do not require corticosteroids);

Medical/Surgical History

3. Previous treatment with rociletinib or MPDL3280A, or other 3rd generation EGFR TKI (eg, AZD-9291, HM61713), or PD-1 axis-targeted therapy (eg, anti-PD-1 or anti-PD-L1);
4. Prior treatment with CD137 agonists or other immune checkpoint blockade therapies, including anti-CTLA-4 therapeutic antibodies;
5. Uncontrolled pleural effusion, pericardial effusion or ascites requiring recurrent drainage procedures (once monthly or more frequently);
6. Uncontrolled hypercalcemia (> 1.5 mmol/L ionized calcium or Ca > 12 mg/dL or corrected calcium > ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab:
    - Patients who are receiving bisphosphonate therapy or denosumab specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemina are eligible;
    - Patients who are receiving denosumab prior to enrollment must be willing and eligible to receive a bisphosphonate instead while on study.
7. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric humanized antibodies or fusion proteins;
8. Known hypersensitivity to Chinese hamster ovary cell products or any component of the MPDL3280A or rociletinib formulations;

9. History of prior allogeneic hematopoietic stem cell transplantation or prior solid organ transplantation;
10. History of autoimmune disease (*please review* Appendix E):
    - Patients with a history of Type 1 diabetes on a stable anti-hyperglycemic regimen; autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone; vitiligo; or alopecia are eligible for this study.
11. Positive test for human immunodeficiency virus (HIV);
12. Patients with active hepatitis B virus (HBV) (defined by a positive hepatitis B surface antigen [HBsAg] test at screening):
    - Patients with past or resolved HBV infection (defined by a negative HBsAg test and a positive anti-hepatitis B core antigen [anti-HBc] antibody test) are eligible. HBV DNA must be obtained in these patients prior to first day of study treatment.
13. Patients with active hepatitis C virus (HCV):
    - Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA.
14. Active tuberculosis;
15. Signs or symptoms of infection within 2 weeks prior to first day of study treatment;
16. Received therapeutic oral or IV antibiotics within 2 weeks prior to first day of study treatment:
    - Patients receiving prophylactic antibiotics (eg, to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible.
17. Administration of a live, attenuated vaccine within 4 weeks before first day of study treatment or anticipation that such a live attenuated vaccine will be required during the study:
    - Influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live, attenuated influenza vaccine (eg, FluMist®) within 4 weeks prior to first day of study treatment or at any time during the study.
18. Class II to IV heart failure as defined by the New York Heart Association functional classification system (Appendix G):
    - Patients with a known left ventricular ejection fraction (LVEF) < 40% will be excluded;
    - Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF < 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate, to be eligible.
19. Patients who have experienced untreated and/or uncontrolled cardiovascular conditions and/or have symptomatic cardiac dysfunction (unstable angina, congestive heart failure,

myocardial infarction within the previous 3 months; coronary angioplasty, or stenting or bypass grafting within the past 6 months; cardiac ventricular arrhythmias requiring medication; any history of 2nd or 3rd degree atrioventricular conduction defects);

20. Any of the following cardiac abnormalities or history:
    - Clinically significant abnormal 12-lead ECG or QT interval corrected using Fridericia's method (QT_CF) > 450 ms;
    - Inability to measure QT interval on ECG;
    - Personal or family history of long QT syndrome;
    - Implantable pacemaker or implantable cardioverter defibrillator;
    - Resting bradycardia < 55 beats/min.
21. History of idiopathic pulmonary fibrosis, organizing pneumonia (eg, bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computerized tomography (CT) scan:
    - History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
22. Females who are pregnant or breastfeeding;
23. Presence of active gastrointestinal (GI) disease (including GI bleeding or ulceration) or other condition that could affect GI absorption (eg, malabsorption syndrome, history of biliary tract disease);
24. Uncontrolled medical, psychological, familial, sociological, or geographical conditions that interfere with the patient's safety, ability to provide informed consent, or ability to comply with the protocol;
25. Malignancies other than NSCLC within 5 years prior to enrollment, with the exception of those with a negligible risk of metastasis or death (such as adequately treated carcinoma *in situ* of the cervix, basal or squamous cell skin cancer, localized prostate cancer, or ductal carcinoma *in situ*);

Previous and Concomitant Medications

26. Patients who are currently receiving treatment with any medications that have the potential to prolong the QT interval if that treatment cannot be either discontinued or switched to a different medication prior to first day of study treatment. The wash out period for the medication should be at least 5 times the medication's half-life (see http://crediblemeds.org/ for a list of QT-prolonging medications);
27. Treatment with systemic immunostimulatory agents (including but not limited to interferon [IFN], interleukin [IL]-2) within 6 weeks or five half-lives of the drug, whichever is shorter, prior to first day of study treatment;

28. Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and antitumor necrosis factor [anti-TNF] agents) within 2 weeks prior to first day of study treatment:
    - The use of inhaled corticosteroids and mineralocorticoids (eg, fludrocortisone) is allowed.

4.4 Patients or Partners of Patients of Reproductive Potential

Pregnancy is an exclusion criterion and females 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 within 7 days prior to administration of the first dose of either study drug. If the serum pregnancy results are not available on first day of study treatment (Day of Run-in-Period for Phase 1; C1D1 for Phase 2), a urine pregnancy test can be performed on the first day of study treatment 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 (EOT) Visit.

Women of childbearing potential must practice double-barrier methods of contraception during treatment and for 90 days after the last dose of either study drug. Adequate contraception is defined as double-barrier protection (ie, condom plus spermicide in combination with a diaphragm, cervical/vault cap, or intrauterine device). Birth control pills, birth control patches and/or injections of hormones to prevent pregnancy are not considered an adequate method of preventing pregnancy.

Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to double-barrier methods of contraception during treatment and for 21 days after the last dose of either study drug to allow for clearance of any altered sperm.

Patients will be instructed to notify the Investigator if pregnancy of a female patient or a partner of a male patient is discovered to have occurred either during the patient's treatment or within 90 days (female patients) or 21 days (partners of male patients) after completion of treatment with rociletinib and MPDL3280A.

4.5 Waivers of Inclusion/Exclusion Criteria

No waivers of protocol-specified inclusion or exclusion criteria will be granted by the Investigator, the Sponsor, or its designee for any patient enrolling into the study.

5 DESCRIPTIONS OF STUDY TREATMENT AND DOSE MODIFICATIONS

5.1 Description of Rociletinib

Rociletinib is provided as yellow, film-coated tablets for PO 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: 125 mg strength is a round tablet and 250 mg strength tablet is an oval tablet. Each tablet consists of rociletinib 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. 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 (59-86°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.

5.2 Description of MPDL3280A

The MPDL3280A drug product is provided in a single-use, 20-cc USP/Ph. Eur. Type 1 glass vial as a colorless-to-slightly yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20 mL (1200 mg) of MPDL3280A solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume. The MPDL3280A drug product is formulated as 60 mg/mL MPDL3280A in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8.

MPDL3280A must be refrigerated at 2°C-8°C (36°F-46°F) upon receipt until use. MPDL3280A vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in the MPDL3280A drug product; therefore, each vial is intended for single use only. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

For further details, see the MPDL3280A IB.

5.3 Preparation and Administration of Study Treatment

Rociletinib is available as 125 or 250 mg tablets. Patients will self-administer oral rociletinib BID at the cohort-assigned dose throughout the treatment period, unless dose reduction is required for adverse event management. Patients should take rociletinib as directed by the treating physician. Patients will be instructed to take each dose of rociletinib with 8 oz. (240 mL) of water and with a meal or within 30 minutes after a meal. (During the PK visit on C1D8 [Phase 1 only], patients will be more specifically guided to take the morning dose of rociletinib within 30 minutes after the start of the meal.) Tablets should be swallowed whole. Missed doses

(ie, patient does not take dose within 6 hours of the scheduled time) or vomited doses will not be made up, and the patient should resume rociletinib dosing with the next scheduled dose.

The Investigator or designee will be responsible for distributing the appropriate strength(s) of PO 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 on a patient diary, and will be instructed to bring their rociletinib tablets and diary to the next scheduled visit for reconciliation by site personnel.

On PK sampling days, patients will be instructed to not administer study drug at home, but to bring rociletinib and their dosing diaries to the clinic along with breakfast. Patients will be instructed when to take their doses of rociletinib in the clinic and when to have their meal, in the context of the PK schedule and/or MPDL3280A dose administration for the given visit (see Table 2).

The only dose of MPDL3280A for all patients in this study is a fixed dose of 1200 mg administered by IV infusion on the first day of each protocol-specified 21-day treatment cycle (see Table 1). MPDL3280A will be delivered in infusion bags with IV infusion lines, product-contacting surfaces of polyvinylchloride (PVC) and polyolefin, and 0.2 μm in-line filters (filter membrane of polyethersulfone). No incompatibilities have been observed between MPDL3280A and PVC or polyolefin infusion materials (bags and infusion lines). Administration of MPDL3280A will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

The initial dose of MPDL3280A will be delivered over 60 (± 15) minutes. If the first infusion is tolerated without infusion-associated AEs, the second infusion may be delivered over 30 (± 10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be determined within 60 minutes before the infusion, every 15 [± 5] minutes during the infusion, and 30 (± 10) minutes and 2 hours (± 15 minutes) after completion of the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before the infusion, during the infusion as clinically indicated or if symptoms occurred in the prior infusion, and 1 hour (± 10 minutes) after the infusion.

No premedication will be allowed for the first dose of MPDL3280A. Premedication may be administered for subsequent infusions at the discretion of the treating physician after consultation with the Medical Monitor.

5.4 Blinding/Masking of Treatment

This is an open-label study; the investigational product will not be blinded or masked. All patients enrolled will receive PO rociletinib and IV MPDL3280A.

5.5 Treatment Compliance

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 of rociletinib and the number of tablets to be taken each day. Patients (or legally authorized representative) will be asked to record dosing information for PO rociletinib taken at home in the diary card and to bring the diary card and all unused tablets with them to scheduled clinic visits. Study site personnel will review the dosing information with the patient (or legally authorized representative) on scheduled clinic visit days and complete a compliance check and tablet count. Study site personnel will record compliance information on the eCRF and retain the diary card in the patient's medical record.

5.6 Study Drug Accountability

All investigational medicinal products (IMPs) required for completion of this study (rociletinib, MPDL3280A) will be provided by the Sponsor. Study personnel will maintain accurate records of rociletinib and MPDL3280A shipments/receipts, administration, and drug reconciliation. The investigational site will acknowledge receipt of IMPs, using the IxRS to confirm the shipment condition and content. The study site is responsible for the return or destruction of rociletinib and MPDL3280A as required. A drug management system will manage rociletinib and MPDL3280A inventory at all sites. The system will be required to manage study treatment requests and shipments.

Any rociletinib and/or MPDL3280A accidentally or deliberately destroyed must be accounted for. All bottles or vials must be accounted for before their destruction at the study center. Unused bottles or vials 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 and vials shipped, destroyed, and returned must be reconciled.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

5.7 Dose Modification Guidelines

5.7.1 Study Treatment Dose Reductions

5.7.1.1 Rociletinib Dose Reductions

From a starting dose of 500 mg BID rociletinib, up to two dose reductions are available (Table 7). No dose reduction below 250 mg is permitted. All dose reductions are permanent.

Table 7: Dose Reductions for Rociletinib

Current Dosage	Dose Reduction
500 mg PO BID	375 mg PO BID
375 mg PO BID	250 mg PO BID
250 mg PO BID	No further dose reduction allowed

BID, twice daily; PO, oral.

5.7.1.2 MPDL3280A Dose Reductions

The only dose of MPDL3280A available on this study is 1200 mg. Dose reductions are not permitted.

5.7.2 Phase 1 – Run-in-Period

Rociletinib monotherapy will be administered orally BID during the 7-day Run-in-Period. Dose reductions of rociletinib during the Run-in-Period are not allowed for reasons other than a DLT. Dose delays of rociletinib for up to 48 hours for toxicity management is allowed. Any patient who experiences an AE(s) that requires either a delay of treatment for more than a total of 48 hours or a dose reduction during the 7-day Run-in Period of rociletinib monotherapy will not be eligible for combination therapy. Such a patient will only receive monotherapy rociletinib for the duration of participation in the study.

5.7.3 Phase 1 – Cycle 1

The first dose of MPDL3280A at 1200 mg will be administered by IV on C1D1. Dose reductions of rociletinib are not allowed for reasons other than a DLT or a decision by the CSC based on emerging safety data. Dose delays of rociletinib are not allowed for reasons other than toxicity. Patients are eligible for safety and DLT evaluation of the cohort if they receive at least 75% of the planned total dose of each study drug within Cycle 1 or they experience a DLT at any time during Cycle 1.

5.7.4 Beyond DLT Assessment (Phase 1 – Cycle 2+ and Phase 2 – All Cycles)

For patients who experience a toxicity that is equivalent to a DLT – If the toxicity is assessed as being related to rociletinib, the next dose of rociletinib should be held until resolution of the toxicity to Grade 1 or to the baseline level (if severity > Grade 1 at baseline) and then reduced to the next dose level of rociletinib (Table 7), unless permanent discontinuation of rociletinib is required per toxicity management guidelines of the protocol (Sections 6.1 and 6.3). If the toxicity is assessed as being related to MPDL3280A, the next dose of MPDL3280A should be held until the toxicity has resolved to Grade 1 or to the baseline level (if severity > Grade 1 at baseline), unless permanent discontinuation of MPDL3280A is required per toxicity management guidelines of the protocol (Sections 6.2 and 6.3). In addition, because there is no available antidote for MPDL3280A and discontinuation of MPDL3280A may not have immediate therapeutic effect, consideration may be given to holding rociletinib doses temporarily even if the toxicity is not attributed to rociletinib.

Dose holds for toxicity or for reasons unrelated to toxicity (eg, elective surgery or intercurrent illness) are allowed for up to 14 days for rociletinib and for up to 42 days (2 cycles) for MPDL3280A. Permission for a longer dose hold must be granted by the Sponsor's Medical Monitor; in the absence of such permission, the patient should permanently discontinue all study treatment (Section 11.1).

Intra-Subject Dose Escalation: For patients in the Dose Finding Phase (Phase 1) who have completed 2 cycles of therapy at their original assigned dose with no DLTs, intra-subject dose escalation to a higher dose level of rociletinib (if applicable) may be permitted with approval from the Sponsor's Medical Monitor after consideration of cumulative safety data and provided that the dose level to which the patient will escalate has already been evaluated and has a DLT rate < 33%. Intra-subject dose escalation will begin at the start of a dosing cycle at the Investigator's discretion and requires prior approval by the Sponsor's Medical Monitor. For patients in the Dose Expansion Phase (Phase 2), no intra-subject dose escalation is allowed.

In cases where a patient must discontinue rociletinib or MPDL3280A for toxicity, monotherapy with the other agent may be continued until the patient meets any of the criteria for permanent treatment discontinuation (see Section 11).

A summary of dose modification allowances is shown in Table 8.

Table 8: Phase 1 and Phase 2 Dose Modification

	Dose Finding Phase (Phase 1)			Phase 1 and Phase 2	
	Run-In	Cycle 1		Cycle 2+	
	Rociletinib	Rociletinib	MPDL3280A	Rociletinib	MPDL3280A
Dose Reduction [a]	Not allowed unless due to DLT [b]	Not allowed unless due to DLT or CSC decision	Not allowed	Allowed for toxicity (see Table 7 for dose reductions)	Not allowed
Dose Hold	Allowed up to 48 hours for toxicity management [b]	Allowed for toxicity; must receive >75% doses to be evaluable for DLT	Not allowed	Allowed up to 14 days [c] for toxicity or reasons unrelated to toxicity	Allowed up to 42 days [c] for toxicity or reasons unrelated to toxicity

CSC, Clinical Safety Committee; DLT, dose-limiting toxicity.

[a] Dose reductions are permanent.

[b] If dose reduction or more than 48-hour delay of rociletinib dosing is required in Run-in-Period, patient will not be eligible for combination therapy but rather will continue rociletinib monotherapy.

[c] If a longer hold is needed for slowly resolving toxicity, Sponsor approval is required. If either study drug must be discontinued for toxicity, monotherapy with the other study drug may be continued.

5.8 Treatment of Study Drug Overdose

There are no known antidotes for overdoses of rociletinib or MPDL3280A. In the event of an overdose of MPDL3280A, discontinuation of MPDL3280A may not have immediate therapeutic effect. In the event of a known or suspected overdose, the patient should be monitored with appropriate hematology and clinical chemistry and should receive supportive therapy, as necessary. Please also refer to Section 6 for guidelines on the management of potential study drug-related toxicities.

Decisions regarding dose interruptions or modifications for rociletinib and/or MPDL3280A dosing in the case of a suspected overdose will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the patient.

A plasma sample for PK analysis may be requested by the Medical Monitor on a case-by-case basis. This plasma sample should be collected as soon as possible, but within 10 days from the date of the last dose of on-study dosing.

Information regarding the quantity of the excess dose as well as the duration of the overdosing should be documented in the appropriate eCRF.

6 MONITORING AND MANAGEMENT OF EXPECTED OR POTENTIAL TREATMENT-RELATED TOXICITY

In general, toxicities should be managed with supportive care and with dose modifications for each of the study drugs (Section 5.7) according to attribution of the toxicity. Certain toxicities may be more likely to occur with rociletinib or MPDL3280A, and some toxicities may be overlapping. This section provides guidance on the monitoring and management of expected or potential toxicities associated with rociletinib or MPDL3280A or both rociletinib and MPDL3280A.

6.1 Rociletinib Expected or Potential Toxicities

6.1.1 Management of Prolonged QTc

Electrocardiograms will be performed throughout the study as described (see Table 1 and Section 8.4.2.4). Readings for QTc prolongation will be based on the average for the triplicate 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 rociletinib treatment, using supplementation if necessary.

Guidelines for dose modification and stopping criteria due to QTc prolongation are provided in Table 9.

Table 9: Withholding and Stopping Criteria for QTc-Prolongation

QTc-Prolongation[a]	Action and Dose Modification
QTcF ≥ 501 msec on at least two separate ECGs[a] (Grade 3)	• Interrupt study treatment until QTcF prolongation resolves to Grade 1 (QTcF > 450-480 msec) or baseline; • Test serum potassium, calcium, phosphorus and magnesium. If abnormal, correct per routine clinical practice to within normal limits; • Review concomitant medication usage for a prolonged QTc; • Restart at a reduced dose level[b]; • **If Grade 3 QTc prolongation recurs after 2 dose reductions, permanently discontinue study treatment[b];** • **If Grade 4 QTc prolongation** (QTcF ≥ 501 or 60 msec increase from baseline and polymorphic ventricular tachycardia or serious arrythmia) **occurs, permanently discontinue study treatment[b]**

msec, milliseconds; QTcF, QT interval on electrocardiogram corrected using Fridericia's formula (see Appendix D)
[a] Based on average QTc value of triplicate ECGs.
[b] If the QTc prolongation resolves to Grade 1 or baseline, the patient may resume study treatment if the Investigator and Medical Monitor agree that the patient will benefit from further treatment.

6.1.2 Management of Hyperglycemia

Rociletinib causes hyperglycemia in some people. 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 order to minimize the risk of symptomatic hyperglycemia. Because later onset of hyperglycemia is also possible with rociletinib treatment, regular monitoring of glucose and of symptoms of hyperglycemia will be required through the end of rociletinib treatment.

Fasting blood glucose (FBG) will be measured by local laboratories for the following visits: Screening/Baseline visit, Day 1 of the Run-in-Period (Phase 1 only), C1D1, C1D4, C1D8, C1D15, Day 1 of each cycle beginning with Cycle 2, and at the EOT Visit (Table 1). Investigators should use discretion on an individual-patient basis to determine the need for more frequent monitoring.

Diabetes and glucose intolerance are not contraindications to the use of rociletinib. Patients with pre-existing diabetes may require more frequent glucose monitoring and/or adjustments of diabetic medication. In addition to the scheduled local laboratory tests for FBG (see Table 1), patients with pre-existing diabetes should perform home monitoring at least once weekly (if not more frequently).

For patients who are not already monitoring their glucose levels, sites are strongly encouraged to implement ***patient home monitoring of fasting urine glucose for Cycle 1 and Cycle 2***. If preferred, home monitoring of blood glucose is also acceptable. Patients should be educated to contact the site if they have any positive urine glucose test or a home blood glucose reading of > 160 mg/dL (> 8.9 mmol/L) and any time they experience symptoms that have correlated with rociletinib-induced hyperglycemia, including increases in nausea, vomiting, anorexia, diarrhea, and/or fatigue. Symptoms more commonly associated with diabetes, such as polydipsia, polyuria, and polyphagia, rarely occur with rociletinib-induced hyperglycemia. Upon reports of positive home tests and/or symptoms suggesting hyperglycemia, local laboratory FBG tests should be performed.

Guidelines for management of hyperglycemia, based on the results of laboratory FBG values and patient symptoms, are presented in Table 10. Sites are encouraged to follow these guidelines, although management of individual patients may be influenced by local practices and the treating physician's judgment.

Table 10: Management Guidelines for Hyperglycemia

FBG Result	Antihyperglycemic Intervention[a]	Rociletinib Dose Modification
Grade 2 (> 160 to 250 mg/dL; > 8.9 to 13.9 mmol/L)	• If asymptomatic,[b] repeat test within 1 week; if results in this range at least twice in 1 week, start antihyperglycemic[c] and continue home monitoring; • If symptomatic,[b] start antihyperglycemic and continue home monitoring.	• Rociletinib may continue without interruption or dose reduction
Grade 3 **(> 250 to 500 mg/dL;** > 13.9 to 27.8 mmol/L)	• Start antihyperglycemic and continue home monitoring.	• If asymptomatic,[b] rociletinib may continue without interruption or dose reduction; • If symptomatic,[b] interrupt rociletinib until resolution/improvement in symptoms and FBG < 250 mg/dL (< 13.9 mmol/L)[c].
Grade 4 (> 500 mg/dL; > 27.8 mmol/L)	• Start antihyperglycemic and continue home monitoring. • Consider adding a second antihyperglycemic agent.[d]	• Interrupt rociletinib dosing until resolution/improvement in symptoms and FBG < 250 mg/dL (< 13.9 mmol/L).[c] •

FBG, fasting blood glucose

[a] Oral antihyperglycemic agent (eg, metformin), which may need to be maintained for duration of rociletinib treatment. Use of insulin or agents which increase insulin production (eg, sulphonyl ureas) is generally not recommended because the mechanism of rociletinib-induced hyperglycemia is not due to a deficit in insulin production.

[b] Increased nausea, vomiting, anorexia, diarrhea, and fatigue have been most common symptoms of hyperglycemia.

[c] Per Investigator discretion, rociletinib may be restarted at the same dose. A reduced dose may also be considered if glucose levels prove difficult to control.

[d] Additional antihyperglycemia agents such as SGLT2 inhibitors (eg, dapagliflozin) or pioglitazone, which increase glucose uptake or increase glucose excretion, may be added to metformin.

6.2 MPDL3280A Expected or Potential Toxicities

Any toxicities associated or possibly associated with MPDL3280A treatment should be managed according to standard medical practice. No reduction of the MPDL3280A dose will be allowed (Section 5.7.1.2). Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology of a toxicity.

Most immune-related adverse events (irAEs) observed with immunomodulatory agents have been mild and self-limiting; however, such events should be recognized early and treated promptly to avoid potential major complications. The primary approach to managing Grade 1-2 irAEs is supportive and symptomatic care. In the case of recurrent Grade 2 events or in severe cases, immune-related toxicities may be acutely managed with topical corticosteroids, systemic corticosteroids, or tumor necrosis factor alpha (TNF-α) inhibitors, as well as delay or permanent discontinuation of MPDL3280A.

There is no available antidote for MPDL3280A, and as a result, discontinuation of MPDL3280A may not have immediate therapeutic effect. In severe cases, immune-related toxicities may be acutely managed with topical corticosteroids, systemic corticosteroids, or TNF-α inhibitors. In addition, consideration may be given to holding rociletinib doses temporarily even if the toxicity is not attributed to rociletinib.

Management of possible infusion reactions, gastrointestinal toxicity (including colitis), hepatotoxicity (including hepatitis and elevated transaminases), dermatologic toxicity, hypothyroidism, pulmonary toxicity, pericardial and pleural effusions, pancreatic toxicity, and ocular toxicity are presented in the following sections. See also Appendix F for precautions for anaphylaxis.

6.2.1 Management of Infusion Reactions

The management of infusion-related reactions will be according to severity as follows:

Table 11: Management Guidelines for Infusion-Related Reactions during Cycle 1

Description	Management
Grade 1 (mild)	• Reduce infusion rate to half the rate being given at the time of event onset; • Once the event has resolved, the Investigator should wait for 30 minutes while delivering the infusion at the reduced rate; • If tolerated, the infusion rate may then be increased to the original rate.
Grade 2 (moderate) OR Flushing, fever, throat pain	• Interrupt MPDL3280A infusion; • Administer aggressive symptomatic treatment; • Restart only after the symptoms have adequately resolved to baseline grade; • The infusion rate at restart should be half of the infusion rate that was in progress at the time of the onset of the infusion-related reaction.
Grade 3 or 4 (severe or life-threatening [see Appendix F])	• Interrupt infusion; • Initiate aggressive resuscitation and supportive measures; • Do not re-administer MPDL3280A; • Manage patient as clinically indicated until the event resolves.

6.2.2 Management of Gastrointestinal Toxicity

Immune-mediated colitis has been associated with the administration of MPDL3280A. Treatment guideline is summarized in Table 12.

Table 12: Management Guidelines for Gastrointestinal Toxicity (Diarrhea)

Description	Management
Grade 2 (4-6 stools/day over baseline) < 5 days	• Hold MPDL3280A and discontinue NSAIDS (or other medication known to exacerbate colitis). • Investigate for etiology. • Restart MPDL3280A once at baseline stool frequency.
Grade 2 (4-6 stools/day over baseline) > 5 days	• Hold MPDL3280A and discontinue NSAIDS (or other medication known to exacerbate colitis) while etiology is being investigated. • Consider referral to a gastroenterologist. • Administer anti-diarrheal agent (eg, Imodium). • Consider oral budesonide, mesalamine, or 10 mg oral prednisone equivalent per day. • Restart MPDL3280A once at baseline stool frequency.
Grade ≥ 3 (≥ 7 stools/day over baseline) with peritoneal signs, ileus, or fever OR Abdominal pain Blood or mucus in stool	• Hold MPDL3280A and discontinue NSAIDS (or other medication known to exacerbate colitis). • Rule out bowel perforation. • Consider administering prednisone 60 mg/day or equivalent (oral budesonide or methylprednisolone IV). • Taper steroids over 1 month. • Restart MPDL3280A if diarrhea is resolved as confirmed by sigmoidoscopy or colonoscopy and systemic steroid dose is ≤ 10mg oral prednisone equivalent per day • Permanently discontinue MPDL3280A for life-threatening immune-related diarrhea or colitis.

IV, intravenous; NSAID, nonsteroidal anti-inflammatory drugs; TNF, tumor necrosis factor.

If the event is of significant duration or magnitude or is associated with signs of systemic inflammation or acute phase reactants (eg, increased C-reactive protein or platelet count or bandemia), it is recommended to do the following:

- Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates for confirmation of the diagnosis of colitis. If possible, one or two biopsy specimens should be snap frozen and stored.
- Perform laboratory tests to rule out alternate etiology (ie, white blood cells [WBCs] and stool calprotectin).

6.2.3 Management of Hepatotoxicity

Immune-mediated hepatitis has been associated with the administration of MPDL3280A. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminase, and liver function will be monitored throughout study treatment.

While on this study, patients presenting with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have LFTs performed immediately and reviewed before administration of the next dose of study drug.

If LFTs increase, neoplastic, concurrent medications, viral hepatitis, and toxic etiologies should be considered and addressed, as appropriate. Imaging of the liver, gall bladder and biliary tree should be performed to rule out neoplastic or other causes for increased LFTs. Anti-nuclear antibody, perinuclear anti-neutrophil cytoplasmic antibody, anti-liver kidney microsomal antibodies, and anti-smooth muscle antibody tests should be performed if an autoimmune etiology is considered.

Patients with LFT abnormalities should be managed according to Table 13.

Table 13: Management Guidelines for Hepatotoxicity (LFT Abnormalities)

Description	Management
AST/ALT (> ULN to 3 × ULN) with total bilirubin < 2 × ULN	• Continue with the standard monitoring plan (ie, LFTs every 3 weeks before dosing).
AST/ALT (> 3 × ULN to < 10 × ULN) with total bilirubin < 2 × ULN	• Continue MPDL3280A. Monitor LFTs at least weekly. Consider referral to a hepatologist.
AST/ALT > 10 × ULN	• Hold MPDL3280A; • Consider administering IV steroids for 24-48 hours (prednisone 60 mg/day equivalent) followed by oral prednisone (or equivalent) taper over 2-4 weeks; • If LFT results do not decrease within 48 hours after initiation of systemic steroids, addition of an alternative immunosuppressive agent (eg, mycophenolate or TNF-α antagonist) to the corticosteroid regimen may be considered; • Monitor LFTs every 48-72 hours until decreasing and then follow weekly; • Restart MPDL3280A after discussion with the Medical Monitor if AST/ALT ≤ 3 × ULN with bilirubin < 2 × ULN and steroid dose is ≤ 10 mg oral prednisone equivalent per day; • Permanently discontinue MPDL3280A for life-threatening immune-related hepatic events.

Table 13: Management Guidelines for Hepatotoxicity (continued)

AST/ALT ≥ 3 × ULN with bilirubin > 2 × ULN	• Hold MPDL3280A; • Consult hepatologist; • Consider administering IV steroids for 24-48 hours (prednisone 60 mg/day equivalent) followed by oral taper over 1 month; • If LFT results do not decrease within 48 hours after initiation of systemic steroids, addition of an alternative immunosuppressive agent (eg, mycophenolate or TNF-α antagonist) to the corticosteroid regimen may be considered; • Monitor LFTs every 48-72 hours until decreasing and weekly after; • Restart MPDL3280A after discussion with the Medical Monitor if AST/ALT ≤ 3 × ULN with bilirubin < 2 × ULN and steroid dose is ≤ 10mg oral prednisone equivalent per day.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; IV, intravenous; LFT, liver function test; TNFα, tumor necrosis factor alpha; ULN, upper limit of normal.

6.2.4 Management of Dermatologic Toxicity

Treatment-emergent rash (eg, maculopapular or purpura) has been associated with MPDL3280A. The majority of cases of rash were mild in severity and self-limited, with or without pruritus.

A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Dermatologic toxicity and rash should be managed according to Table 14.

Table 14: Management Guidelines for Rash

Description	Management
Grade 1 mild < 10% BSA	• Continue MPDL3280A. Symptomatic therapy with antihistamine PRN; • Consider topical steroids and/or other symptomatic therapy (eg, antihistamines).
Grade 2 moderate 10%-30% BSA	• Continue MPDL3280A; • Consider dermatologist referral; • Administer topical steroids; • Consider higher potency topical steroids if rash unresolved.
Grade 3 severe > 30% BSA	• Hold MPDL3280A; • Consult dermatologist; • Administer oral prednisone 10 mg or equivalent. If rash unresolved after 48-72 hours, administer oral prednisone 60 mg or equivalent; • Restart MPDL3280A if rash resolved and systemic dose is ≤ 10 mg oral prednisone equivalent per day; • Permanently discontinue MPDL3280A for life-threatening immune-related dermatologic toxicity.

BSA, body surface area; PRN, as needed.

6.2.5 Management of Endocrine Toxicity (Hypothyroidism)

Hypothyroidism has been associated with the administration of MPDL3280A.

Patients with unexplained symptoms such as fatigue, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies, as well as for hyponatremia or hyperkalemia. An endocrinologist should be consulted if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free T4 levels should be obtained to determine whether thyroid abnormalities are present. TSH, prolactin, and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency.

Hypothyroidism should be managed according to Table 15.

Table 15: Management Guidelines for Hypothyroidism

Description	Management
TSH elevated, asymptomatic	• Continue MPDL3280A; • Start thyroid replacement hormone (as per institutional guidelines); • Monitor TSH weekly.
TSH elevated, symptomatic	• Hold MPDL3280A; • Consider referral to an endocrinologist; • Start thyroid replacement hormone (as per institutional guidelines); • Monitor TSH weekly; • Restart MPDL3280A when symptoms are controlled by thyroid replacement and TSH levels are decreasing.

TSH, thyroid-stimulating hormone.

6.2.6 Management of Pericardial and Pleural Effusions

Pericardial involvement with associated effusions is common in patients with NSCLC and have the theoretical potential to be exacerbated by inflammation associated with antitumor immunity following PD-L1 blockade. Patients presenting with dyspnea, chest pain, or unexplained tachycardia should be evaluated for the presence of a pericardial effusion. Patients with preexisting pericardial effusion should be followed closely for pericardial fluid volume measurements and impact on cardiac function. When intervention is required for pericardial effusions, appropriate workup includes cytology, lactate dehydrogenase (LDH), glucose, cholesterol, and cell count. For patients with a pericardial effusion causing end-diastolic right ventricular collapse, treatment may be restarted following the placement of a pericardial window, demonstration of hemodynamic stability, and resolution of right ventricular dysfunction.

6.2.7 Management of Potential Pancreatic Toxicity

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of other immunomodulatory agents.

The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for obstruction, as well as serum amylase and lipase tests.

Pancreatic toxicity should be managed according to Table 16.

Table 16: Management Guidelines for Amylase/Lipase Abnormalities

Description	Management
Amylase/lipase (> ULN and ≤ 2 × ULN) and asymptomatic	• Continue MPDL3280A; • Monitor amylase/lipase levels prior to dosing.
Amylase/lipase (> 2 × ULN to ≤ 5 × ULN) and asymptomatic	• Continue MPDL3280A; • Monitor amylase/lipase weekly; • Consider oral prednisone 10 mg daily or equivalent for prolonged elevation (eg, more than 3 weeks).
Amylase/lipase (> 5 × ULN) and asymptomatic	• Hold MPDL3280A; • Monitor amylase/lipase every other day and consider oral prednisone 60 mg daily or equivalent; • Consult a gastroenterologist; • Resume MPDL3280A dosing when lipase/amylase levels are less than 2 × ULN.
Autoimmune pancreatitis (abdominal pain and raised amylase/lipase levels)	• Hold MPDL3280A; • Consult a gastroenterologist; • Consider administering IV steroids (prednisone equivalent of 60 mg/day) followed by taper over 2-4 weeks; • Resume MPDL3280A when enzyme levels are less than 2 × ULN and patient is asymptomatic; • Permanently discontinue MPDL3280A for life threatening immune related pancreatitis.

IV, intravenous; ULN, upper limit of normal.

6.2.8 Management of Potential Ocular Toxicity

An ophthalmologist should evaluate visual complaints. Uveitis or episcleritis may be treated with topical corticosteroid eye drops. MPDL3280A should be permanently discontinued for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

Ocular toxicity should be managed according to Table 17.

Table 17: Management Guidelines for Ocular Toxicities

Description	Management
Symptomatic: autoimmune uveitis, iritis, or episcleritis	• Hold MPDL3280A; • Consult ophthalmologist and start topical corticosteroid eye drops; • MPDL3280A may be restarted following resolution of the events and discussions with the Medical Monitor; • Permanently discontinue MPDL3280A for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

6.3 Overlapping Expected or Potential Toxicities

Guidelines for the management of specific expected or potential overlapping toxicities for rociletinib and MPDL3280A are described in Table 18.

Table 18: Management of Overlapping Toxicities

Toxicity	Attribution to both agents
Rash/Skin Toxicity:	**Grade 2**: continue both agents; initiate supportive care. **Grade 3**: ▪ Obtain dermatology consult; ▪ Hold rociletinib and MPDL3280A until resolved to ≤ Grade 1, then reinitiate rociletinib at a dose agreed upon with the Sponsor's Medical Monitor; (dose delays longer than 14 days also require discussion with the Medical Monitor); ▪ Restart MPDL3280A if rash does not occur within 14 days of rociletinib re-initiation; ▪ Hold rociletinib and permanently discontinue MPDL3280A if the patient experiences recurrent Grade ≥ 3 skin toxicity. When rash is Grade 1, restart rociletinib at previous dose. If Grade ≥ 3 rash recurs, rociletinib should be discontinued permanently. **Grade 4**: Permanently discontinue MPDL3280A. Hold rociletinib until rash is Grade 1 and restart at one dose level lower (dose delays longer than 14 days require discussion with the Medical Monitor). If Grade ≥ 3 rash recurs, rociletinib should be discontinued.
Diarrhea:	**Grade 2**: Supportive care unless > 48 to 72 hrs. Then reduce dose of rociletinib and hold MPDL3280A until resolves to < Grade 1. **Grade 3**: Hold rociletinib and MPDL3280A Obtain gastroenterology consult, discontinue NSAIDs or medications known to exacerbate colitis, Initiate steroid treatment. If resolves to < Grade 1, then restart rociletinib at next lower dose. If no recurrent symptoms, within 14 days resume MPDL3280A as long as steroid dose is ≤ 10 mg oral prednisone equivalent per day (dose delays longer than 14 days require discussion with the Medical Monitor). **Grade 4**: MPDL3280A should be permanently discontinued. Hold rociletinib until diarrhea is Grade 1 and restart at one dose level lower. If Grade ≥ 3 diarrhea recurs, rociletinib should be permanently discontinued (dose delays longer than 14 days require discussion with the Medical Monitor).
Nausea/Vomiting:	**Grade1-2:** Continue treatment. Begin maximum supportive care and adequate anti-emetic treatments (see Section 7.6.1 for guidance on avoiding QT-prolonging concomitant medication). **Grade ≥ 3:** ▪ Begin/continue maximum supportive care and adequate combination anti-emetic treatments (see Section 7.6.1 for guidance on avoiding QT-prolonging concomitant medication). Consider gastroenterology consult; ▪ Hold both rociletinib and MPDL3280A until < Grade 1. Restart rociletinib at next lower dose. If no recurrent symptoms, restart MPDL3280A; ▪ If Grade ≥ 3 nausea/vomiting recurs, MPDL3280A should be discontinued.

Table 18: Management of Overlapping Toxicities (continued)

Toxicity	Attribution to both agents
Ocular Toxicity:	**Grade ≥ 2:** ▪ Hold both study drugs until < Grade 1 (dose delays longer than 14 days require discussion with the Medical Monitor); ▪ Obtain ophthalmology consult; uveitis or episcleritis may be treated with topical corticosteroid eye drops; ▪ Reintroduce rociletinib at a reduced dose when symptoms resolved to Grade ≤ 1. If no recurrent symptoms, restart MPDL3280A; MPDL3280A should be permanently discontinued for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.
Laboratory abnormalities	**Grade ≥ 3** Laboratory abnormalities related to study drug that are asymptomatic and deemed by the Investigator not to be clinically significant ▪ After discussion between Investigator and Medical Monitor, rociletinib dosing may be delayed, and treatment subsequently resumed at the current dose level or at a reduced dose. If abnormality persists > 7 days, MPDL3280A dosing may also be held and subsequently resumed at the same dose level when toxicity resolves to baseline grade plus one.
Liver toxicities	**Grade ≥ 3** AST, ALT, or bilirubin abnormalities (or AST or ALT ≥ 10 × ULN in patients with hepatic metastases) related to study drug that are asymptomatic and deemed by the Investigator not to be clinically significant ▪ Hold both study drugs until recovery Grade ≤ 1; ▪ Initiate systemic steroids IV for 48 hours followed by oral taper; ▪ Monitor LFTs QOD until decreasing, then weekly; ▪ If resolved to baseline grade plus one (eg, if baseline Grade 1, then Grade 2) resume MPDL3280A dosing; ▪ If AE persists permanently discontinue MPDL3280A.
Other Grade ≥ 3 non-hematologic or Grade 4 hematologic toxicity	▪ Hold rociletinib and MPDL3280A until recovery to Grade ≤ 1 and then restart rociletinib at a reduced dose and MPDL3280A at the same dose. ▪ If the Grade 4 AE recurs (a second time), then MPDL3280A should be discontinued. ▪ If the Grade 4 AE recurs (a third time), then rociletinib should be discontinued.

Table 18: Management of Overlapping Toxicities (continued)

Pulmonary toxicity	Incidental radiographic findings of ground glass opacities (GGO) or non-infectious infiltrate in absence of symptoms: ▪ Hold rociletinib and MPDL3280A and re-evaluate after 1 week; ▪ If no worsening in GGO/infiltrates and patient is still asymptomatic, resume treatment with rociletinib. Re-evaluate after additional 1 week. If GGO/infiltrates are still present and not worsened, perform pulmonary function tests. If patient is confirmed asymptomaic, resume treatment with MPDL3280A. ▪ If GGO/infiltrates worsen and patient is still asymptomatic, continue to hold rociletinib and MPDL3280A and refer patient for bronchoscopy and pulmonary function tests. Consider starting low-dose oral prednisone 10 mg or equivalent per day. Re-evaluate after 1 week and resume rociletinib if GGO/infiltrates improve. Re-evaluate after additional 1 week and resume treatment with MPDL3280A under the same conditions. ▪ Prior to reintroduction of rociletinib, discuss appropriate dose with Medical Monitor. Symptomatic presentation (eg, hypoxia, cough;Grade 2+): ▪ Hold rociletinib and MPDL3280A dosing and investigate for presence of radiographic changes. ▪ Rule out alternative causes (eg, lymphangitic carcinomatosis, infection, heart failure, chronic obstructive pulmonary disease, pulmonary embolism, or hypertension). Diagnostic evaluation may include oxygen saturation (ie, arterial blood gas), high-resolution CT scan of the chest, bronchoscopy with bronchoalveolar lavage, pulmonary function tests (with DL_{CO}), and pulmonary function testing with a pulmonary embolism protocol. ▪ Grade ≥ 3 dyspnea or hypoxia may require corticosteroid treatment. MPDL3280A should be interrupted if corticosteroids are initiated. ▪ Delay rociletinib and MPDL3280A re-administration if GGOs are observed. Administer steroids if pneumonitis or organizing pneumonia is documented. ▪ If bronchoscopy is consistent with immune-related etiology, start oral prednisone 60 mg or equivalent per day, followed by a taper over 2 weeks. ▪ Rociletinib dosing may be restarted at a reduced dose after resolution of symptoms and steroid use is no more than 10 mg prednisone equivalent per day. If no recurrent symptoms develop within 14 days, MPDL3280A dosing may be reinitiated. ▪ Discussion between the Investigator and Medical Monitor and approval to restart dosing is required before rociletinib or MPDL3280A are restarted. ▪ Permanently discontinue MPDL3280A for life-threatening immune-related pulmonary events.

Table 18: Management of Overlapping Toxicities (continued)

Toxicity	Attribution to both agents
Amylase/Lipase	**Grade ≥ 3** amylase/lipase elevation ▪ Delay MPDL3280A and rociletinib for asymptomatic Grade ≥ 3 amylase and/or lipase elevations and monitor QOD until decreasing; for Grade 4 elevations consider 10 mg prednisone daily; ▪ If symptomatic, MPDL3280A and rociletinib should be held. Methylprednisolone or oral steroids (prednisone equivalent of 60 mg/day) should be administered. Rociletinib dosing may be restarted when symptoms resolve and the amylase/lipase elevation is Grade ≤ 1. If no recurrent symptoms after 14 days then MPDL3280A dosing may be reinitiated at the same dose level. ▪ If the Grade ≥ 3 amylase/lipase elevation recurs with symptoms before MPDL3280A re-initiation then rociletinib should be permanently discontinued. ▪ If the Grade ≥ 3 amylase/lipase elevation recurs with symptoms after MPDL3280A re-initiation then rociletinib should be held until amylase/lipase elevation is Grade ≤ 1 and the MPDL3280A permanently discontinued. ▪ MPDL3280A should be permanently discontinued for life-threatening, immune-related pancreatitis.
Hypothyroidism	▪ No change in MPDL3280A dosing will be implemented for asymptomatic TSH elevation; start thyroid replacement hormone and monitor TSH weekly; ▪ Delay MPDL3280A for symptomatic TSH elevation; start thyroid replacement hormone and monitor TSH weekly; resume MPDL3280A when symptoms improve and TSH is decreasing.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; QOD, every other day; TSH, thyroid-stimulating hormone; ULN, upper limit of normal.

7 PRIOR AND CONCOMITANT THERAPIES

Concomitant therapy includes any prescription medications or over-the-counter preparations used by a patient between the 28 days prior to the first dose of study treatment through 28 days after the last dose of study treatment, or the date of administration of subsequent anticancer therapy, whichever is earlier. All concomitant medications should be reported to the Investigator and recorded on the appropriate eCRF.

7.1 Anticancer or Experimental Therapy

No other anticancer therapies (including chemotherapy, radiation, and 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 treatment with approval from the Sponsor's Medical Monitor. Treatment should be held 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 8.2.1 for more details.

7.2 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.

7.3 Medications for Treatment of Infusion Reactions

Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or famotidine or another H2 receptor antagonist, as per standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (eg, supplemental oxygen and β_2-adrenergic agonists).

7.4 Systemic corticosteroids and TNF-α inhibitors

Systemic corticosteroids and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with MPDL3280A but may be administered at the discretion of the treating physician after consultation with the Medical Monitor. If feasible, alternatives to corticosteroids should be considered. Premedication may be administered for Cycles ≥ 2 at the discretion of the

treating physician after consultation with the Medical Monitor. The use of inhaled corticosteroids and mineralocorticoids (eg, fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed. Megestrol administered as an appetite stimulant is acceptable while the patient is enrolled in the study.

7.5 Other Concomitant Medications

Influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live, attenuated influenza vaccine (eg, FluMist®) within 4 weeks prior to first day of study treatment or at any time during the study but may receive inactivated vaccine.

Therapies considered necessary for the patient's well-being may be given at the discretion of the Investigator 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.

Prophylactic antibiotics (eg, to prevent urinary tract infection or chronic obstructive pulmonary disease exacerbation) are allowed. 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.

7.6 Excluded Therapies Concurrent with Rociletinib

7.6.1 Drugs that prolong QTc interval

Medications known to produce QT prolongation should be avoided during treatment of patients with rociletinib. See http://crediblemeds.org/ for the most up-to-date reference lists of QT-prolonging medications. Please note that the lists contain common supportive medications, such as anti-emetics (ondansetron [and other 5HT3 antagonists], metoclopramide, hydroxyzine), antibiotics (azithromycin, ciprofloxacin, metronidazole) and anti-depressants (escitalopram), which should not be used in combination with rociletinib.

Medications to consider for nausea 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.

If a drug that has the potential to cause QT prolongation is indicated to control AEs (eg, 5HT3 inhibitor for nausea/vomiting), and the investigator believes that the patient is benefiting from rociletinib therapy, then additional ECGs should be performed 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.

7.6.2 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.

7.6.3 P-gp Substrates, Inhibitors and Inducers

Because rociletinib is a P-gp inhibitor *in vitro*, caution should be exercised in patients receiving PO 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, 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.

7.6.4 Proton Pump Inhibitors

Because rociletinib is absorbed optimally in an acidic environment, proton pump inhibitors or H2 blockers should be used with caution. If gastric acid blockade is required, short acting antacids are preferred.

7.7 Excluded Therapies Concurrent with MPDL3280A

The following therapies are excluded while patients are receiving MPDL3280A and for 10 weeks after the last dose of MPDL3280A.

7.7.1 Denosumab

Patients who are receiving a RANKL inhibitor (denosumab) prior to enrollment must be willing and eligible to receive a bisphosphonate instead; denosumab could potentially alter the activity and the safety of MPDL3280A.

7.7.2 Immunomodulatory Agents

Patients are not allowed to receive immunostimulatory agents, including but not limited to IFN-α, IFN-γ, or IL-2. These agents, in combination with MPDL3280A, could potentially increase the risk for autoimmune conditions.

Patients should also not receive immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide. These agents could potentially alter the activity and the safety of MPDL3280A. Systemic corticosteroids and anti-TNF-α agents may attenuate potential beneficial immunologic effects of treatment with MPDL3280A but may be administered at the discretion of the treating physician after consultation with the Medical Monitor. If feasible, alternatives to these agents should be considered.

8 STUDY PROCEDURES

Table 1 summarizes the procedures and assessments to be performed for all patients.

Unless otherwise specified, all procedures and assessments in Cycle 2+ are to be completed within ± 3 days of the scheduled time points relative to C1D1 of combination treatment with PO rociletinib and IV MPDL3280A. Perform assessments scheduled for C1D4 on that day (ie, no window) and assessments for C1D8 and C1D15 within ± 2 days of the scheduled time points.

8.1 Screening Period

After written informed consent, patients will undergo screening assessments within 28 days before the first dose of study drug. Some assessments are required within 7 days (serum pregnancy test) or 14 days prior to the first dose of study treatment (see Table 1). A mandatory fresh tumor biopsy will be collected within 60 days prior to the first day of study treatment. If a biopsy was performed outside of the protocol within this 60-day period, and no intervening treatment was given, a repeat biopsy is not required if adequate tumor tissue can be provided to the Sponsor during the Screening Period. Other assessments performed before the patient signing of informed consent for this protocol are acceptable for the screening purposes of this protocol only if confirmed to have been standard of care. Please refer to Table 1 for details on assessments to be performed during the Screening Period.

Procedures required on Day 1 of Run-in-Period (Phase 1) or C1D1 (Phase 2) may be omitted if completed ≤ 3 days earlier during the Screening Period.

8.2 Treatment Period

Before enrollment of a patient, all eligibility criteria must be satisfied, and enrollment must be approved by the Sponsor's medical monitoring team.

The Treatment Period will consist of 21-day combination treatment cycles, with MPDL3280A administered by IV infusion on the first day of each cycle, beginning with C1D1, and rociletinib administered PO BID continuously. During Phase 1 of the study only, the Treatment Period will also include a 7-day Run-in Period of rociletinib monotherapy prior to C1D1 of combination treatment with rociletinib and MPDL3280A. Study visits will be scheduled as indicated in Table 1. Additional clinic visits will also occur as clinically indicated.

During the Treatment Period, tumor assessments will be conducted every 2 cycles (6 weeks ±1 week) through Cycle 6 (ie, at the end of Cycles 2, 4, and 6); every 3 cycles (9 weeks ±1 week) after Cycle 6 (ie, at the end of Cycles 9, 12, etc); and at the EOT Visit. The frequency of tumor assessments may be further reduced after 2 years with approval of the Medical Monitor (see Section 8.4.3 for details). Tumor scans will be evaluated locally for response evaluation and treatment decision-making.

Patients will be allowed to continue on study as long as they experience no unacceptable toxicities and they continue to receive clinical benefit from the study treatment as assessed by the

Investigator (with agreement from the Sponsor's Medical Monitor) or until the patient meets any of the withdrawal criteria (see Section 11 for details and exceptions).

8.2.1 Post-Progression Treatment

Patients may continue to receive treatment with rociletinib and/or MPDL3280A after radiographic progression of disease if, in the opinion of the Investigator and approved by the Sponsor, the patient is still benefiting from treatment. This must be discussed with the Sponsor's Medical Monitor 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, and blood collection for biomarker analysis, should continue per protocol. The patient should be discontinued from treatment once it is clear that no further clinical benefit can be achieved.

The criteria below are required for treatment post-progression:

- Evidence of clinical benefit as assessed by the Investigator;
- Absence of symptoms and signs (including worsening of laboratory values [eg, new or worsening hypercalcemia]) indicating unequivocal progression of disease;
- No decline in ECOG performance status that can be attributed to disease progression;
- Absence of tumor growth at critical anatomical sites (eg, leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions;
- Patients for whom approved therapies exist must provide written consent to acknowledge deferring these treatment options in favor of continuing study treatment at the time of initial apparent progression;
- Written Sponsor approval for treatment post-progression;
- Patients in whom radiographic disease progression is confirmed at a subsequent tumor assessment may be considered for continued study treatment at the discretion of the Investigator if they continue to meet the criteria above and have evidence of clinical benefit.

8.2.2 End-of-Treatment Visit

Patients will be asked to return to the clinic for the EOT Visit 28 days (+7 days) after the last dose of study treatment, or before the patient initiates another anticancer agent (if sooner), to assess safety of the patients. Safety evaluation assessments for the EOT Visit are outlined in Table 1. All AEs (including SAEs and protocol-defined events of special interest), regardless of attribution, will be recorded until 28 days after the last dose of study treatment or until initiation of another anticancer therapy, whichever occurs first. Ongoing AEs considered related to study treatment and all SAEs, regardless of causality, will be followed until the event has resolved to baseline grade, the event is assessed by the Investigator as stable, new anticancer treatment is initiated, the patient is lost to follow up, the patient withdraws consent, or it is determined that the study treatment or participation is not the cause of the AE.

Tumor assessment scans do not need to be repeated if radiographic disease progression has been documented previously or the last scans were performed < 2 weeks before the last dose of study treatment or the patient had disease progression at the last scan. For patients who provide additional consent, an optional fresh tumor biopsy will be collected at the time of permanent treatment discontinuation due to disease progression (at the time the Investigator believes the patient is no longer deriving clinical benefit from study treatment, if treatment beyond radiographic disease progression is approved). This optional biopsy and associated blood samples scheduled for the EOT Visist (see Table 2) should occur as close as possible to the date of the decision to permanently discontinue study.

8.3 Follow-Up Period

During the Follow-Up-Period, all patients will be contacted by the site every 12 weeks (± 1 week) for the collection of information on all subsequent anticancer therapy and for the monitoring of survival status until the patient's death, patient withdrawal of consent, or a decision by the Sponsor to cease data collection and close the study, whichever comes first. These assessments may be performed during routine clinic visits or by telephone contact.

8.4 Methods of Data Collection

8.4.1 Patient History

Patient information collected during screening will include basic demographics; medical history, including smoking status, medical conditions, and oncology history including date of cancer diagnosis, prior cancer treatment, and any surgical procedures. For patients being considered for enrollment in the study, screening assessments will not begin until patient tumor EGFR mutation status is determined through local assessments.

8.4.2 Safety Evaluations

8.4.2.1 Adverse Event Assessment

The Investigator has the responsibility for assessing the safety of the patients and patient compliance with the protocol to ensure study integrity. Patients will be monitored for AEs from the time of the first dose of study drug is administered through 28 days after the last dose of study drug. Study procedure-related AEs that occur after signing of the Informed Consent Form (ICF) and before administration of rociletinib and MPDL3280A will also be collected. All ongoing AEs related to study treatment and all SAEs, and all protocol-defined events of special interest (Section 9.6) will be followed until resolution or stabilization. Adverse events and laboratory abnormalities will be graded according to the NCI CTCAE grading system (v4.03).

Complete details for monitoring and managing AEs, including the definition of study drug-related AEs, are provided in Section 9.

8.4.2.2 Clinical Laboratory Investigations

Blood for safety evaluations will be analyzed by a local laboratory to inform patient treatment decisions, and results must be reviewed by the Investigator before administration of rociletinib and/or MPDL3280A. Additional tests may be performed at the Investigator's discretion. The panels of laboratory tests to be performed are shown below:

Hematology: Hematology assessments include hemoglobin, hematocrit, WBC and differential (with ANC), reticulocyte count, and platelet count. Hematology results must be reviewed by the Investigator before administration of rociletinib and/or MPDL3280A.

Patients known to require concomitant therapy with anticoagulants such as warfarin should also have INR monitored throughout the study.

Serum Chemistry: Serum chemistry assessments include total protein, albumin, creatinine, BUN or urea, total bilirubin, alkaline phosphatase, ALT, AST, total cholesterol, **fasting** glucose, sodium, potassium, magnesium, chloride, calcium, phosphorus and uric acid.

In addition separate assessments of fasting glucose; hemoglobin A1c; TSH and free T_3 and T_4; will be performed as described in Table 1.

Urinalysis: Urinalysis will be performed on freshly voided clean sample by dipstick for protein, glucose, blood, pH, and ketones per the schedule of evaluations. If dipstick findings are abnormal, then a microscopic evaluation will be performed to assess the abnormal findings. Urinalysis is scheduled at screening only.

Serum ß-hCG Pregnancy Test (Local Lab): Performed on females of childbearing potential ≤ 7 days before first day of study treatment and at the EOT Visit. If the serum pregnancy test results are not available on first day of study treatment, a urine pregnancy test can be performed on first day of study treatment to confirm that the patient is not pregnant before dosing. A negative result must be confirmed by a physician before the first dose of either study drug can be administered. Both values should be entered in the eCRF.

Laboratory reports will be reviewed by the Investigator or delegated physician who will then comment on out-of-range parameters and assess clinical significance. Clinically significant abnormalities and associated panel results, as well as results of any additional tests performed as follow up to the abnormalities, will be documented on the eCRF as an AE.

8.4.2.3 Vital Signs

Vital signs will be measured at all clinic visits as outlined in Table 1. Vital signs include body temperature, heart rate, respiratory rate, and blood pressure. All vital signs will be obtained after the patient has been resting for at least 5 minutes.

Weight will also be measured at all clinic visits as part of physical examinations (see Section 8.4.2.6).

For the first infusion of MPDL3280A, vital signs should be measured within 60 minutes before, every 15 (± 5) minutes during the infusion, and 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before the infusion, during the infusion if clinically indicated or if symptoms occurred in the prior infusion, and 1 hour (± 10 minutes) after the infusion.

8.4.2.4 12-Lead Electrocardiograms

Triplicate serial 12-lead ECGs (10-sec ECG tracings collected in triplicate > 2 min apart) will be taken at time points specified in Table 1 and as clinically indicated. The average of triplicates should be recorded.

Electrocardiograms should be performed after the patient has been resting for at least 5 min. The 12-lead ECGs collected will be read locally to facilitate patient management and analyzed at a central ECG laboratory. Details on recording ECGs and their interpretation will be included in the Investigator's file.

8.4.2.5 Echocardiogram (ECHO) or Multigated Acquisition (MUGA) Scan

An ECHO or MUGA scan will be performed at screening only for patients with a known history of pericardial effusions, or for whom the Investigator suspects has the potential for a pericardial effusion, and otherwise as clinically indicated.

8.4.2.6 Physical Examinations

Physical examinations will be performed at every clinic visit as outlined in Table 1.

Complete physical examinations will include height (at screening only), weight (the patient should be in light indoor clothes; no shoes), and the evaluation of head, eyes, ears, nose and throat (HEENT) and cardiovascular, dematologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems.

Limited physical examinations will include weight, an assessment of all baseline abnormalities and recording of associated changes, questioning of the patient about any skin or vision changes, and any other symptom-directed examination.

8.4.2.7 ECOG Performance Status

ECOG performance status (Appendix C) will be assessed at time points specified in Table 1. 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.

8.4.2.8 Pulmonary Function Tests

Patients are required to have a pulmonary function evaluation conducted at baseline and as clinically indicated. Pulmonary function tests must include an assessment of DLCO.

8.4.3 Efficacy Evaluations

8.4.3.1 Tumor Assessments

Tumor assessments will be performed at screening and during the Treatment Period until permanent discontinuation of all study treatment (patients who continue treatment with rociletinib and/or MPDL3280A after a radiographic progression should continue to be scanned according to the protocol until they permanently discontinue all study treatment).

The frequency of tumor assessments will be every 2 cycles (6 weeks ± 1 week) through Cycle 6 (ie, at the end of Cycles 2, 4, and 6); every 3 cycles (9 weeks ± 1 week) after Cycle 6 (ie, at the end of Cycles 9, 12, etc); and at the EOT Visit. The frequency of tumor assessments may be further reduced after 2 years with the approval of the Medical Monitor. Tumor assessments at the EOT Visit are not required if radiographic disease progression has been documented previously or the last tumor assessments were performed < 2 weeks before the last dose of study treatment. If an initial complete response (CR) or PR is noted, confirmatory scans must be performed 4 to 6 weeks later.

Scans will be evaluated locally for response evaluation and patient treatment decisions. Tumor response will be evaluated using RECIST v1.1 (Appendix A) and modified RECIST incorporating irRC (Appendix B).

Tumor assessments should consist of clinical examination and appropriate imaging techniques (preferably CT scans of the chest, abdomen, and pelvis with ≤5 mm slice thickness); other studies (MRI and X-ray) may be performed if required. Brain imaging is required at baseline. Patients with brain lesions at baseline will require repeat brain imaging as part of the follow-up tumor assessments. Patients without baseline brain lesions do not require brain imaging on study unless clinically indicated. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study.

8.4.4 Pharmacokinetic Evaluations

Blood samples for PK profile analysis of rociletinib (and its metabolites) and MPDL3280A, will be collected at visits and time points described in Table 1 and Table 2. Central laboratories will be used for bioanalysis of these samples. Please refer to the laboratory manual for details on collection and processing of blood PK samples.

On scheduled PK sampling days, patients should be instructed to not administer study drug at home, but to bring rociletinib to the clinic along with breakfast. After a predose PK blood draw, patients will eat breakfast and take the morning dose of rociletinib within 30 minutes after starting their meal. On days of MPDL3280A infusions, patients will be administered IV

MPDL3280A approximately 2 hours after the morning rociletinib dose. Times of the PK blood draws, meals, and administrations of study drugs in the clinic should be recorded.

Additional unscheduled PK blood samples will be collected at the time of fresh tumor biopsy and may also be collected when a patient experiences an AE for which the Investigator would like to have PK data to help understand the safety observation.

8.4.5 Pharmacodynamic Evaluations

A mandatory fresh tumor tissue biopsy specimen will be collected within 60 days prior to the first day of study treatment for all patients. In addition, an optional fresh tumor biopsy may be collected at time of disease progression (or patient is considered by the Investigator to no longer benefit from study treatment, if treatment is continued beyond a radiographic progression).

The baseline tissue biopsy specimen from screening will be used for a retrospective confirmation of EGFR mutation status by a central laboratory. The baseline biopsy as well as the optional tissue biopsy collected at disease progression will also be used to investigate mechanisms of response, primary resistance, and acquired resistance to rociletinib and MPDL3280A. Immunohistochemistry (IHC) using exploratory biomarkers of the EGFR and PD-L1 pathway signaling such as PD-L1, CD8, and MHC Class II may be performed. Samples may also be assessed for genomic alterations (eg, mutations, amplifications, and fusions) in a panel of established cancer genes by next generation sequencing (NGS). A subset of specimens may also be characterized using additional genomic (whole exome), transcriptional (whole transcriptome, RNA-Seq), or protein-based approaches.

Blood samples will be collected for pharmacogenomic and pharmacodynamic analyses to investigate mechanisms of response, primary resistance, and acquired resistance to rociletinib and MPDL3280A. The pharmacogenomic blood sample will be collected predose on Day 1 of the Run-in-Period for Phase 1, and on C1D1 of Phase 2 for genomic DNA purification. The DNA sample may be evaluated by NGS, and molecular alterations in germline and tumor DNA may be compared so that molecular alterations unique to the tumor can be unambiguously identified. Pharmacodynamic blood samples will be collected as outlined in Table 2.

Pharmacodynamic blood samples will be processed to plasma and/or serum and PBMCs to evaluate markers which may include (but are not necessarily limited to) IGF-1, insulin, c-peptide, and T-cell receptor diversity. Cell-free DNA will be purified from plasma samples and evaluated for EGFR mutation status and possibly also for similar DNA analyses as described for tumor biopsies (eg, targeted cancer panel NGS), if sufficient DNA is available.

Changes in biomarker status will be investigated for associations with rociletinib and/or MPDL3280A exposure, safety, and clinical activity.

Please refer to the Laboratory Manual for details on collecting and processing pharmacodynamic samples.

8.4.6 Patient Diary

Patient diary cards will be provided to patients at the beginning of the Run-in-Period (Phase 1 only) and on Day 1 of every treatment cycle when rociletinib study drug is dispensed to the patient. Patients will use diary cards to note the date, time, and dose of rociletinib administration. At each clinic visit, patients will bring the diary with them to the clinic, along with the study drug bottle and any unused study drug, for study staff to review.

9 ADVERSE EVENT REPORTING

9.1 Definition of an Adverse Event (AE)

Patients will be monitored for AEs from the time the first dose of study drug is administered through 28 days after the last dose of study treatment. Study procedure-related AEs that occur after signing of the ICF and before administration of study drug will also be collected.

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 IMP. 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 non-leading 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).

9.2 Definition of a Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that occurs at any dose of rociletinib and MPDL3280A 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 rociletinib and/or MPDL3280A 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.

9.3 Events or Outcomes Not Qualifying as SAEs

The following are not considered SAEs:

- Pre-planned or elective hospitalization including social and/or convenience situations (eg, respite care);
- Overdose of either rociletinib or MPDL3280A 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;
- 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 a 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 a SAE with CTC 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.

9.4 Clinical Laboratory Assessments as AEs and SAEs

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 lab 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.

9.5 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 9.9). **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.

9.6 Adverse Events of Special Interest for MPDL3280A

The conditions listed below are of special interest and should be recorded within 24-48 hours of their occurrence.

Conditions suggestive of an autoimmune disorder:

- Pneumonitis;
- Hypoxia or Dyspnea ≥ Grade 3;
- Colitis;
- Endocrinopathies: diabetes mellitus, pancreatitis, or adrenal insufficiency;
- Vasculitis;
- Hepatitis;
- Transaminitis: AST or ALT > 3 × ULN and bilirubin > 2 × ULN or AST/ALT > 10 × ULN;
- Systemic lupus erythematosus;
- Guillain barre syndrome;
- Myasthenia gravis;
- Pericardial effusion;
- Skin Reactions: vitiligo or pemphigoid;
- Events suggestive of hypersensitivity, cytokine release, influenza-like illness, SIRS, or infusion reaction syndromes.

9.7 Recording of AEs and SAEs

Any AE from the time the first dose of either study drug through 28 days after the last dose of study drug will be recorded on the AE eCRF. Study procedure-related AEs that occur after signing of the ICF and before first dose of either study drug will also be captured on the AE eCRF. Any other AE that occurs before 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 of the patient; from the physical examination; or from special tests such as the ECG, laboratory assessments, or other study-specified procedure.

Each AE is to be evaluated for duration, severity, seriousness, and causal relationship to each study 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 either study drug, whether or not related to rociletinib or MPDL3280A, must be immediately reported to the Sponsor/designee SAE contact (Section 9.9).

9.7.1 Intensity of Adverse Events

The severity of the AE will be graded according to the NCI CTCAE v4.03 grading scale. For AEs not covered by NCI CTCAE v4.03, the severity will be characterized as mild, moderate, severe, or life-threatening according to the following definitions:

- Mild (Grade 1) events are usually transient and do not interfere with the patient's daily activities;
- Moderate (Grade 2) events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities;
- Severe (Grade 3) events interrupt the patient's usual daily activities and hospitalization (or prolongation of hospitalization) may be required;
- Life-threatening (Grade 4) events require urgent intervention to prevent death.

9.7.2 Causal Relationship of Adverse Events to Investigational Study Drugs

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);
- It does not correspond to a reasonable temporal sequence from administration of study drug;
- It does not correspond to 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.

Possibly Related

- An AE that is difficult to assign to alternative causes;
- It corresponds to 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 corresponds to a known response pattern to study drug;
- It is confirmed with a positive rechallenge or supporting laboratory data.

9.7.3 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;
  - Rociletinib dose reduced;
  - Rociletinib temporarily interrupted;
  - Rociletinib permanently discontinued;
  - MPDL3280A temporarily interrupted;
  - MPDL3280A permanently discontinued;
  - Other (specify).
- Outcome:
  - Recovered;
  - Recovered with sequelae;
  - Improved;
  - Ongoing;
  - Death;
  - Lost to follow up.

9.8 Follow-Up of AEs and SAEs

All AEs 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 through 28 days after the last dose of rociletinib and/or MPDL3280A. All ongoing AEs related to study treatment, all SAEs, and all protocol-defined events of special interest (Section 9.6) will be followed until the event has resolved to baseline grade, the event is assessed by the Investigator as stable, new anticancer treatment is initiated, the patient is lost to

follow up, the patient withdraws consent, or it is determined that the study treatment or participation is not the cause of the adverse event.

9.9 Regulatory Aspects of SAE Reporting

All SAEs, regardless of relationship to study drug, must be reported to the safety contract research organization (CRO) within 24 hours of knowledge of the event, according to the procedures below. It is important that the Investigator provide an assessment of relationship of the SAE to study treatment at the time of the initial report. The Clinical Trial Serious Adverse Event 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 CRO 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 CRO 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.

The Sponsor 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 US Food and Drug Administration (FDA), according to 21 Code of Federal Regulations (CFR) 312.32; to the Japanese Pharmaceuticals and Medical Devices Agency; 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), the Sponsor 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. The Sponsor or its designee will submit all safety updates and periodic reports to the regulatory authorities as required by applicable regulatory requirements.

10 STATISTICAL METHODS

10.1 Analysis Populations

The following analysis populations are defined for the study:

Tumor evaluable population—all patients who received at least one dose of rociletinib or MPDL3280A, have at least one measureable tumor lesion at baseline, and have at least one post-baseline tumor assessment as determined by the Investigator.

Safety population—all patients who have received at least one dose of rociletinib or MPDL3280A.

10.2 Statistical Methods

10.2.1 General Considerations

Data will be summarized using descriptive statistics (number of patients, mean, median, standard deviation, minimum, and maximum) for continuous variables and using frequencies and percentages for discrete variables. Data will be presented by dose cohorts, as appropriate.

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.

10.2.2 Patient Disposition

The frequency and percentage of patients in each analysis population will be presented. The primary reason for discontinuation of rociletinib and/or MPDL3280A will be summarized.

10.2.3 Baseline Characteristics

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

10.2.4 Efficacy Analyses

The efficacy endpoints of ORR, DoR, DCR, and PFS will be evaluated using RECIST v1.1 (Appendix A:) and modified RECIST incorporating irRC (Appendix B). Efficacy endpoints evaluated by the Investigator will be presented for the subgroup of patients determined to be tumor evaluable by the Investigator.

Progression-free survival and OS will also be presented for the safety population.

10.2.4.1 Primary Endpoint (Phase 2)

The primary endpoint of the Dose Expansion Phase (Phase 2) of the study is ORR per RECIST as assessed by the Investigator.

The ORR is the best overall response recorded from the start of the treatment until disease progression or recurrence.

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

10.2.4.2 Secondary Efficacy Endpoints

10.2.4.2.1 Overall Response Rate (ORR) based on Modified Response Criteria

The ORR based on the modified response criteria is the best overall response recorded from the start of the treatment until disease progression or recurrence as assessed by the Investigator using the modified RECIST criteria.

The frequency and percentages of patients with a best overall response of CR, PR, SD, or PD will be summarized.

10.2.4.2.2 Duration of Response (DOR)

Duration of response 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. For patients who continue treatment post-progression, the first date of progression will be used for the analysis. Patients without a documented event of radiographic progression will be censored on the date of the most recent tumor assessment.

10.2.4.2.3 Disease Control Rate (DCR)

Disease control rate is defined as the percentage of patients who have achieved CR, PR, or SD lasting at least 12 weeks.

10.2.4.2.4 Progression-Free Survival (PFS)

Progression-free survival (PFS) will be calculated as 1+ the number of days from the first dose of study drug 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, radiologic assessment) or date of first dose of study drug 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.

10.2.4.2.5 Overall Survival

Overall survival (OS) will be calculated as 1+ the number of days from the first dose of study drug 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.

10.2.4.2.6 Exploratory Sub-Group Analyses

For Phase 2 of the study, accrual to Groups A and B will take place independently.

In Group B, T790M+ and T790M– patients will be enrolled concurrently. Exploratory subgroup analyses will be performed.

There are no planned statistical analyses between Group A and B or the sub-groups within Group B.

10.2.4.2.7 PK Analyses

Blood sampling for PK analyses of both rociletinib and MPDL3280A will be conducted in all patients treated with rociletinib and MPDL3280A. PK parameters, including AUC_{0-24}, C_{max}, C_{min}, and t_{max} will be estimated for rociletinib, and C_{max}, and C_{min} for MPDL3280A using non-compartmental models. Comparisons across dose levels will be made to assess proportionality.

10.2.4.2.8 Pharmacodynamics Analyses

Tumor tissue, plasma, and blood specimens will be used for pharmacodynamic assessment of rociletinib and/or MPDL3280A activity, to evaluate the concordance of mutant EGFR detection between tissue and plasma, and to explore biomarkers that may be predictive of response or resistance to rociletinib and/or MPDL3280A. Biomarkers and changes in biomarker status will be investigated for associations with rociletinib and/or MPDL3280A exposure, safety, and clinical activity. Given the limited sample size, no formal statistical analysis is planned.

10.2.5 Safety Analyses

The safety analyses will be performed using the safety population.

Safety data analysis will be conducted on all patients receiving at least one dose of rociletinib or MPDL3280A. The number and percentage of patients experiencing one or more AEs will be summarized by dose level group, relationship to study drug, and severity. AEs will be coded using MedDRA terminology. Listings of patients who experienced DLT during Cycle 1, dose reductions, dosing interruptions, withdrawal due to an AE, SAEs and/or death will be presented. Laboratory parameters will be summarized using descriptive statistics, by post-dosing shifts relative to baseline, and data listings of clinically significant abnormalities. Vital signs, ECOG performance status, and ECG data will be summarized by changes from baseline values at each dose level using descriptive statistics.

A mTPI method will be used to identify the MTD or MAD and the RP2D. The mTPI, a model-based approach that has a pre-specified decision matrix that recommends escalating, reducing or maintaining the same dose or stopping dose escalation, based on the toxicities observed in the dose level under evaluation, reduces the risk of exposing patients to doses above the MTD compared with 3+3 design in which there is a 71% chance of escalation if the true but unknown rate of DLT is 20% and less than 50% chance of escalation if the true but unknown rate of DLT is higher than 30%.

10.2.5.1 Extent of Exposure

The following will be summarized by dose group:

- Number of weeks of treatment initiated;
- Number of dose reductions or interruptions.

The number of weeks of treatment initiated will be investigated by summarizing the number of weeks started by each patient for each study drug. The number of patients with at least one dose reduction or interruption will be summarized with frequencies and percentages separately for each study drug and for the combination.

10.2.5.2 Adverse Events

Adverse event (AE) coding will be performed using MedDRA terminology. The severity of the toxicities will be graded according to the NCI CTCAE v4.03 whenever possible. Treatment-emergent AEs are defined as AEs with an onset date on or after the date of first dose of rociletinib or MPDL3280A until the date of the last dose of either study drug 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 system organ class and preferred term will be presented by dose group. Multiple instances of the treatment-emergent AEs in each System Organ Class and multiple occurrences of the same Preferred Term are counted only once per patient. The number and percentage of patients with at least one treatment-emergent AE will also be summarized by dose group.

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

- All treatment-emergent AEs;
- Treatment-emergent AEs by CTCAE grade;
- Grade 3 or greater treatment-emergent AEs;
- Grade 3 or greater treatment-related, treatment-emergent AEs;
- Treatment-related, treatment-emergent AEs;
- Dose-limiting toxicity AEs;
- Serious treatment-emergent AEs;

- Serious treatment-related, treatement-emergent AEs;
- Treatment-emergent AEs with an outcome of death;
- Treatment-emergent AEs leading to discontinuation of either study drug;
- Treatment-emergent AEs resulting in interruption or reduction of either study drug.

The incidence of treatment-emergent AEs will be summarized by relationship to oral study drug 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 one treatment-emergent AE of the given grade will be summarized.

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

10.2.5.3 Clinical Laboratory Evaluations

Clinical laboratory evaluations include the continuous variables for hematology, serum chemistry, and urinalysis. Laboratory values will be presented in International System of Units. The baseline laboratory value will be defined as the last value before or on the day of the first dose of either study drug. The on-treatment period will be defined as the day after the first dose of either study drug to 28 days after the last dose of rociletinib or MPDL3280A. Laboratory values collected during the on-treatment period will be included in the summary tables. The laboratory values collected after the on-treatment period will only be presented in the data listings.

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 dose group and study phase. 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 dose group and study phase. Separate listings will be produced for clinically significant laboratory abnormalities (ie, those that meet Grade 3 or 4 criteria according to CTCAE) by dose group.

10.2.5.4 Vital Sign Measurements

The baseline vital sign measurement will be defined as the last value before or on the day of the first dose of either study drug. The on-treatment period will be defined as the day after the first dose of either study drug to 28 days after the last dose of rociletinib or MPDL3280A Vital sign measurements collected during the on-treatment period will be included in the summary tables.

The vital sign measurements collected after the on-treatment period will only be presented in the data listings.

The summary of vital sign 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 dose group and study phase. 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 dose group.

10.2.5.5 12-Lead Electrocardiograms

Electrocardiogram (ECG) intervals will be stratified into categories indicative of potential clinical significance. Each patient's maximum QT and QT_C intervals from the pretreatment visit and treatment period visits will be classified as ≤ 450 ms, > 450 to ≤ 480 ms, > 480 to ≤ 500 ms, and > 500 ms. For each patient's maximum change from the pretreatment ECG visit for QT and QT_C, intervals will be classified into < 30 ms, ≥ 30 to < 60 ms, and ≥ 60 ms. The number and percentage of patients in each classified category will be presented. 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 pretreatment ECG visit at each time point. Plots of the mean QT/QT_C over time will be provided.

10.2.5.6 Other Safety Measurements

Concomitant medications/procedures will be tabulated and summarized.

10.3 Sample Size Considerations

Approximately 25 patients will be enrolled into Group A and approximately 50 patients will be enrolled into Group B. The CSC will evaluate the safety and efficacy of the combination of rociletinib and MPDL3280A on a regular basis in order to ensure that the risk/benefit of the combination is at least as beneficial as that of single agent rociletinib. In addition early futility rules will be evaluated as described below.

Within Group A, the expected ORR for single-agent rociletinib in frontline patients is at least 50%. An early futility rule will be evaluated in the first 5 patients such that if 0 out of the first 5 patients have a best response of PR or CR, then the true ORR in these patients is likely to be less than 50% and thus the evaluation of the combination in frontline patients may be discontinued.

Within Group B, it is expected that about 30 (60%) of the patients will be T790M+ and thus, about 20 patients (40%) will be T790M–. The estimated ORR for single-agent rociletinib is greater than 50% in T790M+ patients, so the observed ORR for the combination of rociletinib and MPDL3280A is also expected to be greater than 50% in these patients. An early futility rule will be evaluated in the first five T790M+ patients such that if 0 out of the first 5 T790M+ patients have a best response of PR or CR, then the true ORR in these patients is likely to be less than 50% and thus the evaluation of the combination in T790M+ patients may be discontinued.

In T790M– patients, an ORR less than 30% is probably not worthy of further study. The early futility rule will be based on the first nine T790M– patients. If 0 out of the first 9 patients have a best response of PR or CR, then the true ORR is likely to be less than 30% in these patients and thus the evaluation of the combination in T790M– patients may be discontinued.

11 PATIENT DISPOSITION

11.1 Permanent Discontinuation of Study Treatment

A patient must be discontinued from all study treatment if any of the following applies:

- Consent withdrawal at the patient's own request or at the request of their legally authorized representative;
- Clinical disease progression where the Investigator believes that the patient will not continue to benefit from study treatment (*Note:* patients will be permitted to continue study treatment after a radiographic progression [Appendix A: and Appendix B] if the benefit-risk ratio is judged to be favorable and continued treatment is approved by the Medical Monitor);
- Any event, adverse or otherwise, that, in the opinion of the Investigator, would pose an unacceptable safety risk to the patient;
- Any requirement for dose holds of rociletinib for more than 14 days or dose holds of MPDL3280A for more than 42 days, unless permission from the Sponsor's Medical Monitor for longer dose delay is granted;
- An intercurrent illness that, in the opinion of the Investigator, would affect assessments of the clinical status to a significant degree and requires discontinuation of therapy;
- A positive pregnancy test at any time during the study;
- Investigator decision.

In addition, the Sponsor may discontinue the study early for any of the reasons noted in Section 12.6.

The Sponsor (or designee) should be notified of all study terminations as soon as possible. The date and reason for cessation of PO rociletinib and/or IV MPDL3280A must be documented in the eCRF and source documents.

To the extent possible, EOT assessments should be performed for all patients who receive rociletinib and MPDL3280A. The EOT visit should occur 28 (± 7) days after the last dose of rociletinib and MPDL3280A. After stopping protocol-specified treatment, all patients will remain in the study and will be followed for safety (through 28 days after last dose; those with ongoing SAEs will be followed until either resolution or stabilization has been determined), for disease progression (every 8 ± 1 weeks until disease progression), and for survival status and subsequent NSCLC therapies (at approximately quarterly intervals until death or Sponsor decision).

12 STUDY ADMINISTRATION

12.1 Regulatory and Ethical Considerations

This study will be conducted in compliance with the protocol; Good Clinical Practices (GCPs), including International Conference on Harmonisation (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.

12.1.1 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.

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

12.1.2 Institutional Review Board (IRB)

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 IRB. This also applies to protocol amendments.

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

Verification of the IRB's unconditional approval of the study protocol and the written ICF will be transmitted to the Sponsor. 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 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 IRB at least annually in accordance with applicable national law and/or local regulations and in agreement with the policy established by the IRB and Sponsor.

The 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.

12.2 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 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 the Sponsor or Roche, including, but not limited to, the IB, 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.

12.3 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 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 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.

12.4 Study Monitoring

On behalf of the Sponsor, a CRO monitor will contact and visit the Investigator at the study center before the entry of the first patient and at predetermined appropriate intervals during the study until after the last patient has completed. The 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.

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 the Sponsor may also contact and visit the Investigators and monitor data during the study.

12.5 Electronic Case Report Form (eCRF)

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, reviewed, signed, and dated 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 files. All questions or comments related to electronic capture should be directed to the assigned monitor.

12.6 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, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the patients' interests.

The Sponsor 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 PO rociletinib or IV MPDL3280A.

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.

12.7 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 the Sponsor. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent document. The 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.

12.8 Retention of Study Documents

The study site will maintain a study file, which should contain, at minimum, the IB, the protocol and any amendments, drug accountability records, correspondence with the IRB and the Sponsor, 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 the Sponsor or its designees.

The Investigator shall retain records required to be maintained for a period of 5 years after 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 the Sponsor. 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 the Sponsor. Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in writing of the new responsible person and/or the new location. The Sponsor will inform the Investigator, in writing, when the study-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.

12.9 Clinical Study Report

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

12.10 Study Publication

All data generated from this study are the property of the Sponsor and shall be held in strict confidence along with all information furnished by the Sponsor. 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 the Sponsor. Written permission to the Investigator will be contingent on the review by the Sponsor of the statistical analysis and manuscript, and will provide for nondisclosure of the Sponsor 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.

12.11 Quality Assurance Audits

An audit visit to clinical centers may be conducted by a quality control auditor appointed by the Sponsor. The purpose of an audit, which is independent of and separate from routine monitoring or quality control functions, is to evaluate study conduct and compliance with the protocol, standard operating procedures, 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.

13 REFERENCES

1. Soria J-C, Sequist L, Goldman J, et al. Interim phase 2 results with the irreversible, mutant selective, EGFR inhibitor rociletinib (CO-1686). EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics; November 2014; Barcelona, Spain.

2. Butte MJ, Keir ME, Phamduy TB, et al. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity. 2007;27:111-22. Epub 2007 Jul 12.

3. Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 2014;515:563-7.

4. WHO Fact Sheet N°297. Cancer. October 2011.

5. Ries L, Eisner M, Kosary C, et al, eds. Cancer Statistics Review, 1975-2002. Bethesda, Md: National Cancer Institute, 2005.

6. Herbst RS, Heymach JV, Lippman SM. Molecular origins of cancer: Lung cancer. N Engl J Med 2008; 359:1367-80.

7. Mok TS, Wu YL, Thongprasert S, et al. Getfitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009; 361:947-57.

8. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010; 362:2380-8.

9. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 2010;11:121-8.

10. Rosell R, Carcereny E, Gervais R, et al. Spanish Lung Cancer Group in collaboration with Groupe Français de Pneumo-Cancérologie and Associazione Italiana Oncologia Toracica. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012; 13:239-46.

11. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011;12:735-42.

12. Herbst R, LoRusso P, Purdom M, Ward D. Dermatologic side effects associated with gefitinib therapy: clinical experience and management. Clin Lung Cancer 2003; 4:366-9.

13. Perez-Soler R, Saltz L. Cutaneous adverse effects with HER1/EGFR targeted agents: is there a silver lining? J Clin Oncol 2005; 23:5235-46.

14. Sridhar SS, Seymour L, Shepherd FA. Inhibitors of epidermal-growth-factor receptors: a review of clinical research with a focus on non-small-cell lung cancer. Lancet Oncol 2003; 4:397-406.

15. Wu JY, Shih JY, Yang CH, et al. Second-line treatments after first-line gefitinib therapy in advanced nonsmall cell lung cancer. Int J Cancer 2010; 126:247-55.

16. Goldberg SB, Oxnard GR, Digumarthy S, et al. Chemotherapy with Erlotinib or chemotherapy alone in advanced non-small cell lung cancer with acquired resistance to EGFR tyrosine kinase inhibitors. Oncologist 2013; 18:1214-20.

17. Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. Sci Transl Med 2011; 3:75ra26.

18. Rosell R, Moran T, Queralt C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med 2009; 361:958-67.

19. Pao W, Miller VA, Politi KA, et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. PLoS Med 2005; 2:e73.

20. Sharma SV, Bell DW, Settleman J, Haber DA. Epidermal Growth Factor Receptor Mutations in Lung Cancer. Nat Rev Cancer 2007; 7:169-81.

21. Sequist LV, Besse B, Lynch TJ, et al. Neratinib, an irreversible pan-ErbB receptor tyrosine kinase inhibitor: Results of a Phase II trial in patients with advanced non-small-cell lung cancer. J Clin Oncol 2010; 28:3076-83.

22. Yu HA, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. Clin Cancer Res 2013; 19:2240-7.

23. Walter AO, Sjin RT, Haringsma HJ, et al. Discovery of a mutant-selective covalent inhibitor of EGFR that overcomes T790M-mediated resistance in NSCLC. Cancer Discov. 2013; 3:1404-15.

24. National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03. Available at < http://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf>. Accessed 04 May 2015.

25. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012; 366:2455-65.

26. Topalian SL, Hodi FS, Brahmer, JR, et al. Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer. N Engl J Med 2012; 366:2443-54.

27. Stagg J, Loi S, Divisekera U, et al. Anti-ErbB-2 mAb therapy requires type I and II interferons and synergizes with anti-PD-1 or anti-CD137 mAb therapy. Proc Natl Acad Sci USA 2011; 108:7142-7.

14 APPENDICES

Appendix A: Response Evaluation Criteria in Solid Tumor (RECIST) Version 1.1

The RECIST guidelines (Version 1.1) are described in Eisenhauer (2009) 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 (longestameter 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 (longest diameter < 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 exam 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 longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (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 overall 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 antitumor 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 partial response 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

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; 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

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; NE, Not evaluable.

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) before confirming the CR status.

Confirmatory Measurement/Duration of Response

Confirmation

Radiographic tumor assessments are required every 6-9 weeks (see Table 1). If an initial CR or PR is noted, confirmatory scans must be performed 4-6 weeks 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 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.

Reference:

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228-247.

Appendix B: Modified RECIST Incorporating Immune-Related Response Criteria

Conventional response criteria may not be adequate to characterize the antitumor activity of immunotherapeutic agents like MPDL3280A, which can produce delayed responses that may be preceded by initial apparent radiological progression, including the appearance of new lesions. Therefore, modified response criteria have been developed that account for the possible appearance of new lesions and allow radiological progression to be confirmed at a subsequent assessment. In this protocol, patients will be permitted to continue study treatment even after modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria for progressive disease are met if the benefit-risk ratio is judged to be favorable.

These modified criteria are derived from RECIST version 1.1 (v1.1) conventions and immune-related response criteria (irRC).

Modified RECIST and RECIST, Version 1.1: Summary of Changes

	RECIST v1.1	Modified RECIST
New lesions after baseline	Define progression.	New measurable lesions are added into the total tumor burden and followed.
Non-target lesions	May contribute to the designation of overall progression	Contribute only in the assessment of a complete response
Radiographic progression	First instance of ≥ 20% increase in the sum of diameters or unequivocal progression in non-target disease	Determined only on the basis of measurable disease; may be confirmed by a consecutive assessment ≥ 4 weeks from the date first documented

RECIST = Response Evaluation Criteria in Solid Tumors.

Definitions of Measurable/Nonmeasurable Lesions

All measurable and nonmeasurable lesions should be assessed at screening and at the protocol-specified tumor assessment time points. Additional assessments may be performed, as clinically indicated for suspicion of progression.

Measurable Lesions

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

- 10 mm by CT or MRI scan (CT/MRI scan slice thickness/interval no greater than 5 mm);
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable).

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow up, only the short axis will be measured and followed.

Nonmeasurable Lesions

Nonmeasurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 but < 15 mm), as well as truly nonmeasurable lesions. Lesions considered truly nonmeasurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions

Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques for measuring 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 non-measurable) since they are, by definition, simple cysts.

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

Lesions with Prior Local Treatment

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

Tumor Response Evaluation

Definitions of Target/Non-target Lesions

Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is > 10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition, should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance, the next largest lesion that can be measured reproducibly should be selected.

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

Lesions irradiated within 3 weeks prior to Cycle 1, Day 1 may not be counted as target lesions.

Non-target Lesions

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required.

It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (eg, “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

After baseline, changes in non-target lesions will contribute only in the assessment of complete response (ie, a complete response is attained only with the complete disappearance of all tumor lesions, including non-target lesions) and will not be used to assess progressive disease.

Calculation of Sum of the Diameters

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated as a measure of tumor burden.

The sum of the diameters is calculated at baseline and at each tumor assessment for the purpose of classification of tumor responses.

Sum of the Diameters at Baseline: The sum of the diameters for all target lesions identified at baseline prior to treatment on Day 1.

Sum of the Diameters at Tumor Assessment: For every on-study tumor assessment collected per protocol or as clinically indicated, the sum of the diameters at tumor assessment will be calculated using tumor imaging scans. All target lesions and all new measurable lesions that have emerged after baseline will contribute to the sum of the diameters at tumor assessment. Hence, each net percentage change in tumor burden per assessment with use of modified RECIST accounts for the size and growth kinetics of both old and new lesions as they appear.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Lymph nodes that shrink to < 10 mm short axis are considered normal.

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

Note: The appearance of new measurable lesions is factored into the overall tumor burden but *does not automatically qualify as progressive disease* until the sum of the diameters increases by ≥ 20% when compared with the sum of the diameters at nadir.

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

Progressive Disease (PD): At least a 20% increase in the sum of diameters of all target and all new measurable 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.

Impact of New Lesions on Modified RECIST

New lesions alone do not qualify as progressive disease. However, their contribution to total tumor burden is included in the sum of the diameters, which is used to determine the overall modified RECIST tumor response.

Evaluation of Best Overall Response Using modified RECIST

Timepoint Response

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

Modified RECIST Time point Response Definition

% Change in Sum of the Diameters (Including Measurable New Lesions When Present)	Target Lesion Definition	Non-target Lesion Definition	New Measurable Lesions	New Unmeasurable Lesions	Overall Modified RECIST Timepoint Response
- 100% [a]	CR	CR	No	No	CR
- 100% [a]	CR	Non-CR or not all evaluated	No	No	PR
≤ - 30%	PR	Any	Yes or no	Yes or no	PR
> - 30% to < + 20%	SD	Any	Yes or no	Yes or no	SD
Not all evaluated	Not evaluated	Any	Yes or no	Yes or no	NE
≥ + 20%	PD	Any	Yes or no	Yes or no	PD

CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

[a] When lymph nodes are included as target lesions, the % change in the sum of the diameters may not be 100% even if complete response criteria are met since a normal lymph node is defined as having a short axis of < 10 mm. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm in order to meet the definition of CR.

Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow up only two lesions were assessed but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion

Best Overall Response: All Time Points

The best overall response is determined once all the data for the patient are known. The best overall response according to modified RECIST is interpreted as below:

- **CR**: Complete disappearance of all tumor lesions (target and non-target) and no new measurable or unmeasurable lesions, confirmed by a consecutive assessment ≥ 4 weeks from the date first documented. All lymph nodes short axes must be < 10 mm.
- **PR**: Decrease in the sum of the diameters of all target and all new measurable lesions ≥ 30% relative to baseline, in the absence of CR, confirmed by a consecutive assessment ≥ 4 weeks from the date first documented.
- **SD**: Criteria for CR, PR, and PD are not met.
- **PD**: Increase in the sum of the diameters of all target and all new measurable lesions ≥ 20% relative to the nadir, which may be confirmed by a consecutive assessment ≥ 4 weeks from the date first documented as follows:

The confirmatory assessment shows an additional measurable increase in tumor burden as measured by the sum of the diameters of all target and all new measurable lesions.

This protocol allows patients to continue to receive study treatment even after confirmed radiographic PD per modified RECIST, and patients may achieve a best overall response of PR or CR based on tumor regression achieved at any time prior to study treatment discontinuation.

Appendix C: Eastern Cooperative Oncology Group Performance Status Scale

ECOG Performance Status	
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (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 D: QT Interval on Electrocardiogram Corrected Using the Fridericia's Formula (QTcF)

Fridericia's formula used to correct QT interval for heart rate is:

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

where QT_CF is the QT interval corrected for heart rate, RR is the interval from the onset of one QRS complex to the onset of the next QRS complex, measured in seconds, often derived from the heart rate (HR) as 60/HR, and QT is the QT interval measured in milliseconds.

Reference:

Fridericia LS. Die Systolendauer im Elektrokardiogramm bei normalen Menschen und bei Herzkranken. Acta Med Scand 1920; 53: 3469-486.

Appendix E: Pre-Existing Autoimmune Diseases

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below will be excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (eg, acute Lyme arthritis). Please contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Acute disseminated encephalomyelitis Addison's disease Ankylosing spondylitis Antiphospholipid antibody Syndrome Aplastic anemia Autoimmune hemolytic anemia Autoimmune hepatitis Autoimmune hypoparathyroidism Autoimmune hypophysitis Autoimmune hypothyroidism [a] Autoimmune myocarditis Autoimmune oophoritis Autoimmune orchitis Autoimmune thrombocytopenic purpura Behcet's disease Bullous pemphigold Chronic inflammatory demyelinating polyneuropathy Chung-Strauss syndrome Crohn's disease Dermatomyositis	Diabetes mellitus Type 1 [a] Dysautonomia Epidermolysis bullosa acquista Gestational pemphigoid Giant cell arteritis Glomerulonephritis Goodpasture's syndrome Graves' disease Guillain-Barré syndrome Hashimoto's disease IgA nephropathy Immune-mediated ocular disease (eg, uveitis, episcleritis, iritis) Inflammatory bowel disease Interstitial cystitis Kawasaki's disease Lambert-Eaton myasthenia syndrome Lupus erythematosus Lyme disease - chronic Meniere's syndrome Mooren's ulcer Morphea Multiple sclerosis Myasthenia gravis Myasthenia gravis	Myositis Neuromyotonia Opsoclonus myoclonus syndrome Optic neuritis Ord's thyroiditis Pemphigus Pernicious anemia Polyarteritis nodusa Polyarthritis Polyglandular autoimmune syndrome Primary biliary cirrhosis Psoriasis Reiter's syndrome Rheumatoid arthritis Sarcoidosis Scleroderma Sjögren's syndrome Stiff-Person syndrome Takayasu's arteritis Ulcerative colitis Vasculitis Vogt-Kovanagi-Harada disease Wegener's granulomatosis

[a] Patients with a history of Type 1 diabetes on a stable anti-hyperglycemic regimen or autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone are eligible for this study.

Appendix F: Anaphylaxis Precautions

EQUIPMENT NEEDED

- Tourniquet;
- Oxygen;
- Epinephrine for subcutaneous, IV, and/or endotracheal use in accordance with standard practice;
- Antihistamines;
- Corticosteroids;
- Intravenous infusion solutions, tubing, catheters, and tape.

PROCEDURES

In the event of a suspected severe or life-threatening anaphylactic reaction during study drug infusion, the following procedures should be performed:

1. Stop the study drug infusion.
2. Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. Do not obstruct arterial flow in the limb.
3. Maintain an adequate airway.
4. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
5. Continue to observe the patient and document observations.

Appendix G: New York Heart Association Classification of Functional Cardiac Capacity

Class	Description
I	No limitation: Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation.
II	Slight limitation of physical activity: Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina.
III	Marked limitation of physical activity: Although patients are comfortable at rest, less than ordinary physical activity will lead to symptoms.
IV	Inability to carry on physical activity without discomfort: Symptoms of congestive heart failure are present even at rest. With any physical activity, increased discomfort is experienced.

From: Criteria Committee, New York Heart Association, Inc. Diseases of the heart and blood vessels. Nomenclature and criteria for diagnosis. 6th ed. Boston, Little, Brown and Co, 1964:114.

Appendix H: The Modified Toxicity Probability Interval (mTPI) Method

The modified toxicity probability interval methodology is described in detail in Ji et al, 2010, and Ji et al, 2013. A short summary is given below.

Dose-finding method:

The mTPI design employs a simple beta-binomial hierarchical model. Decision rules are based on calculating the probability of three outcomes corresponding to underdosing, proper dosing, and overdosing in terms of toxicity.

Consider d dose levels of a certain cytotoxic drug in a phase 1 trial. Let p_i be the unknown probability of toxicity associated with the i-th dose, I = 1, . . . , d. The toxicity probability usually increases with the dose level, so we assume $p_1 < p_2 <. . .< p_d$. Suppose that dose i is currently used for treating patients and n_i ($n_i \geq 1$) patients have been treated at this dose. Suppose x_i ($x_i \leq n_i$) patients experienced toxicity. Based on the observed values of x_i and n_i, we assume that physicians choose one of the following three decisions:

1. de-escalate (D) to the next lower dose (i-1);
2. stay (S) at the same dose i; or
3. escalate (E) to the next higher dose (i+1).

Depending on the decision, the next cohort is treated at dose j which can be one of the 3 doses {i-1, i, i+1}; the values of x_j and n_j are then observed for the new cohort, and an appropriate decision is chosen once again. The trial thus proceeds with the next cohort.

These additional rules are important for practical concerns:

- Safety rule 1 (early termination): Suppose that dose 1 has been used to treat patients. If there is greater than a 95% probability that toxicity with dose 1 is greater than the target toxicity level (33%), then terminate the trial due to excessive toxicity.
- Safety rule 2 (dose exclusion): Suppose that the decision is E, to escalate from dose i to (i+1). If there is greater than 95% probability that toxicity with dose i+1 is greater than the target toxicity level (33%), then treat the next cohort of patients at dose i and exclude doses (i+1) and higher from the trial, that is, these doses will never be used again in the trial.
- At the end of the trial, select as the MTD, the dose with the estimated probability of toxicity closest to 33%.

Implementation of the mTPI in Study CO-1686-018:

The decision table for escalating, reducing or maintaining the same dose is based on algorithm provided by Ji et al, 2010, with the following 3 inputs:

1. Maximum of 14 patients treated at any dose
2. Target toxicity probability of 33%
3. Equivalence interval of 5% so that any dose with an estimated probability of toxicity in the interval [28%, 38%] can be selected as the MTD

References:

Ji Y, Liu P, Li Y, Bekele BN. A modified toxicity probability interval method for dose-finding trials. Clin Trials. 2010;7:653-63.

Ji Y and Wang S-J. Modified Toxicity Probability Interval Design: A Safer and More Reliable Method Than the 3+3 Design for Practical Phase 1 Trials. J Clin Oncol 2013;31:1785-91.

Cohort Decision Table

Number of patients treated at current dose

Number of dose limiting toxicities (DLT's)	1	2	3	4	5	6	7	8	9	10	11	12	13	14
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	S	S	S	S	E	E	E	E	E	E	E	E	E
2		DU	D	S	S	S	S	S	S	E	E	E	E	E
3			DU	DU	D	S	S	S	S	S	S	S	S	S
4				DU	DU	DU	D	S	S	S	S	S	S	S
5					DU	DU	DU	DU	D	S	S	S	S	S
6						DU	DU	DU	DU	DU	D	S	S	S
7							DU	DU	DU	DU	DU	DU	D	S
8								DU	DU	DU	DU	DU	DU	DU
9									DU	DU	DU	DU	DU	DU
10										DU	DU	DU	DU	DU
11											DU	DU	DU	DU
12												DU	DU	DU
13													DU	DU
14														DU

E = Escalate to the next higher dose

S = Stay at the current dose

D = De-escalate to the next lower dose

U = The current dose is unacceptably toxic

MTD=33%

Sample size = 14