STUDY RAIN-701

A Phase 2 Study of Tarloxotinib in Patients with Select Gene Alterations and Non-Small Cell Lung Cancer or Other Advanced Solid Tumors

Sponsor:	Rain Therapeutics Inc. 8000 Jarvis Avenue Suite 204 Newark, CA 94560 USA
Sponsor Protocol No.:	RAIN-701
U.S. IND No.:	112290
Study Drug Name:	Tarloxotinib bromide
Phase:	2
Date of Protocol:	14 December 2018 06 March 2019 (Amendment 1) 17 June 2019 (Amendment 2) 11 November 2019 (Amendment 2.1) 24 October 2020 (Amendment 3)

This study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki and with other applicable regulatory requirements

DOCUMENT HISTORY

Version	Replaces	Description of Changes
Amendment 3 24 October 2020	Amendment 2.1 11 November 2019	The protocol was amended to: • Revise the protocol title to reflect the additions of Cohorts B1 and D • Revise the protocol synopsis to align with changes made in the following sections of the protocol • Revise the Schedule of Events to add smoking history, clarify the QTcF criteria for ECGs, and add the allowable window for radiographic tumor assessments (every 8 weeks [± 5 days]) • Section 2: o Revise section headings for clarity o Section 2.3.1: Add data on tarloxotinib-E potency in Ba/F3 cells with EGFR and HER2 mutations o Section 2.4.1: Add further rationale for the patient population chosen for the study, based on preclinical data • Section 3: Revise text to reflect the addition of Cohorts B1 and D • Section 4: o Add Cohorts B1 and D o Increase the number of total patients enrolled from 91 patients to 248 patients to yield 215 evaluable patients (43 patients per cohort), as shown in Table 3 o Update table of eligible mutations and gene fusions (Table 4) o Clarify the allowable window for radiographic tumor assessments (Every 8 weeks [± 5 days]) • Section 5: Revise to add Cohorts B1 and D, and clarify the eligible mutations/gene fusions • Section 5.1: o Revise inclusion criteria #3 to #5 to add Cohorts B1 and D o Revise inclusion criterion #9 to require a calculated creatinine clearance ≥ 30 mL/min using Cockcroft-Gault equation

		○ Revise inclusion criterion #10 to remove requirement for 3 ECG measurements ○ Revise inclusion criterion #14 and add inclusion criterion #15 to clarify contraception requirements. • Section 5.2: ○ Revise exclusion criterion #1 to add the following note for clarification: *If another mutation is present but is deemed to be a tumor suppressor mutation or a variant of unknown significance then the patient may be enrolled with Sponsor approval of the mutation report.* ○ Revise exclusion criterion #2 to reflect the addition of Cohorts B1 and D ○ Revise exclusion criterion #4 to change the allowable period of time since another investigational therapy from 28 days to 21 days and add the following note for clarification: *Exceptions may be made with Medical Monitor approval for investigational therapies where the half-life is unknown or shorter than 5 half-lives have passed between last dose of investigational therapy and Cycle 1 Day 1.* ○ Revise exclusion criterion #5 for interstitial lung disease or interstitial pneumonitis to allow patient enrollment if there is documented resolution ○ Revise exclusion criterion #7 to add exceptions for certain patients with central nervous system malignancies and stipulate that patients must complete stereotactic radiosurgery 7 days prior to Cycle 1 Day 1 and whole brain radiotherapy 21 days prior to Cycle 1 Day 1. ○ Revise exclusion criterion #8 to add the following clarification note for medications associated with QT prolongation: *Exceptions may be made with Medical Monitor approval (e.g., for medications where the half-life is unknown or for QT prolonging medications not listed in Appendix B).* • Section 5.3: ○ Specify that > 2 dose reductions is a reason for discontinuation from study treatment ○ Specify that missing 2 doses is a reason for discontinuation from study treatment unless there is agreement with the Medical Monitor ○ Add guidance for recording patient withdrawals due to COVID-19

		• Section 6.2.3: Clarify text for handling dose delays and missed doses of tarloxotinib. Added instructions for what to do in the event of dose delays due to COVID-19. • Section 6.4: Revised guidance for potassium supplementation and specified that tarloxotinib will not be administered if the serum potassium level is < 3.5 mEq/L. • Section 6.5: Revise treatment and retreatment criteria according to: o QTcF levels (e.g., ≥ 601 msec and ≥ 501 msec and < 601 msec) observed during previous infusion o Serum electrolytes • Section 6.6: Add the text, *Patients may receive palliative radiation to disease sites of progression, including brain metastases, following discussion with and approval by the Medical Monitor (or designee).* • Sections 6.7 and 6.7.1: Revise the thresholds for QTcF prolongation to better align with NCI CTCAE criteria • Section 6.9.1: Revise to align with the Schedule of Events • Section 6.9.2.1: Added this subsection to specify the ECG guidance • Section 7: Revised to reflect the allowable window for radiographic tumor assessments (Every 8 weeks [± 5 days]) • Section 8.1.1.5: Removed mandatory reporting of SAEs of QTc prolongation to Health Canada. • Section 8.5: Revise text to align with the NCI CTCAE grading for QTc prolongation and clarify that only Grade 3 events of QTc prolongation require expedited reporting. • Section 8.7: Remove the requirement for 3 ECG tracings and clarify the requirements for ECGs in patients with QT prolongation during a previous infusion • Section 8.10: Text revised to specify that male patients must use a condom and refrain from sperm donation during the study and for at least 30 days after the last dose of study treatment • Section 8.13: Revise the window for PK blood samples from 5 minutes to 5 or 10 minutes • Section 9.1: Modify text to reflect that all cohorts will use a Simon's 2-stage minimax design • Section 9.2.3: Revise text to specify which patients are considered evaluable for response: o *All enrolled patients who receive study treatment, have a baseline tumor assessment with documentation of measurable disease, have at least 1 on-study tumor assessment, whether or not this occurs at the specified imaging interval, and have no major protocol violations including*

		inclusion/exclusion criteria or prohibited concomitant medication while on study, will be considered evaluable for response. Patients who are treated and removed from study prior to on-study tumor assessments for reasons other than clinical progression will be considered unevaluable for response and may be replaced. In addition, if a patient is enrolled without central laboratory confirmation of the specific gene alteration, and then is subsequently found not to have the specific gene alteration by central review, this patient will not be included in the efficacy evaluable (evaluable for response) population. • Section 9.6.1.2: Revise statistical methods to clarify how analyses will be conducted with respect to efficacy evaluable patients. • Section 9.7.1: Revise QTc interval thresholds to align with the NCI CTCAE grading for QTc prolongation • Section 11.3: Extend the expected study duration from 24 months to 36 months to allow for 24 months of accrual • Section 12: Revise wording to allow for remote monitoring • Section 14: Updated reference list to reflect citations added. • Appendix B: Update the list of medications with a known risk for TdP • Include additional minor changes for clarity and consistency

Amendment 2.1 11 November 2019	Amendment 2 17 June 2019	The protocol was amended to: • Section 4: Modify total number of patients to 83 (20 patients in Cohorts A and B and 43 patients in Cohort C) and add that Cohort C will use a Simon 2-stage design • Section 4.2.1 Increase confirmation of primary endpoint from 4 weeks to 8 weeks after initial documentation • Section 5.1: Add details of prior therapy for Cohort C • Section 5.2: Add exclusion criteria for upper limit of ALT, AST, and bilirubin values • Section 6.7: Clarify treatment guidelines for QTc prolongation • Section 8.5: Clarify reporting procedures for QTc prolongation • Section 9.1: Add determination of Cohort C sample size • Include additional minor changes for clarity and consistency
Amendment 2 17 June 2019	Amendment 1 01 March 2019	The protocol was amended to: • Revise the protocol title to reflect the addition of Cohort C • Add new Section 2.2.2: Add study population background and rationale for the inclusion of patients with solid tumors and NRG1/HER-family gene fusions (Cohort C) • Section 4 (and throughout): Include a 3rd cohort (Cohort C) of patients with advanced solid tumors that harbor NRG1 or HER-family gene fusions • Section 4: Modify total number of patients to 60 (20 patients each in Cohorts A, B, and C) and add that Cohort C will use a Simon's 2-stage design • Section 5: Expand Table 3 to include NRG1 and HER-family gene fusions • Section 5.1: Add details of prior therapy for Cohort C • Section 6.4: Revise potassium supplementation guidelines. • Section 6.7: Provide further description of the QTc prolongation observed in prior tarloxotinib studies and clarify treatment guidelines for QTc prolongation • Section 6.9.2: Clarify that a window of ± 10 minutes is acceptable for all timed assessments relative to infusions

		• Section 6.9.2: Clarify that the optional tumor biopsy may be performed after any study treatment infusion in consenting patients • Created new Section 8.1.1.5: Move the information on SUSAR reporting timeframe out of Section 8.3 (SAEs) • Section 8.5: Clarify reporting procedures for QTc prolongation • Section 9.1: Add determination of Cohort C sample size • Additional minor changes were made for clarity and consistency.
Amendment 1 06 March 2019	Original Protocol 14 December 2018	Following review and comments by Health Canada, the following edits were made to the protocol and a revised document submitted to Health Canada: • Section 2.9: To add text regarding symptoms associated with QT prolongation and language regarding limiting sun exposure due to potential phototoxicity • Section 4.1, Section 4.4, Section 5.3: To add text specifying that hepatotoxicity meeting Hy's Law criteria is defined as unacceptable toxicity • Section 5.2: To clarify Exclusion Criteria #7 to exclude all medications that prolong QT interval, with a risk of causing Torsade de Pointes (TdP) regardless of stable dose • Section 6.7.3, Table 8: To add the following, tarloxotinib will be permanently discontinued for tarloxotinib-related toxicity meeting the definition of Hy's Law • Section 6.10.1: To add text stating that all medications that prolong QT interval, with a risk of causing Torsade de Pointes (TdP) regardless of stable dose at study entry are prohibited • Section 8.1, Section 8.2.3: To state that all adverse events will be followed until stabilization or resolution • Section 8.3: To state that Rain Therapeutics will report all serious unexpected adverse drug reactions to regulatory agencies per local requirements and that all serious QT prolongations will be reported to Health Canada • Section 12.4: To add a statement that Rain Therapeutics will maintain copies of study records for a period of no less than 25 years • Schedule of Events (Appendix A): Correction of typographical error regarding Footnote 2 and Footnote 3. In addition, the protocol was amended to: o Allow baseline labs to be obtained within 7 days rather than 3 days before Cycle 1 Day 1

		○ Remove the requirement of triplicate ECGs being obtained and transmitted to a central reader; triplicate ECGs will be replaced by a single locally read ECG ○ Remove ECOG assessments after eligibility determination • Additional minor edits may have been made for clarity and consistency.

STATEMENT OF THE SPONSOR

Protocol Title: **A Phase 2 Study of Tarloxotinib in Patients with Select Gene Alterations and Non-Small Cell Lung Cancer or Other Advanced Solid Tumors**

This study was designed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and is consistent with Good Clinical Practice (GCP) and applicable regulatory requirements. Foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial patient and society. Review of the available nonclinical and clinical information support this study and the anticipated benefits justify the risks.

The rights, safety, and well-being of the trial patients are the most important consideration. While foreseeable risks have been identified, strategies are included to help mitigate both anticipated and unanticipated risks.

This clinical trial is scientifically sound, and the study design is clearly described in this document.

Lucio Tozzi
VP, Head of Clinical Operations
Rain Therapeutics Inc.

Date

Robert C Doebele, MD, PhD
Acting Chief Medical Officer
Rain Therapeutics Inc.

Date

SYNOPSIS

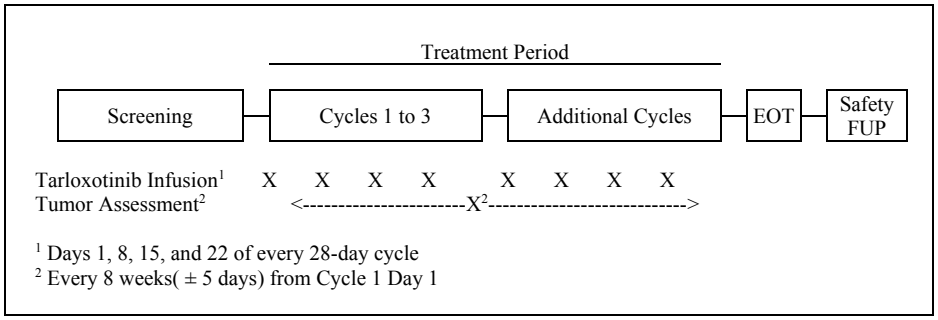
Study Number	RAIN-701
Sponsor	Rain Therapeutics Inc.
Phase	2
Objectives	Primary Objective • The primary objective of this study is to evaluate the objective response rate (ORR) of tarloxotinib according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Secondary Objectives • To evaluate further measures of antitumor activity of tarloxotinib including best overall response (BOR), duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) • To investigate the pharmacokinetics (PK) of tarloxotinib and tarloxotinib-E using population PK (PopPK) methods and explore correlations between PK, exposure, response, and/or safety findings • To evaluate the safety and tolerability of tarloxotinib in this population including to determine whether there is an association between plasma exposure to tarloxotinib and effects on cardiac repolarization Exploratory Objectives • To evaluate the concordance of epidermal growth factor receptor (EGFR) mutation, ERBB2 (HER2) mutation, and NRG1, EGFR, ERBB2 (HER2), and ERBB4 (HER4) fusion detection between tissue and plasma using circulating tumor deoxyribonucleic acid (ctDNA) • To evaluate exploratory biomarkers of hypoxia in tumor tissue including 6 transmembrane epithelial antigen of the prostate, family member 4 (STEAP4) expression and ERBB family and cancer cell signaling pharmacodynamic markers • To evaluate the pharmacokinetics of tarloxotinib and tarloxotinib-E in tumor tissue
Study Design	This is a Phase 2 multicenter, open-label study to evaluate the antitumor effect of tarloxotinib in patients with: • Previously treated advanced/metastatic non-small cell lung cancer (NSCLC) who have a tumor harboring one of the following: o An EGFR exon 20 insertion (Cohort A) o A HER2-activating mutation (including HER2 exon 20 insertions) who have not received prior HER2-directed therapy (Cohort B) o A HER2-activating mutation (including HER2 exon 20 insertions) who have received prior HER2 antibodies or antibody-drug conjugates (Cohort B1) • Previously treated advanced solid tumors harboring: o NRG1 or ERBB/HER-family gene fusions (Cohort C) o HER2-activating mutations (including HER2 exon 20 insertions), excluding NSCLC (Cohort D) Cohorts B1 and/or D may not be pursued, at the discretion of the Sponsor. All cohorts will use a Simon's 2-stage minimax design. In the first stage, 21 patients will be accrued. If more than 3 patients in a cohort have a partial or complete response, up to

22 additional patients may be enrolled to the cohort, for up to a total of 43 patients per cohort. However, if there are 3 or fewer responses among these patients the cohort will be stopped based on futility. Patients who are not evaluable for tumor response assessment may be replaced.

Number of Patients by Cohort

Cohort	Description	N
A:	• Patients with advanced NSCLC harboring an EGFR exon 20 insertion mutation • Patients who have received at least 1 platinum-based chemotherapy-containing regimen	43
B:	• Patients with advanced NSCLC harboring a HER2-activating mutation • Patients who have received at least 1 platinum-based chemotherapy-containing regimen • Patients who have not received prior HER2-directed therapy	43
B1*:	• Patients with advanced NSCLC harboring a HER2-activating mutation • Patients who have received at least 1 platinum-based chemotherapy-containing regimen • Patients who have received prior HER2 antibodies or antibody-drug conjugates	43
C:	• Patients with advanced solid tumors who have failed all standard therapies appropriate for their tumor type and stage of disease, or, in the opinion of the Investigator, would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard-of-care therapy • Patients with tumors harboring an NRG1 gene fusion, EGFR gene fusion, EGFR kinase domain duplication, ERBB2 gene fusion, or ERBB4 gene fusion	43
D*:	• Patients with advanced solid tumors who have failed all standard therapies appropriate for their tumor type and stage of disease, or, in the opinion of the Investigator, would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard-of-care therapy • Patients with tumors (excluding NSCLC) harboring a HER2-activating mutation	43
	Total	215

*Cohorts B1 and/or D may not be pursued, at the discretion of the Sponsor.

Treatment	Tarloxotinib 150 mg/m^2 will be administered as a 1-hour intravenous (IV) infusion weekly until progressive disease or unacceptable toxicity. **Study Schema (Not to Scale)**  [1] Days 1, 8, 15, and 22 of every 28-day cycle [2] Every 8 weeks(± 5 days) from Cycle 1 Day 1 EOT = End-of-Treatment Visit; FUP = Follow-up Visit
Eligibility	**Inclusion Criteria** 1. ≥ 18 years old 2. Signed and dated written informed consent 3. Histologically and/or cytologically confirmed primary diagnosis of cancer a. Cohorts A, B and B1: NSCLC, (Stage IV, Stage IIIB, or IIIC) not amenable to definitive curative-intent therapy, or recurrent disease after prior diagnosis of Stage I-III disease **Note:** NSCLC staging is according to American Joint Committee on Cancer, 8th edition, lung cancer staging criteria. b. Cohort C and D: Locally advanced or metastatic solid tumor 4. Progression of disease on or after a platinum-based chemotherapy regimen (Cohorts A, B, and B1) or after standard of care (Cohorts C and D) a. Cohorts C and D: Must have received all standard therapy appropriate for their tumor type and stage of disease, or, in the opinion of the Investigator, would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard-of-care therapy **Note:** If it is determined by the Investigator that a patient would be unlikely to tolerate or derive clinically meaningful benefit from standard-of-care therapy, the specific reason(s) for such a determination will be documented in the electronic case report form. 5. CLIA diagnosis of cancer mutation or fusion a. Cohort A: EGFR exon 20 insertion mutation b. Cohort B, B1, and D: HER2-activating mutation c. Cohort C: NRG1 or ERBB family gene fusions 6. Must have at least 1 target lesion evaluable by RECIST v1.1 7. Eastern Cooperative Oncology Group performance status of 0 or 1 8. Minimum life expectancy of 3 months or more 9. Clinical laboratory values meeting the following criteria within the 7 days prior to Cycle 1 Day 1: a. Calculated creatinine clearance ≥ 30 mL/min using Cockcroft-Gault equation b. Total bilirubin • ≤ 1.5 x upper limit of normal (ULN) or • ≤ 3 x ULN in the presence of liver metastases c. Aspartate aminotransferase and alanine aminotransferase • ≤ 2.5 x ULN, • ≤ 5 x ULN, in the presence of liver metastases

d. Absolute neutrophil count ≥ 1,500 cells/μL
e. Hemoglobin ≥ 9 g/dL or 5.6 mmol/L
f. Platelet count ≥ 100,000/μL

10. Adequate cardiac function meeting all of the following electrocardiogram (ECG) criteria:
    a. No evidence of second- or third-degree atrioventricular block
    b. No clinically significant arrhythmia (i.e., pauses > 4 seconds, ventricular tachycardia of any duration, supraventricular tachycardia of > 4 beats/minute)
    c. QRS interval ≤ 110 msec
    d. QTc interval of < 450 msec as calculated according to Fridericia's formula ($QTcF = QT/[R \text{ to } R \text{ interval}]^{0.33}$)
    e. PR interval ≤ 200 msec (does not apply to people with chronic stable atrial fibrillation or atrial flutter as determined by the Investigator)
11. Adequate pretreatment tumor sample (125 μm of formalin-fixed paraffin embedded block or at least 8 to 10 prepared slides)

    Note: Tumor tissue should be from the most recent pretreatment biopsy; if only archival tissue from the initial biopsy is available, it is acceptable.

12. All toxicities from prior therapy (except alopecia and neuropathy) must have resolved to baseline or to ≤ Grade 2 according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 prior to Cycle 1 Day 1
13. For women of childbearing potential (WOCBP), documentation of negative serum pregnancy test (β-human chorionic gonadotropin) within 7 days prior to Cycle 1 Day 1

    Note: WOCBP is defined as fertile, following menarche and until becoming post-menopausal (no menses for 12 months without an alternative medical cause) unless permanently sterile (had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).

14. For WOCBP, agreement to use a highly effective method of contraception during the study and for at least 90 days after the last dose of study treatment

    Note: Highly effective birth control includes a) intrauterine device; b) oral, implantable or injectable combined hormonal (estrogen and progestogen containing) or progestogen-only contraceptive associated with inhibition of ovulation; c) intrauterine hormone-releasing system; or d) bilateral tubal occlusion, vasectomized partner, sexual abstinence.

15. For male patients, agreement to use a condom and a highly effective method of contraception during the study and for at least 30 days after the last dose of study treatment. Male patients should also refrain from sperm donation during this time period.
16. Willingness and ability to comply with scheduled visits and study procedures

Exclusion Criteria

1. Has another known activating oncogene-driver mutation, including, but not limited to KRAS, ALK, ROS1, RET, BRAF, NTRK1/2/3, MET, MEK1, NRAS, and HRAS.

   Note: If another mutation is present but is deemed to be a tumor suppressor mutation or a variant of unknown significance then the patient may be enrolled with Sponsor approval of the mutation report.

2. Cohorts A, B, B1, and D only: Previously received anti-EGFR or anti-HER2 tyrosine kinase inhibitors including but not limited to erlotinib, gefitinib, afatinib, dacomitinib, osimertinib, poziotinib, TAK788, nazartinib, lapatinib, or neratinib
3. Cohorts A and B only: Previously received anti-EGFR or anti-HER2 monoclonal antibodies or EGFR or HER2 antibody-drug conjugates including, but not limited

	to, cetuximab, necitumumab, panitumumab, trastuzumab, trastuzumab emtansine (TDM-1), or pertuzumab 4. Received other recent antitumor therapy including: a. Investigational therapy administered within the 21 days prior to Cycle 1 Day 1 or 5 half-lives, whichever is shorter. **Note:** Exceptions may be made with Medical Monitor approval for investigational therapies where the half-life is unknown or shorter than 5 half-lives have passed between last dose of investigational therapy and Cycle 1 Day 1. b. Any standard chemotherapy or radiation within 14 days prior to Cycle 1 Day 1 **Note:** Adequate time must have passed from the last treatment to first scheduled treatment in this study to clear the timeframe for actual or anticipated toxicities of such treatment c. Any immunotherapy (e.g., pembrolizumab, nivolumab, atezolizumab, or durvalumab) within 21 days prior to Cycle 1 Day 1 5. Clinically active or symptomatic interstitial lung disease (ILD) or interstitial pneumonitis. **Note**: A patient with a history of clinically significant ILD or radiation pneumonitis with documented resolution will be eligible for enrollment. 6. Has any of the following within 28 days prior to the first dose of study drug: • Alanine aminotransferase and aspartate aminotransferase > 3 × ULN if no hepatic metastases are present; > 5 × ULN if hepatic metastases are present • Total bilirubin > 1.5 × ULN; > 3 × ULN with direct bilirubin > 1.5 × ULN in the presence of Gilbert's syndrome 7. Untreated central nervous system (CNS) metastases and/or untreated/treated leptomeningeal disease. **Note:** Patients who require steroids for CNS metastases must be on a stable or tapering dose of corticosteroids for at least 2 weeks prior to Cycle 1 Day 1 to be eligible for the trial. If applicable, patients must complete stereotactic radiosurgery 7 days prior to Cycle 1 Day 1 and whole brain radiotherapy 21 days prior to Cycle 1 Day 1. 8. Receiving medication that prolongs QT interval, with a risk of causing Torsade de Pointes (TdP), per protocol Appendix B, unless one of the following criteria are met: a. Enrollment is allowed if discontinuation of such medication occurs at least 5 half-lives before Cycle 1 Day 1 OR b. The patient is on a stable dose of a concomitant medication listed in Appendix B, prior to study entry and Sponsor approval is obtained Note: Exceptions may be made with Medical Monitor approval (e.g., for medications where the half-life is unknown or for QT prolonging medications not listed in Appendix B). 9. Personal or familial history of Long QT Syndrome, sudden death, or TdP 10. History of significant cardiovascular disease, including: a. Cardiac failure New York Heart Association class III or IV or LVEF < 55% b. Myocardial infarction, severe or unstable angina within 6 months prior to enrollment c. TdP, ventricular arrhythmia (i.e., ventricular tachycardia or ventricular fibrillation) d. Clinically significant thrombotic or embolic events within 3 months prior to enrollment

	Note: Significant thrombotic or embolic events include but are not limited to stroke or transient ischemic attack. Catheter-related thrombosis is not a cause for exclusion. Diagnosis of deep vein thrombosis or pulmonary embolism is allowed. e. Any uncontrolled or severe cardiovascular disease 11. Known concurrent malignancy that is expected to require active treatment within 2 years or may interfere with the interpretation of the efficacy and safety outcomes of this study in the opinion of the treating Investigator and confirmed by the Medical Monitor **Note:** Prior malignancy that is at a low risk of progression or recurrence (e.g., superficial bladder cancer, non-melanoma skin cancers, or low-grade prostate cancer not requiring therapy) may be allowed after discussion and approval by the Medical Monitor. 12. Major surgery within 4 weeks prior to Cycle 1 Day 1 13. Infection requiring systemic treatment within the 7 days prior to Cycle 1 Day 1 14. History of severe allergic or anaphylactic reactions or hypersensitivity to compounds of similar chemical or biologic composition as tarloxotinib 15. Known human HIV infection or active hepatitis B or C 16. Women who are pregnant or breastfeeding 17. Any other medical condition (e.g., alcohol abuse) or psychiatric condition that, in the opinion of the Investigator, might interfere with the patient's participation in the trial or interfere with the interpretation of trial results
Criteria for Efficacy Evaluation	The primary efficacy endpoint is ORR, based on patients who had complete response or partial response or by RECIST v1.1 as determined by the Investigator. Secondary efficacy endpoints include: BOR, DOR, DCR, PFS and OS, as measured from the date of first study drug dose to the date of death by any cause.
Criteria for Safety Evaluation	Safety endpoints include the incidence of treatment-emergent AEs; changes in clinical laboratory parameters (hematology, serum chemistry, urinalysis, and serum pregnancy test), vital signs, and ECG parameters; physical examination results; and use of concomitant medications.
Statistical Methods	Analysis Populations • The Safety Population will consist of all patients who received at least 1 dose of tarloxotinib. The Safety Population will be the analysis population for the safety and primary efficacy analyses. Analysis • ORR and DCR will be summarized by cohort along the corresponding 2-sided 95% confidence intervals (CIs). • Time-to-event endpoints (DOR, PFS, and OS) will be summarized using the Kaplan-Meier method and displayed graphically when appropriate. Median event times and the corresponding 2-sided 95% CIs for each cohort will be provided. Kaplan-Meier estimates and survival curves will also be presented for each treatment group. • Incidence of treatment-emergent AEs and use of concomitant medications will be summarized descriptively by cohort and total. Results for clinical laboratory parameters, vital signs, ECGs, and physical examinations will be summarized by cohort and by study visits. Descriptive summary statistics in observed values as well as changes from baseline will be presented. In addition, thresholds of marked laboratory abnormalities based on NCI CTCAE v5.0 will be predefined for specific safety parameters.

Schedule of Events	SCR	Cycle 1 (Day)				Cycle 2 (Day)				Cycles 3+ (Day)				OBX	EOT	FUP
		1	8	15	22	1	8	15	22	1	8	15	22			
Informed Consent	X															
Eligibility	X															
Medical/Disease History/ Smoking History	X															
Demographics	X															
Physical Examination	X	X				X				X					X	X
ECOG	X	X														
Weight	X	X				X				X					X	X
Vital Signs	X														X	X
Pre-infusion		X	X	X	X	X	X	X	X	X	X	X	X			
EOI		X	X	X	X	X	X	X	X	X	X	X	X			
30, 60, and 90 min after EOI[†]		X	X	X	X	X	X	X	X	X	X	X	X			
Electrocardiogram (12-lead)[1]	X														X	X
Pre-infusion		X	X	X	X	X	X	X	X	X	X	X	X			
EOI		X	X	X	X	X										
1 h after EOI[†]		X	X	X	X	X										
2 h after EOI[†]		X	X	X	X	X	X	X	X	X	X	X	X			
3 h after EOI[†]		X	X	X	X	X										
4 h after EOI[†]		X	X	X	X	X	X	X	X	X	X	X	X			
hourly thereafter as needed[†]		X	X	X	X	X	X	X	X	X	X	X	X			
Hematology Panel	X	X				X				X					X	X
Serum Chemistry Panel	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Serum Potassium																
EOI		X				X										
3 h after EOI[†]		X				X										
Urinalysis	X	X	X	X	X	X				X						X
Pregnancy Test [2]	X	X				X				X					X	
PK Samples																
Pre-infusion[‡]		X				X										
EOI[‡]		X				X										
3 h after EOI[‡]		X				X										
7 h after EOI[‡]		X[3]														
at optional tumor biopsy														X[4]		
Biomarker Sample		X				X								X[4]	X	
Potassium Supplementation[5]		X	X	X	X	X	X	X	X	X	X	X	X			
Tarloxotinib Infusion		X	X	X	X	X	X	X	X	X	X	X	X			
Tumor Tissue	X															
Optional Tumor Biopsy				X[4]										X[4]	X[6]	
Tumor Assessment[7]	X	← Every 8 weeks (± 5 days) from Cycle 1 Day 1→														
Concomitant Medications	X	← Every Visit →												X	X	
Adverse Events Assessment		← Every Visit →												X	X	X

CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; EOT = End-of-Treatment Visit; FUP = Follow-up Visit; MRI = magnetic resonance imaging; OBX = optional biopsy; PET = positron emissions tomography; PK = pharmacokinetic; QTcF = corrected QT interval as calculated according to Fridericia's formula; SCR = Screening Period

* Patients will be asked about their previous smoking history (including cigarettes, cigars, pipes, and vaping devices).

† For patients with Grade 3 QTcF prolongation (≥ 501 msec or > 60 msec increase compared to pre-infusion), repeat ECG every 15 to 30 minutes until resolved to Grade 2 (481 to 500 msec) or lower (≤480 msec) and then obtain ECGs every hour.

‡ Can be made ± 5 minutes (pre-infusion and EOT) and ± 10 minutes (3 hours and 7 hours) of scheduled event.

[1] = For patients with ≥ Grade 3 (≥ 501 msec) QTcF prolongation with current or prior infusion

[2] = Serum pregnancy at baseline, then urine dipstick, for women of childbearing potential

[3] = In a subset of patients

[4] = Collect blood (plasma samples for PK and biomarker including circulating tumor deoxyribonucleic acid) at time of biopsy

[5] = If applicable (see Section 6.4)

[6] = Collect blood (plasma sample for biomarker) at time of biopsy

[7] = Perform radiographic tumor assessments according to institutional practice; include CT or MRI of the chest and abdomen, brain scan, and bone scan at baseline. The baseline radiographic tumor assessment is required within 28 days prior to the first dose of tarloxotinib. A recently completed negative PET scan can be substituted for the baseline bone scan. The same imaging modality used for baseline imaging (i.e., CT or MRI) must be used for subsequent tumor assessments in each patient.

Note: Day 1 of Cycles 2+ is Day 29 of the prior cycle. The EOT Visit should be conducted within ± 7 days of the last dose of tarloxotinib, and the safety FUP should occur 30 days (± 7 days) after the last dose of tarloxotinib.

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LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
ADC	Antibody-drug conjugate
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BOR	Best overall response
BSA	Body surface area
CI	Confidence interval
C_{max}	Maximum peak plasma concentration
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CR	Complete response
CT	Computed tomography
DCR	Disease control rate
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EOI	End of infusion
EOT	End-of-Treatment Visit
FDA	Food and Drug Administration
FUP	Follow-up Visit
HED	Human effective dose
HER	Human epidermal growth factor receptor
IC_{50}	50% inhibitory concentration
IEC	Independent ethics committee
ILD	Interstitial lung disease
IND	Investigational New Drug
IP	Intraperitoneal
IRB	Institutional review board
IRR	Infusion-related reactions
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NRG1	Neuregulin 1
NSCLC	Non-small cell lung cancer

Abbreviation or Specialist Term	Explanation
ORR	Objective response rate
PD	Progressive disease
PK	Pharmacokinetic(s)
PP	Per Protocol
PR	Partial response
QTc	Corrected QT interval
QTcB	Corrected QTc interval as calculated according to Bazett's formula
QTcF	Corrected QTc interval as calculated according to Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SCC	Squamous cell carcinoma
SD	Stable disease
SEM	Standard error of the mean
STEAP4	Six transmembrane epithelial antigen of the prostate, family member 4
T790M	Mutation within exon 20 of EGFR substituting methionine for threonine at position 790
TdP	Torsade de Pointes
T-DXd	Trastuzumab deruxtecan
TGF-α	Transforming growth factor alpha
TKI	Tyrosine kinase inhibitor
ULN	Upper limit of normal
US	United States
WOCBP	Women of childbearing potential
WT	Wild type

1. INTRODUCTION

Tarloxotinib was designed and initially developed at the University of Auckland, New Zealand. The program was subsequently evaluated in the clinic by Proacta Inc. (as PR610) and later by Threshold Pharmaceuticals, Inc. (as TH-4000). Rain Therapeutics, Inc. is now developing tarloxotinib for the treatment of patients with advanced solid tumors with qualifying genetic mutations and/or fusions.

The first-in-human Phase 1 clinical trial investigated the safety and pharmacokinetics of tarloxotinib administered as a weekly 1-hour infusion to 27 patients with advanced solid tumors. Tarloxotinib doses ranged from 10 to 200 mg/m^2. A maximum tolerated dose (MTD) of 150 mg/m^2 was declared for the 1-hour infusion duration. A 24-hour duration was also evaluated for an improved toxicity profile, but none was observed with this extended infusion. The most common treatment-related adverse events (AEs) appeared to be dose-dependent and included skin rash, diarrhea, nausea and vomiting, QTc prolongation, and infusion-related reactions (see Section 2.3.2).

Two Phase 2 open-label studies were subsequently performed to evaluate the safety and preliminary efficacy of tarloxotinib administered as a 150 mg/m^2 weekly 1-hour infusion in patients with epidermal growth factor receptor (EGFR)-mutant, T790M-negative, advanced non-small cell lung cancer (NSCLC) that was resistant to EGFR tyrosine kinase inhibitors (TKIs), and in patients with recurrent or metastatic squamous cell carcinoma (SCC) of the head and neck or skin. These studies failed to show significant antitumor activity. Both trials enrolled a patient population unlikely to respond to EGFR inhibition (see Section 2.3.2). However, results from preclinical models with qualifying genetic mutations or fusions have suggested the potential for therapeutic benefit from tarloxotinib treatment in human cancers with few effective available therapies.

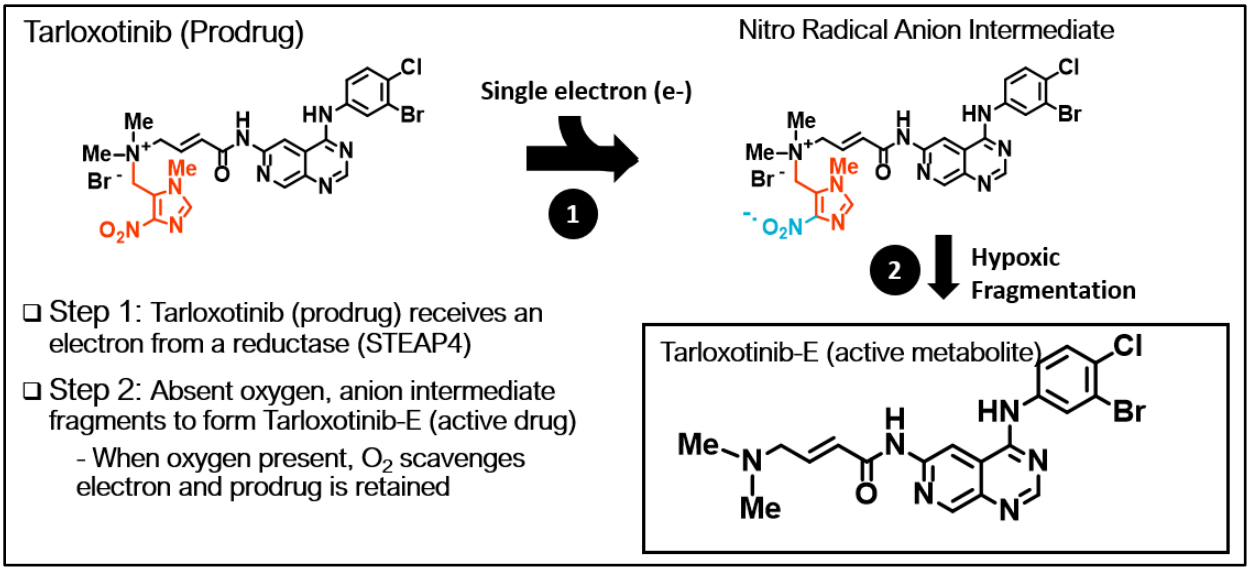
2. BACKGROUND INFORMATION

2.1 Investigational Product: Tarloxotinib

Tarloxotinib is a hypoxia-activated prodrug of a pan-ERBB (EGFR, HER2, and HER4) TKI. It is classified as a pan-ERBB TKI based on results of isolated enzyme kinase inhibition studies. Tarloxotinib is designed to be inactive under normal oxygen conditions (normoxia) but undergoes fragmentation under low oxygen conditions (hypoxia) to release the potent irreversible active metabolite (tarloxotinib-E) that has activity against both the normal/wild-type (WT) and mutant versions of the ERBB family.

Solid tumors demonstrate significant areas of hypoxia, which can lead to resistance to radiotherapy and chemotherapy (Muz 2015). Tarloxotinib was designed to exploit this characteristic to generate a therapeutic window; the prodrug selectively fragments under hypoxic conditions to release its active metabolite tarloxotinib-E, an irreversible EGFR/HER2 inhibitor (Figure 1). Tarloxotinib-E, once produced, may then diffuse to surrounding hypoxic and normoxic tumor tissue alike to exert its pharmacological action. A single reductase, STEAP4, is responsible for the first reduction step of the fragmentation process and is highly expressed in tumors that are also EGFR positive (Figure 1).

Figure 1: Structure of the Prodrug Tarloxotinib and Mechanism of Activation to Tarloxotinib-E



Selective production of tarloxotinib-E from tarloxotinib under hypoxic conditions in the tumor may allow delivery of higher, more effective concentrations of tarloxotinib-E to the tumor tissue with significantly reduced systemic tarloxotinib-E levels. Diminished systemic exposure of tarloxotinib-E is anticipated to lead to reduced WT EGFR inhibition and reduced WT EGFR-mediated toxicities than standard EGFR TKIs. This strategy is expected to broaden the therapeutic window translating to both improved efficacy and tolerability for patients, with minimal tarloxotinib-E generated in the gastrointestinal tract, skin, and other normoxic healthy tissues.

See Appendix A for tarloxotinib packaging, labeling, and storage instructions.

2.2 Study Diseases

2.2.1 Non-Small Cell Lung Cancer

Lung cancer is one of the most common solid tumors and is the leading cause of cancer-related death worldwide (World Health Organization 2018). In 2018, it is expected that there will be approximately 234,000 new cases of lung cancer, and approximately 154,000 deaths in the United States (US) (American Cancer Society 2018). NSCLC is the most common subtype, accounting for approximately 85% of all lung cancers (Heuvers 2012). Although early stages of the disease are potentially curable with surgery or chemoradiation, most lung carcinomas are diagnosed at an advanced stage, leading to a poor prognosis (Howington 2013). Treatment of advanced disease is in part segmented by the presence of certain molecular drivers that are targetable by approved drugs (e.g., EGFR-sensitizing mutations, anaplastic lymphoma kinase (ALK) fusions, ROS1 fusions, and BRAF V600E mutations). Therapy for patients in the EGFR-mutated segment of NSCLC has been well established over the past decade and will be further discussed in the following sections.

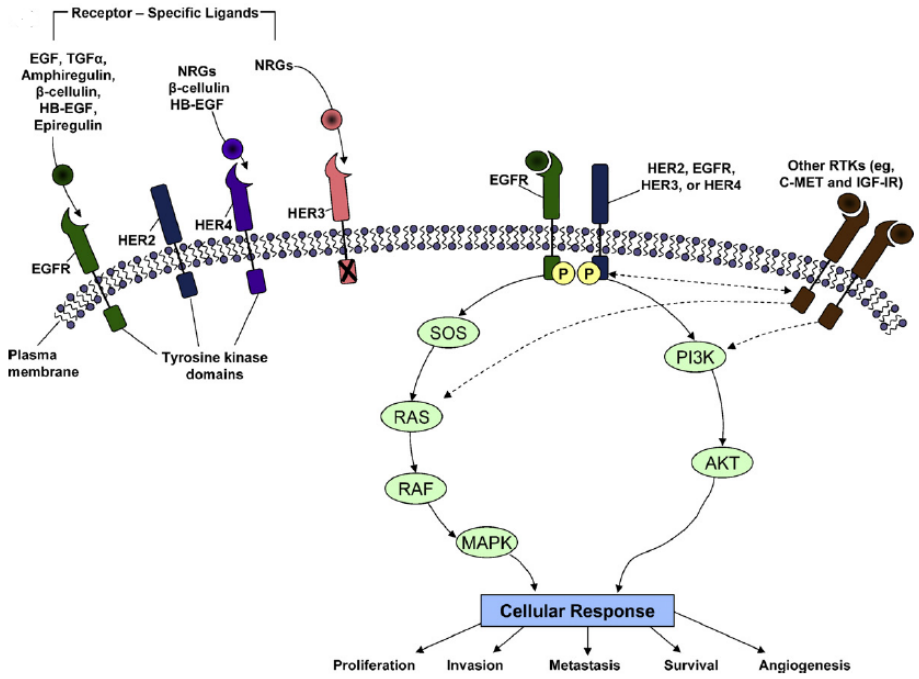
2.2.1.1 The ERBB Family of Receptors and Their Role in Cancer

The EGFR is a 170-kDa transmembrane protein that is widely expressed in several malignancies, including lung cancer (Doebele 2010). EGFR, also known as HER1 (ERBB1), is a member of a family of 4 closely related receptor tyrosine kinases that also include HER2/NEU (ERBB2), HER3 (ERBB3), and HER4 (ERBB4) (Gazdar 2009, Doebele 2010).

The ERBB (HER) family of receptors share important structural similarities across 4 extracellular domains (I through IV), a transmembrane domain, and intracellular domains consisting of a kinase domain and tyrosine phosphorylation sites in the carboxy-terminal tail (Doebele 2010).

Multiple ligands bind to the ERBB family of receptors with varying specificity (Figure 2), inducing ERBB receptor homodimerization (e.g., EGFR–EGFR) or heterodimerization (e.g., EGFR–HER2). HER2 has no known ligand but is the preferred binding partner of EGFR and the other ERBB family members (Doebele 2010).

Figure 2: EGFR and Downstream Signaling



Ligand-bound receptors form functionally active homodimers or heterodimers, resulting in the activation of downstream signaling pathways that promote cellular proliferation and survival. No known ligand exists for HER2, and HER3 has no functional TK activity. Other receptor TKs (e.g., IGF-1R, MET) can modulate EGFR downstream pathways.
EGFR = epidermal growth factor receptor; HB-EGF = heparin-binding epidermal growth factor; IGF-1R = insulin-like growth factor receptor-1; NRG = neuregulin; RTK = receptor tyrosine kinase; TGFα = transforming growth factor alpha; TK = tyrosine kinase.
Adapted from Doebele 2010

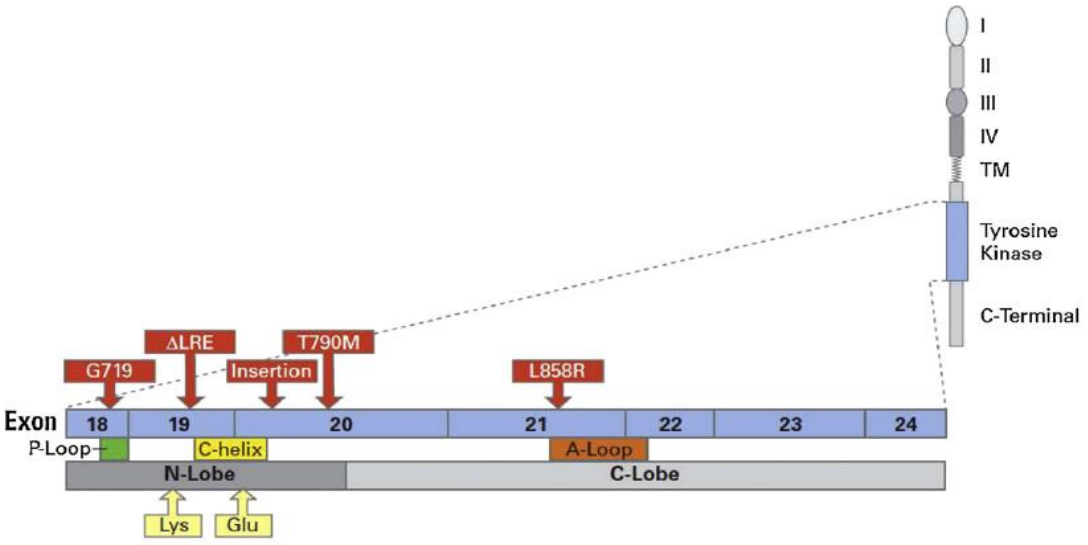
EGFR mutations shift the equilibrium of protein structures from an inactive to an active state, resulting in the increased and sustained phosphorylation of EGFR and other ERBB family

proteins without ligand stimulation (Kobayashi 2016). Downstream signaling networks controlled by ERBB family activation consist of several interconnected and overlapping pathways that regulate many physiological events including cell proliferation, apoptosis, angiogenesis, cell adhesion and motility, embryonic development, and organogenesis (Jacobi 2017). A broad range of cancers, including lung, breast, stomach, colorectal, head and neck cancers, have been associated with hyperactivation of these pathways via mutation or increased expression of members of the ERBB family of receptors (Jacobi 2017, Roskoski 2014).

2.2.1.2 EGFR and HER2 Mutations in NSCLC

Activating mutations in the EGFR kinase domain occur in 10% to 15% of patients with NSCLC in North American and European populations and in up to 40% among Asian populations (Lindeman 2013, Kobayashi 2016). Most mutations are present in the first 4 exons (18 to 21) that encode a portion of the EGFR kinase domain (Figure 3). Deletions in exon 19 and the L858R mutation in exon 21 are the most common, accounting for approximately 85% to 90% of all EGFR mutations (Kobayashi 2016, Takeda 2018). These "oncogene-addicted" tumors depend on the growth and survival signaling emanating from the EGFR.

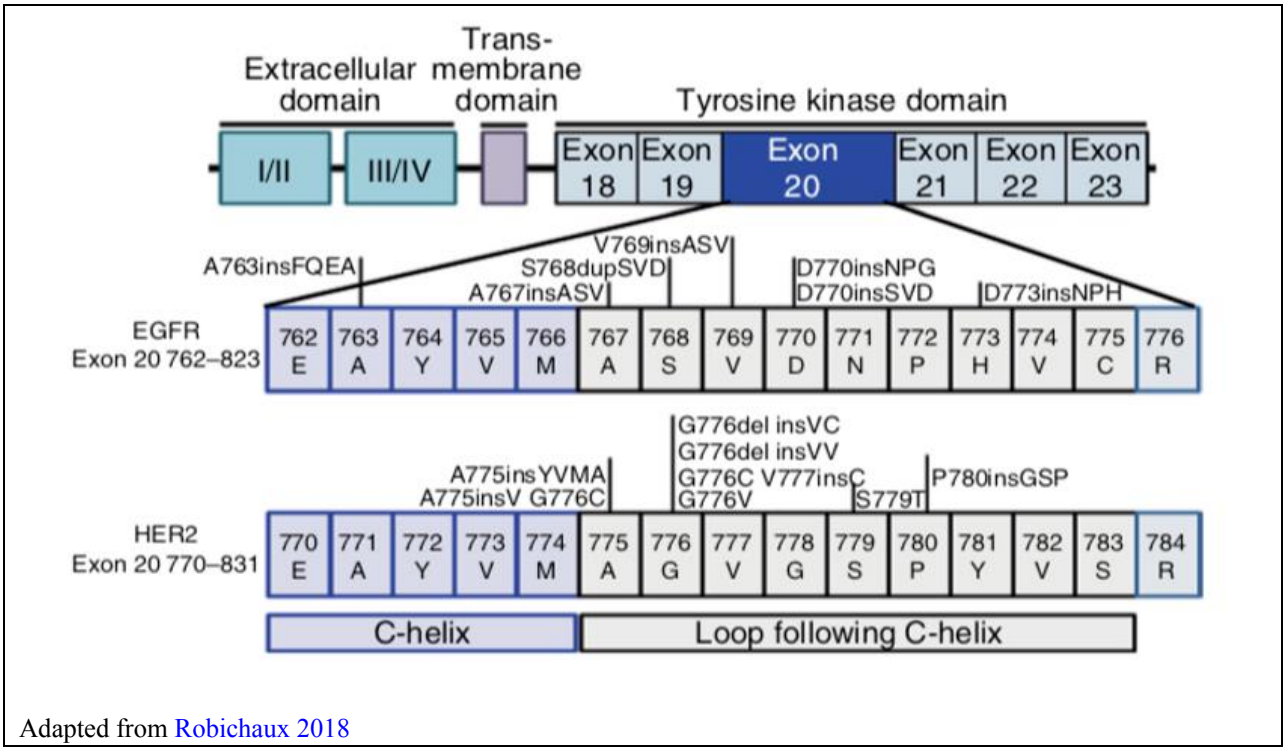
Figure 3: Schematic Representation of the Structure of EGFR with the Locations and Regions of Commonly Occurring Mutations in the EGFR Tyrosine Kinase Domain Shown in the Exon Boundary Map



Adapted from Doebele 2010

Insertions in exon 20 are the third most common family of EGFR mutations and account for approximately 5% to 9% of EGFR mutations (Oxnard 2013, Takeda 2018, Arcila 2013). They represent a combination of in-frame insertions and/or duplications of 3 to 21 base pairs, predominantly clustered between codons 767 and 774 (Figure 4) (Arcila 2013).

Figure 4: EGFR and HER2 Exon 20 Mutations



Adapted from Robichaux 2018

Mutations of the HER2 gene have also been identified as oncogenic drivers in NSCLC with a frequency of 2% to 3% (Takeda 2018). The most common mutations are in-frame insertions in exon 20 such as YVMA as well as substitutions at L755 and S310 (Chmielecki 2015). They are typically mutually exclusive with mutations in EGFR, KRAS, and BRAF, and rearrangements involving ALK and ROS1 (Lindeman 2018). The most common HER2 mutations consist of a 12-base pair duplication of codons 775 to 778 in-frame insertion encoding amino acids YVMA (Takeda 2018). They are more commonly observed in younger patients and patients with no smoking history (Lindeman 2018).

Together, EGFR exon 20 insertion and HER2 mutations are found in approximately 4% to 5% of all patients with NSCLC (Robichaux 2018).

2.2.1.3 Treatment of NSCLC Patients with Activating Mutations

International treatment guidelines now recommend molecular testing for all patients with NSCLC to assess the presence of EGFR-activating mutations (Lindeman 2018). The most recently updated guidelines published in 2018 recommend testing of EGFR, ALK, and ROS1 as an absolute minimum. A second group of genes including BRAF, MET, RET, ERBB2 (HER2) should be included in any expanded panel that is offered for lung cancer patients. KRAS testing may also be offered as a single-gene test to exclude patients from expanded panel testing (Lindeman 2018).

Successful oncogene-targeted therapies have been developed and approved for NSCLC that harbor the more common EGFR-activating mutations such as exon 19 deletions and exon 21 L858R mutations; however, there are currently no approved targeted therapies for patients with lung cancer harboring EGFR exon 20 insertion or HER2-activating mutations.

TKIs such as erlotinib, gefitinib, dacomitinib, afatinib, and osimertinib are directed at sensitizing mutations (and the T790M resistance mutation for osimertinib) in the EGFR gene by binding to the adenosine triphosphate (ATP)-binding pocket of EGFR and preventing ATP binding to this site (Kobayashi 2016). Approximately 70% of patients treated with TKIs experience an objective response, improved progression free-survival (PFS), and improved quality of life compared to those treated with chemotherapy alone (Robichaux 2018, Mok 2009, Rosell 2012, Soria 2018). Patients with HER2-activating mutations (most of which are located in exon 20) have shown responses to TKI (afatinib) treatment with an objective response rate (ORR) of 19% and disease control rate (DCR) of 69%; time to failure was 2.9 months (Peters 2018).

The structural changes of EGFR exon 19 and 21 mutations enable higher binding affinity of EGFR inhibitors as compared to WT EGFR. Additionally, EGFR exon 19 and 21 mutations are associated with lower binding affinity for ATP as compared to WT EGFR (Yasuda 2013). However, TKIs have been associated with dose-limiting toxicities due to simultaneous inhibition of WT EGFR (Sullivan 2017). Toxicities associated with WT EGFR inhibition in normal tissues include adverse skin and gastrointestinal events (Sullivan 2017).

Exon 20 EGFR insertion mutations are generally resistant to EGFR TKIs. In contrast to EGFR exon 19 and 21 mutations, EGFR exon 20 insertion mutations present binding affinity for ATP and for EGFR inhibitors more similar to WT EGFR (Yasuda 2013). *In vitro*, *in vivo*, and clinical data support the conclusion that standard first- and second-generation EGFR inhibitors such as erlotinib, gefitinib, and afatinib have suboptimal efficacy against the exon 20 insertion class of EGFR mutations; ORRs of approximately 3% to 8% have been reported to first-line therapy (Robichaux 2018). TKIs targeting HER2, such as afatinib, lapatinib, neratinib, and dacomitinib, also have limited activity in patients with HER2-mutant tumors, demonstrating ORRs of 12% or below in many studies (Robichaux 2018).

Approved treatment options for patients with exon 20 mutations in the first-line setting are limited to platinum-containing chemotherapy with or without bevacizumab or immune-checkpoint inhibitors. Single-agent pembrolizumab in first-line therapy, or other checkpoint inhibitors in second-line therapy, have emerged as treatment options especially in patients whose expression levels of the programmed cell death protein 1 ligand is elevated, however, EGFR mutations appear to be a negative predictive factor for clinical benefit (Garassino 2018, Gainor 2016). It is yet not known if the same negative correlation exists in patients with uncommon mutations (including exon 20 insertions). Retrospective data suggest patients with EGFR or HER2 exon 20 mutations are less likely to benefit from nivolumab therapy (Takeda 2018). Only 1 of 7 patients achieved a partial response (PR) despite seeing tumor proportion score of 50% in 2 patients, and 10%, 5%, 0% in 3 patients, respectively, while 2 patients had unknown scores.

2.2.2 Advanced Solid Tumors

Cancer is a leading cause of death worldwide, accounting for an estimated 9.6 million deaths in 2018. The most common cancers are: lung (2.09 million cases), breast (2.09 million cases),

colorectal (1.80 million cases), prostate (1.28 million cases), skin cancer (non-melanoma) (1.04 million cases), and stomach (1.03 million cases) (World Health Organization 2018). The molecularly targeted cancer therapies have resulted in improving the lives of a large number of cancer patients due to their specificity toward cancer cells while sparing toxicity to off-target cells (Gerber 2008).

Structural gene rearrangements resulting in gene fusions are frequent events in solid tumors. Gene fusions arise as a result of genomic rearrangements, including chromosomal inversions, interstitial deletions, duplications, or translocations, and can drive both the development and progression of the cancer. Using contemporary sequencing techniques, at least 1 gene fusion can be identified in up to 17% of solid tumors. Many of these fusions lead to a state of oncogene addiction and their products are ideal targets of anticancer drugs (Schram 2017). Many of these events, such as fusions involving ALK, ROS1, RET, NTRK1/2/3, FGFR1/2/3, and PDGFB, are clinically actionable and targeted therapies are highly effective (Schram 2017, Drilon 2018a).

2.2.2.1 HER-Family Gene Fusions in Cancer

Fusions involving HER-family receptor tyrosine kinases, i.e., EGFR, HER2, and HER4, are reported in multiple cancers. EGFR fusions were detected in glioblastoma, glioma (EGFR/SEPT14) (Stransky 2014) and in lung adenocarcinoma (EGFR-RAD51 and EGFR-PURB, 0.05%) (Konduri 2016).

Kinase fusions commonly share a mechanism of activation whereby the fusion partner drives dimerization of the kinase and leads to ligand-independent activation. EGFR-RAD51 fusion is oncogenic in Ba/F3 cells and activates downstream oncogenic signaling via the PI3K/AKT and MAPK pathways. EGFR-RAD51 fusion proteins could be activated by RAD51 oligomerization and can be therapeutically targeted with available EGFR TKIs and therapeutic antibodies (Konduri 2016). EGFR kinase domain duplications represent a novel form of EGFR–EGFR gene fusion in which a second EGFR kinase domain is fused in tandem to a full-length EGFR gene. These alterations have been demonstrated to be functionally activated oncogenes, potentially targetable by EGFR inhibitors, and identified in multiple different tumor types including lung, sarcoma, and gliomas (Gallant 2015).

ZNF207-HER2, and MDK-HER2 fusions have been detected in gastric cancer. The HER2 fusions were oncogenic and led to aberrant activation of the HER2 pathway (Yu 2015). Gene rearrangement generating ERBB2-GRB7 fusions have been reported in breast and bladder cancers and provide a novel mode of activation by directly tethering a dominant SH2 adaptor protein directly to the HER2 kinase domain (Ross 2013; Chmielecki 2015). EZR-ERBB4 fusion was detected in invasive mucinous adenocarcinoma of the lung. The EZR-ERBB4 fusion protein contains the EZR coiled-coil domain, which functions in protein dimerization, and activates downstream signaling. NIH3T3 cells expressing ERZ-ERBB4 fusion is oncogenic and form tumors in nude mice (Nakaoku 2014).

Overall, the HER-family gene fusions occur at low frequency and represent actionable oncogenic drivers.

2.2.2.1.1 Treatment of Patients with Solid Tumors Harboring HER-Family Gene Fusions

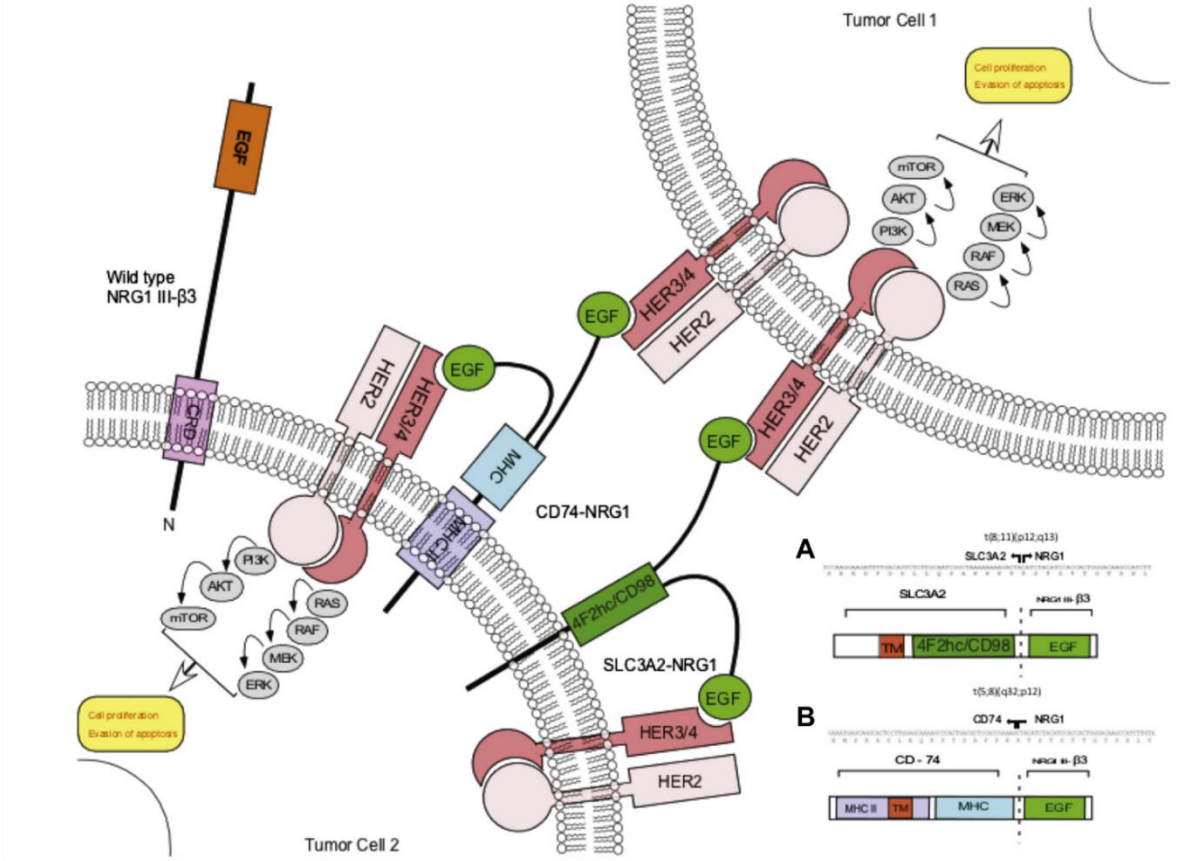
Responses to EGFR fusions have been observed with EGFR TKIs. Four patients with EGFR-RAD51 and EGFR-PURB fusions demonstrated antitumor responses from treatment with the EGFR TKI erlotinib (Konduri 2016). Response to erlotinib has also been reported recently in a Chinese patient with EGFR-RAD51 fusion (Zhu 2018).

2.2.2.2 NRG1 Gene Fusion in Cancer

Gene fusions involving the neuregulin-1 gene (NRG1) were identified in NSCLC in lung adenocarcinomas (Fernandez-Cuesta 2014). NRG1 fusions are particularly enriched in invasive mucinous adenocarcinomas of the lung, where they are found in 27% to 31% of cases. These are often mutually exclusive with KRAS mutations, a driver known to be enriched in mucinous adenocarcinomas (Fernandez-Cuesta 2014, Trombetta 2018). NRG1 rearrangements were detected across a variety of other cancers, including breast (0.01%), head and neck (0.49%), renal (0.19%), ovarian (0.24%), pancreatic (0.55%), prostate (0.3%), and uterine (1.75%) cancers, using MSK-IMPACT and the MSK solid fusion assays (Drilon 2018b). NRG1 fusions were also reported in cholangiocarcinoma (0.8%), thyroid (0.7%), ovarian (0.5%), pancreatic (0.4%), NSCLC (0.3%), breast (0.2%), sarcoma (0.2%), and other (0.1%) cancers using ArcherDx fusion assay with an overall incidence of 0.2% in solid tumors (Jonna 2019).

NRG1 gene fusions are drivers of cancer growth. NRG1 encodes several isoforms that contain an EGF-like domain that serves as the ligand of the receptor HER3 (Fernandez-Cuesta 2015). Chimeric transmembrane proteins encoded by NRG1 fusions are predicted to maintain this extracellular domain, thus activating HER3 in a para/juxtacrine or autocrine fashion (Schaefer 1997). NRG1 binding to HER3 results in heterodimerization with HER2, activation of downstream signaling, including the MAPK, PI3K-AKT, and NF-κB pathways, and increased tumor cell proliferation and growth. CD74-NRG1 fusion activates HER3 as well as PI3K-AKT signaling promoting anchorage-independent growth of NIH-3T3 cells, and the signaling could be suppressed by clinically approved kinase inhibitors afatinib and lapatinib (Nakaoku 2014). Numerous N-terminal partners have been reported for NRG1 fusions which retain an EGF-like domain (Drilon 2018b, Jonna 2019).

Figure 5: NRG1-Fusion Signaling



Graphic depiction of DNA splice site and protein fusion products solute carrier family 3 member 2 (SLC3A2-NRG1) (A) and CD74 molecule (CD74)-NRG1 (B) along with depiction of how they drive ERBB-mediated cellular proliferation through overactive autocrine and paracrine signaling through the EGF-like domain.
CRD = cysteine rich domain; HER2 = receptor tyrosine-protein kinase erbB-2; HER3/4 = receptor tyrosine-protein kinase erbB-3/4; NRG1 = neuregulin 1; PI3K = phosphoinositide 3-kinase; mTOR = mammalian target of rapamycin; MHC = major histocompatibility complex; TM = transmembrane domain.
Adapted from Gay 2017

HER3 Networks and NRG Signaling in NRG1-Rearranged Lung Tumors

NRG1 proteins act as ligands of HER3 receptors. The interaction NRG1-HER3 triggers the receptor, inducing its heterodimerization with HER2 and the consequent activation of the PI3K-AKT and MAPK pathway, both in autocrine (*cell-1*) and juxtacrine (*cell-2*) ways, resulting in irregular cell proliferation and tumor growth. Mechanisms of evasion of the apoptosis are activated too. In the NRG1 fused protein, the part belonging to the 5' partner gene is colored in blue (Trombetta 2017).

2.2.2.2.1 Treatment of Patients with Solid Tumors Harboring NRG1 Gene Fusions

Clinical responses to various HER-directed therapies have been reported for NRG1 gene fusions. Afatinib displayed responses in 2 patients with SDC4-NRG1 (lung adenocarcinoma) and ATP1B1-NRG1 (cholangiocarcinoma) (Jones 2017) and SLC3A2-NRG1 (lung adenocarcinoma) fusions (Gay 2017). GSK2849330, HER3 monoclonal antibody demonstrated durable response in CD74-NRG1 (lung invasive mucinous adenocarcinoma) fusion (Drilon 2018b). The combination of lumretuzumab and erlotinib showed stable disease (SD) in a patient harboring SLC3A2-NRG1 fusion (Han 2017). These initial reports of activity provide clinical concept validation to target NRG1 gene fusions.

2.3 Summary of Nonclinical Studies and Clinical Trials Using Tarloxotinib

2.3.1 Nonclinical Studies

Tarloxotinib and tarloxotinib-E inhibitory activity were compared directly against gefitinib, afatinib, and osimertinib across patient-derived cell lines harboring EGFR exon 20 insertion mutations, HER2 amplification, and HER2 exon 20 insertion mutations along with various EGFR and HER2 mutations in Ba/F3 cells under normoxic conditions (Table 1).

- For cell lines with EGFR exon 20 insertion mutations, tarloxotinib-E tended to be the most potent inhibitor with 1.5-, 4.6-, and 5.3-fold higher potency in CUTO-14, CUTO-17, and CUTO-18 cell lines, respectively, than afatinib.
- Tarloxotinib (prodrug) was > 63-fold less potent than tarloxotinib-E (active metabolite) in CUTO-14, CUTO-17, and CUTO-18 patient-derived cell lines.
- In ERBB2/HER2 amplification cell lines H-2170 and CALU-3, tarloxotinib-E was the most potent compared to the tested drugs. Tarloxotinib-E was 130.8- and 162.5-fold more potent than tarloxotinib, respectively.
- Tarloxotinib-E was 53-fold more potent than tarloxotinib in H-1781 cell line containing HER2 exon 20 insertion mutation and was more potent than afatinib.
- Tarloxotinib-E was potent across various EGFR/HER2 mutations and fusions in Ba/F3 cells (Suda 2019).

Table 1: Comparative Cellular ERBB Kinase Inhibitory Activity of Tarloxotinib-E

NSCLC Cellular Anti-Proliferative Assay IC_{50} (nM) ±SEM							
Cell Line	**Kinase**	**Gefitinib**	**Afatinib**	**Osimertinib**	**Tarloxotinib**	**Tarloxotinib-E**	**N**
CUTO-14	EGFR A767_V769dupASV	3741 ± 1.4	111 ± 5	303 ± 1.9	4645 ± 5.5	72 ± 5.2	3
CUTO-17	EGFR N771_H773dupNPH	4197 ± 1.4	220 ± 2.6	426 ± 3	3090 ± 1.6	48 ± 1.3	3
CUTO-18	EGFR S768_D770dupSVD	> 10000	841 ± 3	647 ± 3	> 10000	158 ± 1.3	3

NSCLC Cellular Anti-Proliferative Assay IC_{50} (nM) ±SEM							
Cell Line	**Kinase**	**Gefitinib**	**Afatinib**	**Osimertinib**	**Tarloxotinib**	**Tarloxotinib-E**	**N**
PC9	EGFR Del 746_L750	30 ± 1.5	< 1	-	18 ± 1.2	< 1	3
H3255	EGFR L858R	0.80 ± 2.3	< 1	-	3.54 ± 1.3	< 1	3
H2170	ERBB2 amplification	1156.1 ± 2.4	11.4 ± 1.3	112.7 ± 1.4	588.8 ± 1.9	4.5 ± 4.7	3
Calu-3	ERBB2 amplification	1324 ± 1.9	31.1 ± 3.4	187.9 ± 20.2	325 ± 1.5	2 ± 1.2	3
H1781	ERBB2 p.G776Ins V_G/C	4168 ± 5	66 ± 4	406.4 ± 17.1	816 ± 1.2	15.4 ± 4.4	3
MDA-MB-175	DOC4-NRG1	404	1.2	37	307	0.3	3

EGFR = epidermal growth factor receptor; IC_{50} = 50% inhibitory concentration; NSCLC = non-small cell lung cancer; SEM = standard error of the mean

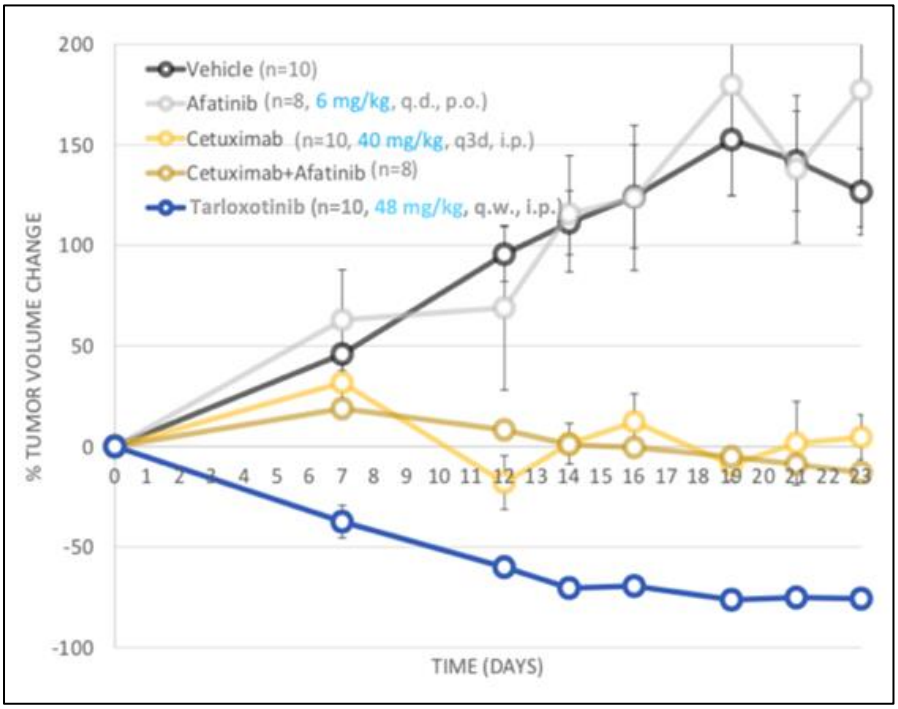
Table 2: Tarloxotinib-E Potency in Ba/F3 Cell Lines

Ba/F3 Cellular Anti-Proliferative Assay IC_{50} (nM)							
Cell Line	Kinase	Gefitinib	Afatinib	Osimertinib	Tarloxotinib	Tarloxotinib-E	N
Ba/F3 HER2	A775_G776insYVMA	-	8.1	68.3	122.9	0.7	3
Ba/F3 HER2	G776delinsVC	-	2.1	**7.2**	**22.2**	**0.03**	3
Ba/F3 HER2	P780_Y781insGSP	-	6.5	**88.45**	**73.53**	**0.87**	3
Ba/F3 HER2	V659E	-	6.09	**22.2**	**407.2**	**0.80**	3
Ba/F3 HER2	L755A	-	21.4	**67.0**	**595.2**	**4.52**	3
Ba/F3 HER2	L755P	-	7.58	**27.6**	**162.8**	**0.90**	3
Ba/F3 EGFR	A763insFQEA	-	0.7	14.6	15.2	**<0.5**	3
Ba/F3 EGFR	V769insASV	-	35.5	118.4	675.9	**7.6**	3
Ba/F3 EGFR	D770insSVD	-	86.0	184.7	990.1	**7.3**	3
Ba/F3 EGFR	H773insNPH	-	35.8	61.9	714.0	**9.9**	3
Ba/F3 EGFR	H773insH	-	325	77.7	>1000	73.1	3
Ba/F3 EGFR–EGFR	EGFR kinase domain duplication	228	0.015	2.4	4.6	0.015	2
Ba/F3 EGFR-RAD51	EGFR-RAD51 fusion	4.5	0.024	8.6	6.6	0.026	3

EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor 2; IC_{50} = 50% inhibitory concentration.

Tarloxotinib was evaluated in the CUTO-14 patient-derived xenograft, a model of EGFR exon 20 insertion (ASV)-driven cancer and compared to cetuximab, cetuximab with afatinib, and afatinib. Tarloxotinib dosed at a once a week intraperitoneal (IP) dosing schedule resulted in tumor regression and was more effective than the comparator agents when dosed at 48 mg/kg, a dose providing a similar unbound plasma area under the curve in mice as is achieved in humans at the MTD of 150 mg/m^2 (comparator agents were dosed at approximately their human effective dose [HED]; Figure 6). Treatments were associated with modest (< 5%) changes in body weight.

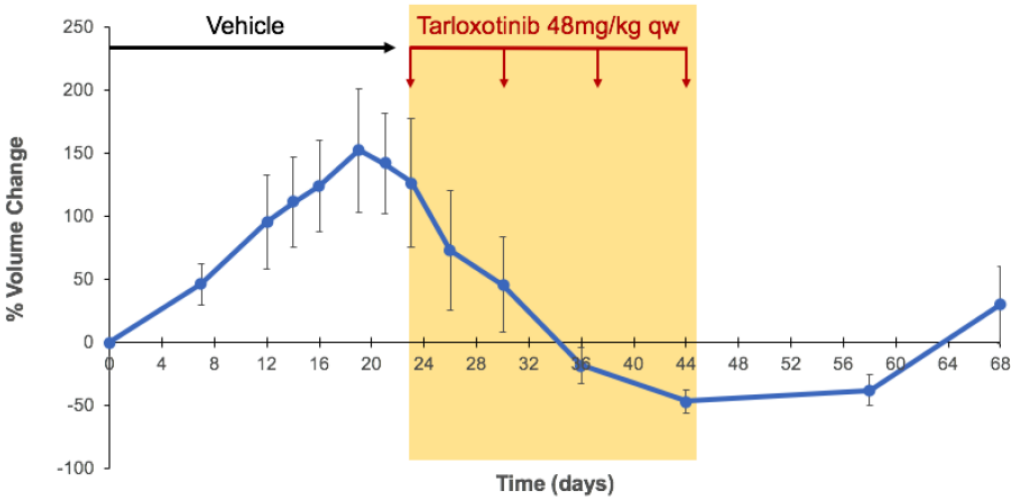
Figure 6: Comparative Activity of Tarloxotinib, Cetuximab, and Afatinib Against EGFR exon 20 Insertion (ASV)-Driven CUTO-14 Tumors



EGFR = epidermal growth factor; i.p. intraperitoneal; p.o. = oral; q3d = every 3 days; q.d. = every day

Tarloxotinib activity was evaluated in mice with large tumors by using the vehicle group bearing CUTO-14 tumors with average tumor size of 573 mm^3 (range 120 to 1623 mm^3). Tarloxotinib was dosed at the same dose of 48 mg/kg once a week on Day 23 for a total of 4 doses. Rapid tumor regression was observed in these mice despite large tumors at the start dose and the tumor regression persisted for 2 weeks after the last dose (Figure 7).

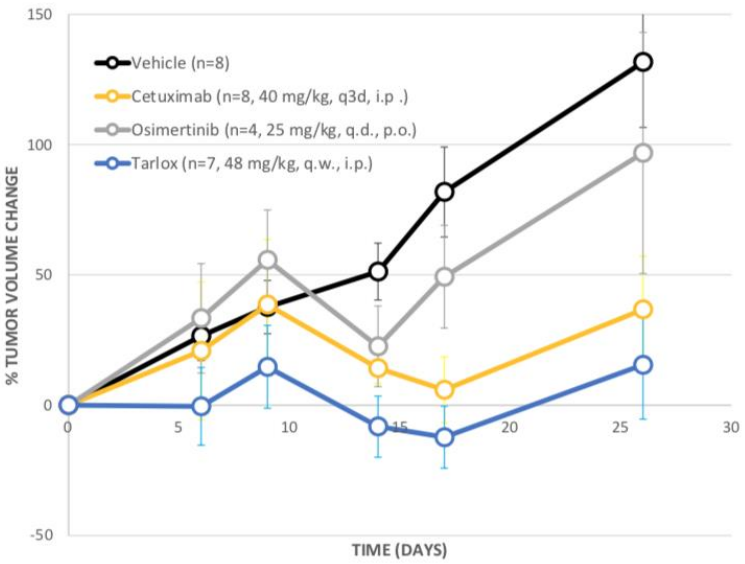
Figure 7: Activity of Tarloxotinib in Mice-bearing Large CUTO-14 EGFR exon 20 Insertion (ASV)-Driven Tumors



EGFR = epidermal growth factor; qw = every week

CUTO-17 patient-derived xenograft, a model of EGFR exon 20 insertion (NPH)-driven cancer was used to test tarloxotinib and compare to cetuximab and osimertinib. Tarloxotinib dosed at a once a week, IP dosing of 48 mg/kg schedule resulted in tumor volume reduction and was more effective than the comparator agents dosed at approximately their HEDs (Figure 8).

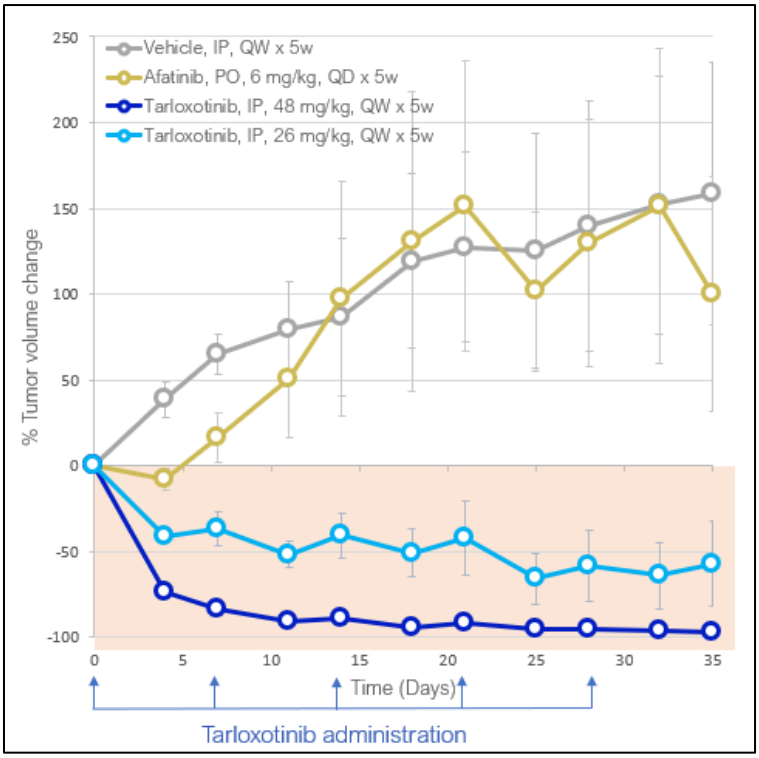
Figure 8: Comparative Activity of Tarloxotinib (Tarlox), Cetuximab, Afatinib and Osimertinib Against EGFR exon 20 Insertion (NPH)-Driven CUTO-17 Tumors



i.p. = intraperitoneal; p.o. = oral; q3d = every 3 days; q.w. = every week

OV-10-0050 ovarian cancer patient-derived xenograft, a model of CLU-NRG1 fusion-driven cancer was used to test tarloxotinib and to compare to afatinib. Tarloxotinib dosed at a once a week, IP dosing of 48 mg/kg and 26 mg/kg schedules led to significant tumor volume regression at both doses, while afatinib dosed at approximately the HED was not effective (Figure 9). Tarloxotinib and tarloxotinib-E exhibited sustained tumor exposure in the OV-10-0050 tumors for up to 168 hours (Figure 10) and demonstrated sustained inhibition of multiple pathways downstream of HER2/HER3 signaling (Figure 11).

Figure 9: Comparative Activity of Tarloxotinib (Tarlox) and Afatinib Against CLU-NRG1-Driven OV-10-0050 Tumors



IP = intraperitoneal; PO = oral; QW = every week

Figure 10: Plasma and Tumor Pharmacokinetics of a Single Dose of Tarloxotinib in OV-10-0050 (CLU-NRG1) Tumor-bearing Mice Depicting the Profiles of Tarloxotinib and Tarloxotinib-E when Tarloxotinib Was Administered at 48 mg/kg (A) or 26 mg/kg (B)

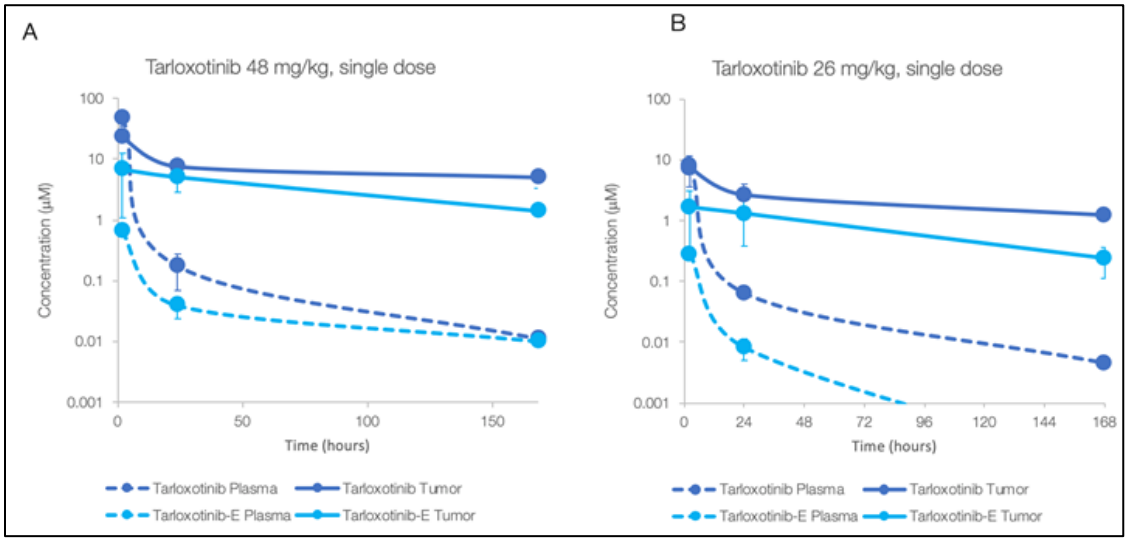
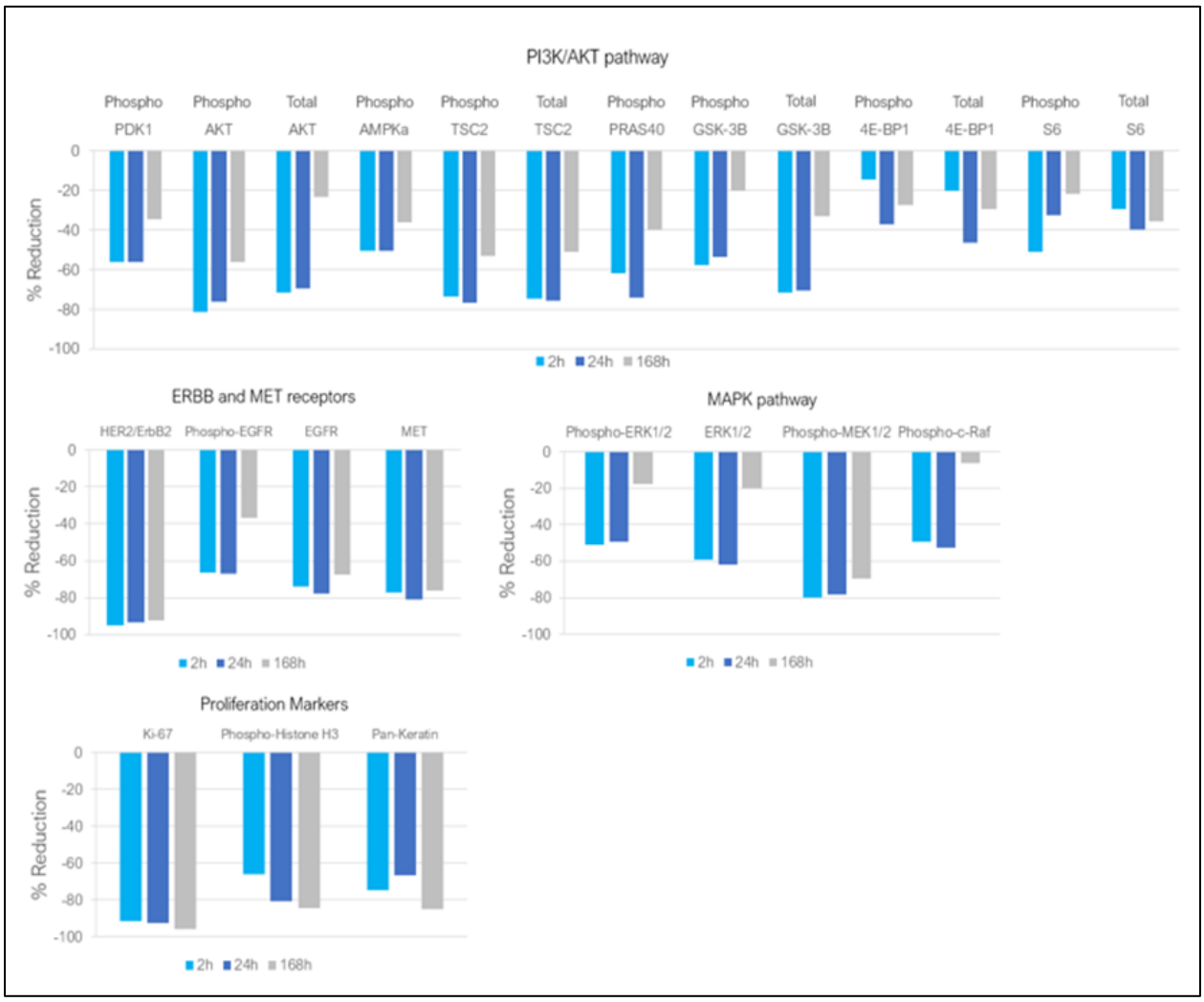


Figure 11: Sustained Downregulation of Multiple Cancer Signaling Pathways in OV-10-0050 (CLU-NRG1) PDX Model Using nCounter® Vantage 3D™ Protein Solid Tumor Panel After Single Dose of Tarloxotinib (48 mg/kg)



h = hour(s)

Please refer to the Tarloxotinib Investigator's Brochure for additional nonclinical information.

2.3.2 Clinical Trials

Study PR610-1001

A first-in-human Phase 1 clinical trial (Study PR610-1001) evaluated tarloxotinib administered as either a 1-hour or a 24-hour weekly intravenous (IV) infusion. The study was designed to determine the MTD and dose-limiting toxicities (DLTs) of tarloxotinib in patients with locally advanced or metastatic solid tumors. Twenty-seven patients received tarloxotinib administered weekly as a 1-hour infusion at doses ranging from 10 mg/m^2 to 200 mg/m^2 and 6 patients received tarloxotinib administered weekly as a 24-hour infusion at doses of 200 mg/m^2 or 335 mg/m^2. Of the patients who received tarloxotinib administered as a weekly 1-hour infusion, 6 patients received tarloxotinib at the recommended Phase 2 dose of 150 mg/m^2 tarloxotinib.

DLTs with the 1-hour infusion included Grade 3 infusion-related reaction (150 mg/m^2), Grade 3 facial pain (200 mg/m^2), and Grade 4 QTc prolongation (200 mg/m^2). An MTD of 150 mg/m^2 was declared for the 1-hour infusion duration. Other treatment-related AEs observed in the Phase 1 study included perioral paresthesia, musculoskeletal pain, nausea and vomiting, and dose dependent signs and symptoms of EGFR inhibition, notably skin rash, and diarrhea.

After the DLTs of Grade 3 facial pain (1) and Grade 4 QTc prolongation (1) were observed at 200 mg/m^2 administered as a 1-hour infusion, a 24-hour infusion duration was evaluated to determine if a reduced maximum peak plasma concentration (C_{max}) would reduce toxicities and allow higher weekly dosing. Three patients each were treated with a 24-hour infusion of tarloxotinib at 200 mg/m^2 or 335 mg/m^2. Treatment-related AEs were similar to those observed with the 1-hour infusion including nausea and diarrhea, skin rash and QT prolongation. A DLT of Grade 3 QTc prolongation was reported in 1 patient at 335 mg/m^2 at the 24-hour infusion duration.

Pharmacokinetic (PK) samples were collected from patients after administration of the first dose in Cycles 1 and 2. No accumulation of tarloxotinib was observed on Cycle 2 Day 1 as compared to Cycle 1 Day 1 for any PK parameter. The data obtained across all dose levels were consistent with linear pharmacokinetics for both tarloxotinib and tarloxotinib-E. The mean elimination half-life of tarloxotinib was approximately 5 hours at the 150 mg/m^2 dose level, and mean C_{max} was 20.54 μg/mL. Across the range of doses, plasma concentrations of tarloxotinib-E averaged about 1% of those of tarloxotinib.

Study TH-CR-601 and Study TH-CR-602

Two Phase 2, open-label studies were subsequently performed to evaluate tarloxotinib administered as a 150 mg/m^2 weekly 1-hour IV infusion in patients with EGFR-mutant, T790M-negative, advanced NSCLC that was resistant to EGFR TKIs (Study TH-CR-601), and in patients with recurrent or metastatic SCC of the head and neck or skin (Study TH-CR-602). These studies failed to show significant antitumor activity. It is believed that both trials enrolled a study population unlikely to respond to EGFR inhibition. Tumors lacking EGFR T790M as their EGFR TKI resistance mechanism are not likely to be EGFR dependent due to enrichment for tumors with bypass signaling or other non-EGFR-dependent signaling mechanisms; therefore, no EGFR inhibitor, including tarloxotinib, would be expected to show benefit in this population. Additionally, SCC is not known to be dependent on EGFR signaling. Data from these 2 studies are in the process of being analyzed and should be considered preliminary and subject to change.

Study TH-CR-601 enrolled 21 subjects. A total of 223 AEs related to tarloxotinib were reported in 21 subjects during the study. Of these, 17 subjects (81%) experienced Grade 3 AEs, and 1 subject (5%) experienced a Grade 4 AE. QTc prolongation accounted for most of the Grade 3 toxicities (10 subjects, 48%). This was mainly due to corrected QTc interval as calculated according to Fridericia's formula (QTcF) change from baseline of > 60 msec (38%) while 2 subjects (10%) developed QTcF ≥ 501 msec. None were associated with clinically significant arrhythmia. Other Grade 3 toxicities included hypertension in 2 subjects and various other events in 1 subject each. Grade 4 events related to tarloxotinib included 1 event of cerebrovascular accident, while no one experienced Grade 5 toxicity.

Study TH-CR-602 enrolled 30 patients. In combining the results of both studies, the most common AE was ECG QT prolongation, which occurred in 35/51 (68.6%) of the patients and in these 35 patients, 19 (54.3%) were Grade 3 severity and 16 (45.7%) less than Grade 3. Skin and subcutaneous tissue disorders were experienced by patients and the most frequent were dermatitis acneiform 13/51 (25.5%), rash 7/51 (13.7%), and pruritus 5/51 (9.8%) and most were ≤ Grade 2 in severity. The other most common treatment-related AEs were diarrhea (35.3%, 18/51) and fatigue (17/51, 33.3%).

Special emphasis was placed on QT monitoring in both studies. This included Holter monitoring during Cycle 1 Day 1 and calibrated ECG machines with central reading of ECG measurements throughout the study duration. Holter monitoring was used to record and extract triplicate QT measurements at 9 predefined time points during the first 24 hours of Cycle 1 Day 1 in both studies. The mean maximum QTcF change from baseline was 51 msec occurring 3 hours after the end of infusion and 55 msec occurring 2 hours after the end of infusion in Study TH-CR-601 and Study TH-CR-602, respectively. Across the 2 studies, 10 patients (21%) developed QTcF values ≥ 501 msec and 16 patients (34%) developed a QTcF change from baseline of > 60 msec. The time-matched PK and QTcF data suggest a QT prolongation hysteresis of up to 2 to 3 hours after the tarloxotinib C_{max} which occurs at the end of infusion. T-wave segmentation analysis suggests that tarloxotinib is a hERG channel blocker and that it does not possess mitigating multichannel blocking properties.

Please refer to the Tarloxotinib Investigator's Brochure for the most current safety assessment.

2.4 Rationale for Selection of the RAIN-701 Study Population

2.4.1 NSCLC with EGFR Exon 20 Insertion Mutation or HER2-Activating Mutation

The selection of patients with NSCLC that harbor EGFR exon 20 insertion or HER2-activating mutations is based on the hypothesis that tarloxotinib will overcome the inherent resistance of tumors harboring these mutations to standard EGFR, HER2 or pan-HER TKIs.

Preclinical *in vitro* evidence from 3 patient-derived cell lines, which harbor the 3 most common EGFR exon 20 insertion variants, has demonstrated that the active metabolite (tarloxotinib-E) causes potent tumor cell proliferation inhibition compared to US Food and Drug Administration (FDA)-approved EGFR inhibitors afatinib or gefitinib. These cell lines depend on EGFR signaling for their proliferation and are resistant to approved EGFR inhibitors compared to sensitizing EGFR mutations in exon 19 and 21.

Preclinical *in vitro* evidence from Ba/F3 cells harboring HER2 mutations and 3 cell lines, which harbor HER2 amplification and HER2 exon 20 insertion (ERBB2 p.G776Ins V_G/C), has demonstrated that the active metabolite (tarloxotinib-E) causes potent tumor cell proliferation inhibition compared to FDA-approved EGFR inhibitors afatinib, osimertinib, or gefitinib. These cell lines depend on HER2 signaling for their proliferation and are resistant to approved ERBB inhibitors compared to sensitizing EGFR mutations in exon 19 and 21.

In vitro, the active metabolite (tarloxotinib-E) inhibits HER2 downstream signaling and proliferation of HER2 exon 20 insertion mutation cell lines. Nonclinical data demonstrated that tarloxotinib can significantly inhibit growth of xenograft tumors *in vivo* and reduce tumor

volume. Additionally, tarloxotinib has 30- to 70-fold lower activity *in vitro* under normoxic conditions compared to tarloxotinib-E, depending on the cell line. As such, administration of tarloxotinib may selectively deliver higher concentrations of the active irreversible TKI, tarloxotinib-E, to the hypoxic tumor relative to normoxic normal tissues, thereby achieving inhibition of EGFR or HER2 signaling without high incidence of dose-limiting side effects.

Standard EGFR inhibitors such as erlotinib, gefitinib, and afatinib are not effective against NSCLC harboring the exon 20 insertions, these patients have no other known effective therapy other than standard chemotherapy. Other investigational agents currently being tested in this patient population include poziotinib, TAK788, and osimertinib. Results from 2 ongoing studies reported an ORR of 14.8% and 43% for poziotinib and TAK788, respectively, which provides important proof-of-concept information that an oral ERBB-selective TKI is able to produce relevant tumor responses in the target population (Heymach 2018, Doebele 2018, Le 2020, Riely 2020). However, approximately 65% of the patients receiving poziotinib required dose reduction due to typical EGFR-related toxicities, such as skin rash and diarrhea, suggesting poziotinib lacks adequate exon 20 selectivity over the WT EGFR receptor, which is consistent with *in vitro* data showing that poziotinib/HM781-36b has greater selectivity for WT EGFR than EGFR exon 20 mutations.

Additionally, because HER2 inhibitors such as lapatinib and neratinib are not effective against NSCLC harboring the exon 20 insertions, these patients have no other known effective therapy other than standard chemotherapy. Other investigational agents currently being tested in this patient population include trastuzumab deruxtecan (T-DXd), TAK-788, and poziotinib. Preliminary results from an ongoing study reported an ORR of 61.9% for T-DXd, which provides important proof-of-concept information that a HER2 targeted antibody-drug conjugate (ADC) is able to produce relevant tumor responses in the target population (Smit 2020). However, 64.3% patients had ≥ Grade 3 treatment-emergent AEs including decreased neutrophil count (26.2%), anemia (16.7%) and drug-related interstitial lung disease (ILD, 11.9%); 59.5% of the patients receiving T-DXd required dose interruption, 38.1% dose reduction and 23.8% treatment discontinuation. Results from a TAK-788 Phase 2 trial in HER2 exon 20 insertion cohort have not been reported yet, but Phase 1 results demonstrated a confirmed ORR of 8%. Poziotinib demonstrated an ORR of 27.8% of NSCLC with HER2 mutations, but with significant ≥ Grade 3 treatment-emergent AEs including rash and diarrhea (Socinski 2020).

Antibody therapies (including ADCs) bind to the extracellular domain of HER2 leading to internalization of the HER2-monoclonal antibody/ADC complex and intracellular release of the chemotoxic payload. In addition to the cytotoxic effects of the payload, antibody-dependent cell-mediated cytotoxicity also contributes to the efficacy of the ADC. While resistance mechanisms have not been reported for T-DXd, multiple resistance mechanisms are reported for another HER2-ADC complex, T-DM1. These include altered internalization of HER2-ADC complex, reduced T-DM1 binding, dependence on alternate receptor tyrosine kinases such as EGFR and HER3, intra-tumoral heterogeneity of HER2 expression, altered lysosomal catabolism, and impaired lysosomal release of the payload (Hunter 2020). Most of these mechanisms are involved in the binding and processing of ADC and present a favorable environment for a small molecule TKI-dependent activity based on direct binding to the HER2 kinase domain, suggesting that patients who progressed on antibody therapies may benefit from a TKI therapy.

2.5 Rationale for Dose Selection and QT Prolongation Mitigation

This study will evaluate tarloxotinib 150 mg/m^2 as a weekly 1-hour IV infusion (the MTD declared in the first-in-human Phase 1 study (Patterson 2013) and the dose level explored in the 2 Phase 2 studies). Preclinical xenograft studies utilizing weekly doses of tarloxotinib at human equivalent of the clinically assessed dose (48 mg/kg intraperitoneally weekly equivalent to 150 mg/m^2 IV weekly) induced marked tumor shrinkage and marked inhibition of EGFR phosphorylation for 7 days suggesting protracted tumor residence time for tarloxotinib-E. Furthermore, this dose was associated with low-grade skin rash and diarrhea, suggesting limited systemic EGFR inhibition, indicating an on-target pharmacodynamic effect in man. It is expected that enhanced activation in the tumor compared to normal tissue may offer a therapeutic advantage over standard TKIs in terms of the potential for enhanced intra-tumoral blockade of EGFR signaling with acceptable tolerability.

Tarloxotinib was associated with Grade 1 or Grade 2 QTc prolongation starting at a dose of 40 mg/m^2 and more consistent QTc prolongation at 150 mg/m^2 suggesting a dose-dependent effect. However, extending the infusion duration from 1 hour to 24 hours, which reduced the tarloxotinib C_{max} approximately 6-fold, did not appear to have an impact on QTc prolongation at the 200 mg/m^2 dose of tarloxotinib in the 2 patients evaluated. Time-matched assessment of QTc changes from baseline with tarloxotinib plasma concentrations after a 150 mg/m^2 dose from the Phase 2 studies did not suggest an exposure correlation. What is evident, is that there was a time-delay of the maximum QTc prolongation from baseline from the time to maximum tarloxotinib exposure of about 3 hours (QT prolongation hysteresis). During this period, patients are at greatest risk of developing QT-related cardiac arrhythmias, such as Torsade de Pointes (TdP). The QT prolongation risk mitigation strategy includes several layers of precautions, as follows:

- Eligibility criteria that exclude patients at increased risk, such as:
  - History of long QT syndrome, TdP, or family history of sudden death
  - Receiving medication that prolongs QTc interval
  - Baseline QTcF ≥ 450 msec
  - Significant cardiovascular disease
- Repeated ECG measurements during the study (prior to and following the infusion)
- Potassium supplementation prior to dosing, as needed (Section 6.4)
- All patients are under direct supervision of qualified personnel with immediate availability of appropriate resuscitation equipment. Patients will therefore be under intense monitoring and supervision during the entire period they are at risk for QT prolongation.
- Patients will not be discharged unless they have ≤ Grade 2 QTcF.

In the prior Phase 1 and 2 Phase 2 studies, the main identified risk of tarloxotinib treatment (QT prolongation) was observed primarily within a 3- to 4-hour period following the start of infusion.

Given the absence of effective treatment options for NSCLC patients with EGFR exon 20 insertion or HER2-activating mutations and based upon the manageability of observed risks associated with tarloxotinib, the risk-to-benefit ratio for participants in this study is acceptable. This risk of QT prolongation is mitigated in this study by the medical supervision of patients during first 3 to 4 hours of drug administration, when the risk of an event is greatest, with additional guidance on management of QT prolongation provided in the protocol and the Tarloxotinib Investigator's Brochure.

2.6 Potential Risks

Cancers harboring the mutations and fusions under evaluation in study RAIN-701 have been generally refractory to currently available therapies. Tarloxotinib is an investigational agent with no proven clinical benefits. As of the start of this clinical trial, tarloxotinib had been administered to 84 adults with a variety of cancer types. In the combined dataset of Studies TH-CR-601 and TH-CR-602 (n = 51), where tarloxotinib was administered as a 1-hour weekly IV infusion at a dose level of 150 mg/m^2, the most commonly reported AEs included ECG QT prolongation, diarrhea, fatigue, dermatitis, rash, pruritus, nausea, and cough. Infusion-related reactions characterized by flushing, urticarial skin rash, pruritus, and hypotension have been observed during and immediately following infusion of tarloxotinib. All patients receiving tarloxotinib should be instructed to seek immediate medical care in the event allergic symptoms develop.

Prolongation of the QT interval have been observed up to 4 hours following completion of tarloxotinib infusion. At the recommended dose of 150 mg/m^2, AEs of QT prolongation were reported by 35/51, 68.6% (19 of these patients experienced Grade 3 QTc prolongation). There was 1 patient who experienced a Grade 3/Grade 4 event at the 335 mg/m^2 dose level in the Phase 1 study). QT prolongation can infrequently lead to serious (rarely fatal) fast and irregular heart rhythms and other symptoms, such as severe dizziness and/or fainting, seizure, and palpitations. Patient eligibility criteria and monitoring have been implemented based on these past findings.

Due to the possibility of phototoxicity, patients should be instructed to avoid prolonged exposure to sunlight while on study treatment and when exposure cannot be avoided to use a broad-spectrum sunscreen.

Please refer to the most recent version of the Tarloxotinib Investigator's Brochure for the most current understanding and management of the potential risks associated with the use of tarloxotinib.

3. TRIAL OBJECTIVES AND PURPOSE

The purpose of this study is to evaluate the safety and efficacy of tarloxotinib when administered to patients with NSCLC whose tumors harbors either an EGFR exon 20 insertion or a HER2-activating mutation (including exon 20 insertions) or patients with advanced solid tumors expressing NRG1/ HER-family gene fusions or a HER2-activating mutation (including exon 20 insertions). All patients will have received at least 1 prior platinum-based chemotherapy-containing regimen in the advanced/metastatic setting (Cohorts A, B, and B1) or standard of care for cancer (Cohorts C and D). Patients in Cohorts C and D must have received

all standard therapy appropriate for their tumor type and stage of disease, or, in the opinion of the Investigator, would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard-of-care therapy.

3.1 Primary Objective

The primary objective of this study is to evaluate the ORR of tarloxotinib according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

3.2 Secondary Objectives

Secondary objectives are:

- To evaluate further measures of antitumor activity of tarloxotinib including best overall response (BOR), duration of response (DOR), DCR, progression-free survival (PFS), and overall survival (OS)
- To investigate the pharmacokinetics (PK) of tarloxotinib and tarloxotinib-E using population PK (PopPK) methods and explore correlations between PK, exposure, response, and/or safety findings
- To evaluate the safety and tolerability of tarloxotinib in this population including to determine whether there is an association between plasma exposure to tarloxotinib and effects on cardiac repolarization

3.3 Exploratory Objectives

Exploratory objectives are:

- To evaluate the concordance of EGFR mutation, ERBB2 (HER2) mutation, and NRG1, EGFR, ERBB2 (HER2), and ERBB4 (HER4) fusion detection between tissue and plasma using circulating tumor deoxyribonucleic acid (ctDNA)
- To evaluate exploratory biomarkers of hypoxia in tumor tissue including STEAP4 expression and ERBB family and cancer cell signaling pharmacodynamic markers
- To evaluate the pharmacokinetics of tarloxotinib and tarloxotinib-E in tumor tissue

4. TRIAL DESIGN

4.1 Trial Design Overview

This is a Phase 2 multicenter, open-label study to evaluate the antitumor effect of tarloxotinib in patients with:

- Previously treated advanced/metastatic NSCLC who have a tumor harboring one of the following:
  - An EGFR exon 20 insertion (Cohort A)
  - A HER2-activating mutation (including HER2 exon 20 insertions) who have not received prior HER2-directed therapy (Cohort B)

  - A HER2-activating mutation (including HER2 exon 20 insertions) who have received prior HER1 antibodies or ADCs (Cohort B1)
- Previously treated advanced solid tumors harboring:
  - NRG1 or ERBB HER-family gene fusions (Cohort C)
  - HER2-activating mutations (including HER2 exon 20 insertions), excluding NSCLC (Cohort D)

Cohorts B1 and/or D may not be pursued, at the discretion of the Sponsor. All cohorts will use a Simon's 2-stage design. In the first stage, 21 patients will be accrued. If more than 3 patients in a cohort have a partial or complete response, up to 22 additional patients may be enrolled to the cohort, for up to a total of 43 patients per cohort. However, if there are 3 or fewer responses among these 21 patients, the cohort will be stopped based on futility.

Table 3: Number of Patients by Cohort

Cohort	Description	N
A:	• Patients with advanced NSCLC harboring an EGFR exon 20 insertion mutation o At least 1 prior platinum-based chemotherapy-containing regimen	43
B:	• Patients with advanced NSCLC with a HER2 activating mutation • Patients who have received at least 1 prior platinum-based chemotherapy-containing regimen	43
B1*:	• Patients with advanced NSCLC harboring a HER2-activating mutation • Patients who have received at least 1 platinum-based chemotherapy-containing regimen • Patients who have received prior HER2-directed therapy	43
C:	• Patients with advanced solid tumors who have failed standard therapies appropriate for their tumor type and stage of disease, or, in the opinion of the Investigator, would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard-of-care therapy • Patients with tumors harboring an NRG1 gene fusion, EGFR gene fusion, EGFR kinase domain duplication, ERBB2 gene fusion, or ERBB4 gene fusion	43
D*	• Patients with advanced solid tumors who have failed all standard therapies appropriate for their tumor type and stage of disease, or, in the opinion of the Investigator, would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard-of-care therapy • Patients with tumors (excluding NSCLC) harboring a HER2-activating mutation	43
	Total	215

*Cohorts B1 and/or D may not be pursued, at the discretion of the Sponsor.

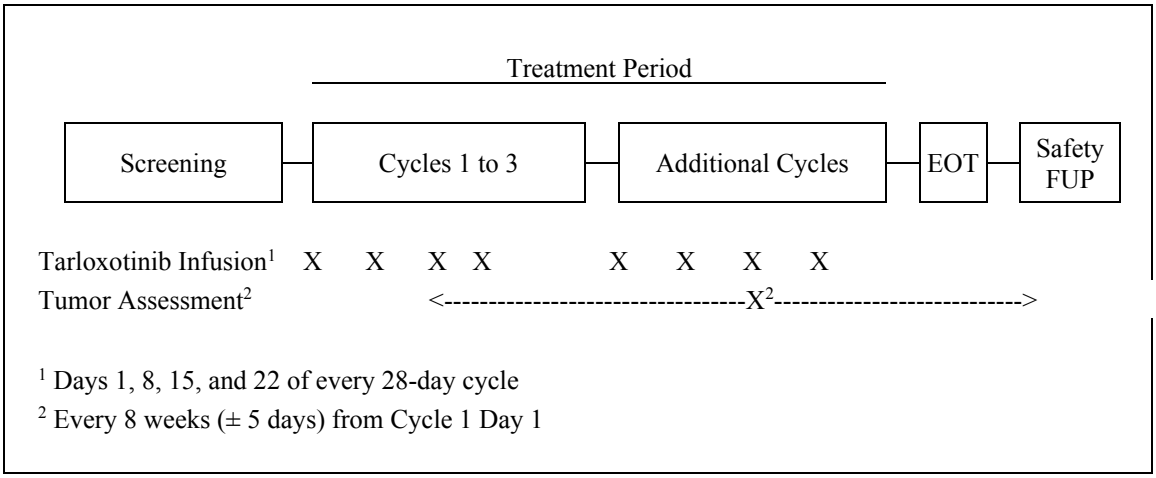
Patients who are not evaluable for tumor response assessment may be replaced; accordingly, the study is expected to enroll approximately 248 patients to yield 215 evaluable patients.

Prior to screening, potential patients will have tested positive for an EGFR exon 20 insertion mutation (Cohort A) or a HER2-activating mutation (Cohort B, B1, and D) or tumors harboring NRG1 or other HER-family gene fusions (Cohort C) using a CLIA-certified test (or similar accredited laboratory for non-US sites) to determine their eligibility for treatment with

tarloxotinib. Results will be reviewed by the Medical Monitor (or designee) and participants will be assigned to one of the cohorts based on disease and mutation type.

Based on the determined recommended Phase 2 dose, all patients will receive tarloxotinib 150 mg/m^2 administered as a weekly 1-hour IV infusion on Days 1, 8, 15, and 22 of each 28-day cycle until disease progression or unacceptable toxicity (e.g., hepatotoxicity meeting Hy's law criteria or serious arrhythmias of ventricular origin). Radiographic tumor assessment including computed tomography (CT) scans or magnetic resonance imaging (MRI) of chest and abdomen will be performed every 8 weeks (± 5 days) from Cycle 1 Day 1, using the same imaging modality per patient (Section 7). Safety assessments will be performed on an ongoing basis.

Figure 12: Study Schema



[1] Days 1, 8, 15, and 22 of every 28-day cycle
[2] Every 8 weeks (± 5 days) from Cycle 1 Day 1

EOT = End-of-Treatment Visit; FUP = Follow-up Visit
Note: This schematic is not to scale.

4.2 Endpoints and Criteria for Evaluation

4.2.1 Primary Endpoint

The primary efficacy endpoint is ORR based on patients who had PR or complete response (CR) with confirmation at least 8 weeks after initial documentation. Tumor response will be assessed by the investigators in accordance with RECIST v1.1. If disease progression according to RECIST v1.1 is documented at any time, no further disease response assessment will be required. Patients who are alive with no objective documentation of disease progression by the data cut-off date for ORR analysis will be censored at the date of their last evaluable tumor assessment.

4.2.2 Secondary Endpoints

Secondary efficacy endpoints include:

- BOR defined as best response during the study SD, PR, or CR
- DOR defined as the time from date of first response to date of disease progression or death

- DCR defined as CR, PR, or SD at least 2 cycles (8 weeks) recorded in the period between first study drug dose and disease progression or death to any cause
- PFS defined as the time from the date of first dose to the earliest date of the first objective documentation of radiographic disease progression or death due to any cause
- OS as measured from the date of first dose to the date of death by any cause

Safety endpoints include the incidence of treatment-emergent AEs; changes in clinical laboratory parameters (hematology, serum chemistry, urinalysis, and serum pregnancy test), vital signs, and ECG parameters (especially QT); physical examination results; and use of concomitant medications.

4.2.3 Exploratory Endpoints

Archived tumor samples or samples from newly obtained tumor tissue will be collected prior to baseline and will be used to confirm mutation status retrospectively in all patients and to assess STEAP4 expression and other biomarkers in consenting patients.

Blood samples will be collected for biomarker analysis (e.g., ctDNA) at Cycle 1 Day 1, Cycle 2 Day 1, and end of treatment. Tumor tissue will be collected for retrospective concordance mutation testing and correlation with biomarkers. An optional tumor tissue biopsy will be collected for measurements of tarloxotinib and the active metabolite (tarloxotinib-E) in consenting patients.

Blood samples for tarloxotinib and tarloxotinib-E PK analyses will be collected in all patients and correlated with response and safety parameters including QTcF.

4.3 Measures Taken to Minimize/Avoid Bias

If a patient withdraws from the study, the data (including tested and untested samples) collected to the point of withdrawal will remain part of the study database and will not be removed.

Response criteria are based on objective measurements as defined in RECIST v1.1 by site radiologists. All responses will be source verified; copies of tumor assessment scans will be collected and provided to an independent third party for evaluation, as necessary.

4.4 Duration of Study Treatment

Patients will continue to receive tarloxotinib until documented disease progression or unacceptable toxicity (e.g., hepatotoxicity meeting Hy's law criteria). See Section 6.6 for treatment beyond progression.

5. SELECTION AND WITHDRAWAL OF PATIENTS

Cohorts A, B, and B1:

To be considered for inclusion, the patient's cancer must have recurred or progressed following at least 1 standard-of-care chemotherapy regimen (platinum-based chemotherapy). This would include regimens that may also contain biologic agents, such as bevacizumab, or immunotherapy agents, such as pembrolizumab, nivolumab, atezolizumab, or durvalumab.

Cohorts C and D:

To be considered for inclusion, the patient's cancer must have failed standard therapies appropriate for their tumor type and stage of disease, or, in the opinion of the Investigator, would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard-of-care therapy

Potential patients must have a tumor with one of the following (see Table 4 for examples):

- An EGFR exon 20 insertion mutation (Cohort A)
- A HER2-activating mutation (Cohort B, B1 and D)
- An NRG1/HER-family fusion (Cohort C)

Mutation testing will be performed in a CLIA-certified laboratory (US sites) or similar accredited laboratory (non-US sites) using tissue and/or plasma.

Table 4: Eligible Mutations/Gene Fusions

Example Mutations and Gene Fusions (See Footnote)					
Cohort A	**Cohorts B, B1, and D**	**Cohort C**			
EGFR Exon 20	**HER2 (ERBB2) Mutations**	**NRG1 Fusions**	**EGFR Fusions**	**HER2 (ERBB2) Fusions**	**ERBB4 (HER4) Fusions**
A763X	S310F/Y	**CD74-NRG1**†	EGFR–EGFR (KDD)	ZNF207-ERBB2	EZR-ERBB4
Y764X	V659E/D	DOC4-NRG1	EGFR-RAD51	MDK-ERBB2	IKZF2-ERBB4
V765X	G660D	SLC3A2-NRG1	EGFR-PURB	NOS2-ERBB2	BGALT-ERBB4
M766X	L755P/S	RBPMS-NRG1	EGFR-SHC1	ERBB2-GRB7	
A767X	Del755-759	SDC4-NRG1	SEC61G–EGFR	ERBB2-CTTN	
S768X	D769H/Y	RAB2IL1-NRG1		ERBB2-PPP1R1B	
V769X	V773L	VAMP2-NRG1		ERBB2-PSMB3	
D770X	**A775_G776insYVMA***	KIF13B-NRG1			
N771X	G776V/L, Cins	ATP1B1-NRG1			
P772X	V777L	CDH6-NRG1			
H773X	P780_Y781insGSP	AKAP13-NRG1			
V774X	V842I	THBS1-NRG1			

X = insertion, duplication, or mutation
* Most common HER2 mutation in NSCLC; note there are multiple nomenclature designations for insertions/duplications.
† Most common NRG1 fusion; CD74-NRG1 is the only NRG1 fusion detected by Foundation Medicine.
Note: These are examples and not meant to be a comprehensive list. Patients who have failed standard therapies but

have other gene alterations not specifically mentioned in this table, may still be eligible. Please discuss with the Medical Monitor the eligibility of patients with other scientifically supported gene alterations.

Potential patients with a qualifying mutation must meet all the following eligibility criteria.

5.1 Inclusion Criteria

Potential patients must meet all the following criteria to be considered for inclusion:

1. ≥ 18 years old
2. Signed and dated written informed consent
3. Histologically and/or cytologically confirmed primary diagnosis of cancer
    a. Cohorts A, B and B1: NSCLC (Stage IV, Stage IIIB, or III C) not amenable to definitive curative-intent therapy, or recurrent disease after prior diagnosis of Stage I-III disease

       Note: NSCLC staging according to American Joint Committee on Cancer, 8th edition, lung cancer staging criteria
    b. Cohort C and D: Locally advanced or metastatic solid tumor
4. Progression of disease on or after a platinum-based chemotherapy regimen (Cohorts A, B, and B1) or after standard of care (Cohorts C and D)
    a. Cohorts C and D: Must have received all standard therapy appropriate for their tumor type and stage of disease, or, in the opinion of the Investigator, would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard-of-care therapy

       Note: If it is determined by the Investigator that a patient would be unlikely to tolerate or derive clinically meaningful benefit from standard-of-care therapy, the specific reason(s) for such a determination will be documented in the electronic case report form (eCRF).
5. CLIA diagnosis of eligible cancer mutation or fusion
    a. Cohort A: EGFR exon 20 insertion mutation
    b. Cohorts B, B1 and D: HER2-activating mutation
    c. Cohort C: NRG1 or ERBB/HER-family gene fusions
6. Must have at least 1 target lesion evaluable by RECIST v1.1
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
8. Minimum life expectancy of 3 months or more
9. Clinical laboratory values meeting the following criteria within the 7 days prior to Cycle 1 Day 1
    a. Calculated creatinine clearance ≥ 30 mL/min using Cockcroft-Gault equation
    b. Total bilirubin
        - ≤ 1.5 x ULN or
        - ≤ 3 x ULN in the presence of liver metastases
    c. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT)
        - ≤ 2.5 x ULN or

- ≤ 5 x ULN, in the presence of liver metastases

d. Absolute neutrophil count ≥ 1,500 cells/μL
e. Hemoglobin ≥ 9 g/dL or 5.6 mmol/L
f. Platelet count ≥ 100,000/μL

10. Adequate cardiac function meeting all of the following ECG criteria:
    a. No evidence of second- or third-degree atrioventricular block
    b. No clinically significant arrhythmia (i.e., pauses of > 4 seconds, ventricular tachycardia of any duration, supraventricular tachycardia > 4 beats/minute)
    c. QRS interval ≤ 110 msec
    d. QTc interval of < 450 msec as calculated according to Fridericia's formula ($QTcF = QT/[R \text{ to } R \text{ interval}]^{0.33}$)
    e. PR interval ≤ 200 msec (does not apply to people with chronic stable atrial fibrillation or atrial flutter as determined by the Investigator)
11. Adequate pretreatment tumor sample (125 μm of formalin-fixed paraffin embedded (FFPE) block or at least 8 prepared slides)
    Note: Tumor tissue should be from the most recent pretreatment biopsy; if only archival tissue from the initial biopsy is available, it is acceptable
12. All toxicities from prior therapy (except alopecia and neuropathy) must have resolved to baseline or to ≤ Grade 2 according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 prior to Cycle 1 Day 1
13. For women of childbearing potential (WOCBP), documentation of negative serum pregnancy test (β-human chorionic gonadotropin) within 7 days prior to Cycle 1 Day 1
    Note: WOCBP is defined as fertile, following menarche and until becoming post-menopausal (no menses for 12 months without an alternative medical cause) unless permanently sterile (had a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy)
14. For WOCBP, agreement to use a highly effective method of contraception during the study and for at least 90 days after the last dose of study treatment
    Note: Highly effective birth control includes a) intrauterine device; b) oral, implantable or injectable combined hormonal (estrogen and progestogen containing) or progestogen-only contraceptive associated with inhibition of ovulation; c) intrauterine hormone-releasing system; or d) bilateral tubal occlusion, vasectomized partner, sexual abstinence
15. For male patients, agreement to use a condom and a highly effective method of contraception during the study and for at least 30 days after the last dose of study treatment. Male patients should also refrain from sperm donation during this time period.
16. Willingness and ability to comply with scheduled visits and study procedures

5.2 Exclusion Criteria

Potential patients who meet any of the following criteria will be excluded:

1. Has another known activating oncogene-driver mutation, including, but not limited to KRAS, ALK, ROS1, RET, BRAF, NTRK1/2/3, MET, MEK1, NRAS and HRAS.

Note: If another mutation is present but is deemed to be a tumor suppressor mutation or a variant of unknown significance then the patient may be enrolled with Sponsor approval of the mutation report.

2. Cohorts A, B, B1 and D only: Previously received anti-EGFR or anti-HER2 TKIs including but not limited to erlotinib, gefitinib, afatinib, dacomitinib, osimertinib, poziotinib, TAK788, nazartinib, lapatinib, or neratinib
3. Cohorts A and B only: Previously received anti-EGFR or anti-HER2 monoclonal antibodies or EGFR or HER2 antibody-drug conjugates including but not limited to cetuximab, necitumumab, panitumumab, trastuzumab, trastuzumab emtansine (TDM-1), or pertuzumab
4. Received other recent antitumor therapy including:
    a. Investigational therapy administered within the 21 days prior to Cycle 1 Day 1 or 5 half-lives, whichever is shorter.
    Note: Exceptions may be made with Medical Monitor approval for investigational therapies where the half-life is unknown or shorter than 5 half-lives have passed between last dose of investigational therapy and Cycle 1 Day 1.
    b. Any standard chemotherapy or radiation within 14 days prior to Cycle 1 Day 1
    Note: Adequate time must have passed from the last treatment to first scheduled treatment in this study to clear the timeframe for actual or anticipated toxicities of such treatment
    c. Any immunotherapy (e.g., pembrolizumab, nivolumab, atezolizumab, or durvalumab) within 21 days prior to Cycle 1 Day 1
5. Clinically active or symptomatic ILD or interstitial pneumonitis.

    Note: A patient with documented resolution of prior clinically significant ILD or radiation pneumonitis will be eligible for enrollment.

6. Has any of the following within 28 days prior to the first dose of study drug:
    - ALT and AST > 3 × ULN if no hepatic metastases are present; > 5 × ULN if hepatic metastases are present
    - Total bilirubin > 1.5 × ULN; > 3 × ULN with direct bilirubin > 1.5 × ULN in the presence of Gilbert's syndrome
7. Untreated central nervous system (CNS) metastases and/or untreated/treated leptomeningeal disease
    Note: Patients who require steroid for CNS metastases must be on a stable or tapering dose of corticosteroids for at least 2 weeks prior to Cycle 1 Day 1 to be eligible for the trial. If applicable, patients must complete stereotactic radiosurgery 7 days prior to Cycle 1 Day 1 and whole brain radiotherapy 21 days prior to Cycle 1 Day 1.
8. Receiving medication that prolongs QT interval, with a risk of TdP per protocol Appendix B, unless one of the following criteria are met:
    a. Enrollment is allowed if discontinuation of such medication occurs at least 5 half-lives before Cycle 1 Day 1 OR

b. The patient is on a stable dose of a concomitant medication listed in Appendix B prior to study entry and Sponsor approval is obtained

Note: Exceptions may be made with Medical Monitor approval (e.g., for medications where the half-life is unknown or for QT prolonging medications not listed in Appendix B).

9. Personal or familial history of Long QT Syndrome, sudden death, or TdP
10. History of significant cardiovascular disease, including:
    a. Cardiac failure New York Heart Association class III or IV or LVEF < 55%
    b. Myocardial infarction, severe or unstable angina within 6 months prior to enrollment
    c. TdP, ventricular arrhythmia (i.e., ventricular tachycardia or ventricular fibrillation)
    d. Clinically significant thrombotic or embolic events within 3 months prior to enrollment

       Note: Significant thrombotic or embolic events include but are not limited to stroke or transient ischemic attack. Catheter-related thrombosis is not a cause for exclusion. Diagnosis of deep vein thrombosis or pulmonary embolism is allowed.
    e. Any uncontrolled or severe cardiovascular disease
11. Known concurrent malignancy that is expected to require active treatment within 2 years or may interfere with the interpretation of the efficacy and safety outcomes of this study in the opinion of the treating Investigator and confirmed by the Medical Monitor

    Note: Prior malignancy that is at a low risk of progression or recurrence (e.g., superficial bladder cancer, non-melanoma skin cancers, or low-grade prostate cancer not requiring therapy) may be allowed after discussion and approval of the Medical Monitor
12. Major surgery within 4 weeks prior to Cycle 1 Day 1
13. Infection requiring systemic treatment within 7 days prior to Cycle 1 Day 1
14. History of severe allergic or anaphylactic reactions or hypersensitivity to compounds of similar chemical or biologic composition as tarloxotinib
15. Known human HIV infection or active hepatitis B or C
16. Women who are pregnant or breastfeeding
17. Any other medical condition (e.g., alcohol abuse) or psychiatric condition that, in the opinion of the Investigator, might interfere with the patient's participation in the trial or interfere with the interpretation of trial results

5.3 Patient Withdrawal Criteria

All patients are free to discontinue study treatment or withdraw from the study at any time. All patients wishing to discontinue from study treatment or withdraw from the study will be queried to determine the reason for withdrawal while respecting the privacy of the patient. The reason a patient decided to withdraw from study treatment will be recorded.

In the event of consent withdrawal, the Investigator should make every effort to ensure that the patient is followed for AEs for a minimum of 30 days after their last dose of study treatment, with documented patient agreement.

Patients will be discontinued from study treatment if any of the following events occurs:

- Any unacceptable toxicity attributable to study treatment (e.g., hepatotoxicity meeting Hy's Law criteria)
- Progressive disease according to RECIST v1.1 at any time during the study
  - Unless approved by the Medical Monitor (See Section 6.6)
- Clinical progression (e.g., symptomatic deterioration) not meeting the RECIST v1.1 criterion for progressive disease but considered by the Investigator to require withdrawal from study treatment
- Patient is unable to tolerate dosing after more than 2 dose reductions
- Patient misses 2 doses
  - Exception: Patients who miss 2 doses may continue study treatment following agreement between the Investigator and the Medical Monitor.
- Significant deviation from the protocol or eligibility criteria. These patients may continue study treatment following a discussion and agreement between the Investigator and the Medical Monitor and subsequent approval by the institutional review board (IRB) or independent ethics committee (IEC).
- Pregnancy
- Patient withdrawal of consent and/or election to discontinue study treatment
- Termination of the study by the Sponsor
- Any other reason which, in the opinion of the Investigator, would justify removing the patient from the study treatment

A patient may also be withdrawn from study treatment by the Sponsor, Regulatory Authorities, or IECs/IRBs.

If a patient discontinues study treatment due to the ongoing coronavirus disease 2019 (COVID-19) global pandemic, information should be captured on the eCRF so that this can be summarized in the clinical study report at the end of the study, in line with the FDA Guidance (FDA 2020). The reason for discontinuation should be recorded in the eCRF as COVID-19, if applicable, and include as many details as possible. For example, specific reasons may include, but are not limited to:

- The patient exhibits symptoms consistent with COVID-19.
- The patient has a positive test result for COVID-19.
- The patient has neither symptoms nor a positive test for COVID-19 but has decided to discontinue treatment due to personal choice related to COVID-19 concerns.

Patients who are discontinued from study treatment for reasons other than progressive disease by RECIST v1.1 should undergo scans for tumor assessment according to the original tumor assessment schedule (every 8 weeks [± 5 days] from Cycle 1 Day 1) until any of the following occurs, whichever comes first:

- Progressive disease (PD) by RECIST v1.1,
- Initiation of new anticancer treatment, or
- Discontinuation from the study (death, withdrawal of consent, or loss to follow-up).

After discontinuation from study treatment, all patients will have an End-of-Treatment Visit (EOT). All patients, including those discontinued due to PD, will undergo a post-treatment Safety Follow-up Visit at 30 days (± 7 days) after last tarloxotinib infusion.

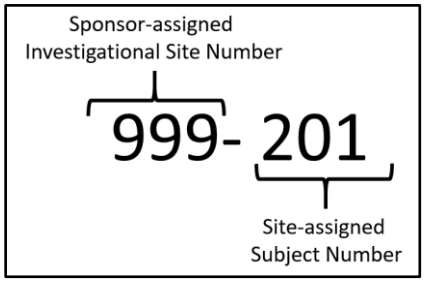
Withdrawal from the study should be in a step-wise fashion. As mentioned above, patients may withdraw or be withdrawn from study treatment. Any patient who withdraws or is withdrawn from study treatment should be encouraged to complete all planned safety and follow-up assessments. If the patient wished to withdraw from all study assessments, permission should be requested to contact the patient, a designated contact person, or the patient's primary care provider. If the patient does not wish any direct follow-up, permission should be requested to conduct periodic medical record review and/or contact the patient's medical care provider.

6. TREATMENT OF PATIENTS

6.1 Patient Enrollment

Prior to any study-related assessments, all potential patients will provide written informed consent. Informed consent can be obtained any time prior to Cycle 1 Day 1. All patients who provide informed consent will be assigned a unique patient identification number consisting of 6 digits, the first 3 digits will represent investigational site and the second 3 digits will identify the patient within that site (Figure 13); patient numbering within sites will begin with the number "– 201." Once a patient identification number has been assigned, it will be used to identify the patient throughout the study and it cannot be reassigned to another patient.

Figure 13: Sample Patient Identification Number



All potential patients must be approved by the Medical Monitor prior to enrollment. Investigational sites will provide the Medical Monitor with a completed Eligibility Checklist and relevant redacted source documents. The Medical Monitor (or designee) will review the provided documentation and confirm the patient's preliminary eligibility. The Medical Monitor

(or designee) should be able to respond within 1 business day. Following review of the provided documentation, the Medical Monitor (or designee) will notify the investigational site if the patient appears eligible. Patients who meet eligibility criteria may be enrolled. Patients will be considered enrolled after receiving any tarloxotinib.

6.2 Tarloxotinib Administration

Tarloxotinib will be administered as an IV infusion using an IV infusion or syringe pump and a 0.2-micron inline filter. Tarloxotinib may be infused with latex-free polyvinyl chloride or polyolefin containers and equipment.

6.2.1 Tarloxotinib Dose Calculation

Tarloxotinib will be administered at a dose level of 150 mg/m^2. The dose administered will be based on the patient's body surface area (BSA) determined on Day 1 of each cycle or within 7 days (e.g., Day 21 of the prior cycle). The DuBois and DuBois formula for BSA calculation is:

$$BSA = (W^{0.425} \times H^{0.725}) \times 0.007184$$

Investigational sites are instructed to use the DuBois and DuBois formula but may also use the formula/method in current institutional practice if accurate dose calculation can be assured.

Tarloxotinib doses within a cycle do not need to be adjusted unless there is a > 10% change in weight.

6.2.2 Tarloxotinib Infusion Duration

Tarloxotinib infusions must be at least 1 hour (60 minutes) in duration. The tarloxotinib infusion can be slowed or interrupted in the event of infusion-related reactions. If the tarloxotinib infusion is interrupted, it should be restarted at one-half the infusion rate after the symptoms of the infusion-related reaction have resolved.

6.2.3 Tarloxotinib Administration Schedule

Tarloxotinib will be administered on Day 1, Day 8, Day 15, and Day 22 of every 28-day cycle. All infusions after Cycle 1 Day 1 will be administered 7 days ± 1 day after the prior infusion. Investigators are instructed to avoid dose schedule modifications whenever possible, especially within the first 3 cycles of study treatment. The reason for the dose schedule modification should be recorded in the eCRF.

Dose Delays

All dose schedule modifications of > 1 day must be discussed with the Medical Monitor (or designee). Intentional cycle delays of > 1 day (e.g., patient vacation, physician requested "drug holiday") must be approved by the Medical Monitor (or designee). Study visits will align with tarloxotinib infusion days. If a tarloxotinib dose must be delayed > 3 days, this will be considered a missed dose.

Missed Doses

If a patient misses a dose due to hospitalization or any other reason, the next dose received will be referred to as the next scheduled dose (e.g., If a patient misses their Cycle 1 Day 22 infusion, the next dose will be administered at their Cycle 2 Day 1 visit.). If a patient must miss their Cycle 2 Day 1 dose, the assessments that were planned for this visit (e.g. PK assessments and ECGs) should be collected at the Cycle 2 Day 8 visit to ensure adequate data is collected for these endpoints. For other missed visits, any assessments that were part of the missed visit, but are not part of the next visit (i.e., no need to duplicate tests) should be collected, if possible, at the next visit. Radiographic tumor assessments should continue per the Study Schedule (i.e., every 8 weeks [± 5 days] from Cycle 1 Day 1) regardless of changes to the dosing schedule.

If there is an unavoidable delay of an infusion due to COVID-19, the Medical Monitor should be informed as soon as possible. The infusion should be rescheduled based on Investigator judgment, taking into consideration the patient's safety.

6.3 Premedication

All patients may receive steroid or anti-emetics premedication prior to tarloxotinib infusions. The premedication regimen will be determined by the Investigator and may be adjusted at subsequent infusions based on the signs and symptoms observed during or after prior infusions.

Additionally, patients may be discharged with take-home prophylactic medications.

The tarloxotinib Phase 1 and 2 studies demonstrated that tarloxotinib is associated with non-hematologic toxicities. These included mainly low-grade skin rash and diarrhea typical of that observed with EGFR TKIs. For this reason, prophylaxis and treatment for these toxicities should be considered following institutional guidelines, similar to another EGFR TKI such as erlotinib or afatinib.

Infusion-related reactions were observed in patients receiving tarloxotinib. These reactions were characterized by flushing, urticarial skin rash, pruritus, and hypotension occurring during or immediately following the infusion of tarloxotinib. Patients who experienced an infusion reaction with the first dose of tarloxotinib received prophylactic steroids prior to subsequent doses, which reduced the severity of infusion reactions. Therefore, prophylaxis for drug hypersensitivity reactions that may include a glucocorticoid and an anti-histamine may be considered prior to each tarloxotinib dose according to institutional guidelines.

Nausea and vomiting have occurred in patients in the Phase 1 and 2 studies; therefore, anti-emetic prophylaxis for minimally to moderately emetogenic regimens should be considered after Cycle 1 Day 1 according to institutional guidelines. Prophylaxis against nausea and vomiting in the tarloxotinib studies was based on metoclopramide as a single agent. If a 5-HT3 antagonist is required, palonosetron should be employed, if possible, as it is considered to have the least potential among 5-HT3 antagonists for QT prolongation.

6.4 Potassium Supplementation

Serum electrolytes (including potassium) will be checked prior to each tarloxotinib infusion.

- Tarloxotinib will not be administered if the serum potassium level is < 3.5 mEq/L.
- Patients with a serum potassium of < 3.5 mEq/L will receive potassium replacement per institutional policy (IV and/or oral) and have the scheduled tarloxotinib infusion delayed at least 24 hours and potassium levels rechecked within 1 hour prior to the rescheduled infusion.

All patients who present with a serum potassium level of ≥ 3.5 mEq/L will be given potassium supplementation prior to tarloxotinib infusion based on pre-infusion serum potassium result (Table 5).

Table 5: Potassium Supplementation Guidelines

Pre-infusion Serum Potassium (mEq/L)	**Potassium Supplement Strategy**
< 3.5	• Hold tarloxotinib • Administer potassium replacement per institutional policy (IV and/or PO) • Delay the scheduled tarloxotinib infusion delayed at least 24 hours and potassium levels rechecked within 1 hour prior to the rescheduled infusion
3.5 to 4.0	• All patients will be supplemented daily with 20 mEq of potassium (IV or PO).
> 4.0	• Administer potassium replacement per institutional policy (IV and/or PO)

IV = intravenous; PO = oral

6.5 Treatment and Retreatment Criteria

The result of tumor assessments is not required for the initiation of subsequent cycles, but patients must meet the following criteria before receiving each tarloxotinib infusion. **Note:** all ECG dose modifications will be based on the average manually measured QTcF.

- No QTcF of ≥ 601 msec during any previous infusion

Note: Patients with QTcF of ≥ 501 msec and < 601 msec during or following the prior infusion MUST be dose reduced. If QTcF prolongation is ≥ Grade 3, an ECG may need to be repeated more frequently during a patient's visit as indicated in Table 7, depending on the degree of the prolongation and per institutional standards.

- Check serum electrolytes
  - Pre-infusion magnesium and calcium in normal range, unless an exception is approved by the Medical Monitor.
  - If other electrolytes (eg, sodium, chloride) are outside of the normal range, patient can receive tarloxotinib infusion if it is deemed safe per Investigator discretion.
  - Pre-infusion serum potassium must be ≥ 3.5 mEq/L.
- Pre-infusion ECG

  - No evidence of second- or third-degree atrioventricular block
  - QTcF interval of < 450 msec
- Skin rash of ≤ Grade 2
- Gastrointestinal toxicity of ≤ Grade 2
- Any other clinically significant tarloxotinib-related toxicity must return to at least Grade 2.

All patients not meeting retreatment criteria must be discussed with the Medical Monitor (or designee) and possible dose/schedule modification and/or study treatment discontinuation discussed.

6.6 Treatment Beyond Progression

Patients with disease progression may continue to receive tarloxotinib if, in the opinion of the Investigator, the patient is still benefiting (e.g., asymptomatic systemic progression or local symptomatic progression) following discussion with and approval by the Medical Monitor (or designee). The IRB/IEC will be notified of any planned treatment beyond progression. Patients may receive palliative radiation to disease sites of progression, including brain metastases, following discussion with and approval by the Medical Monitor (or designee).

6.7 Tarloxotinib Dose Modifications

All patients will begin study treatment with a dose level of 150 mg/m^2 based on the body weight measured on Day 1 of each cycle (or within 7 days prior [e.g., Day 22 of the prior cycle]). As described above, tarloxotinib dose calculations do not need to be adjusted within a cycle unless the patient has a > 10% change in body weight. Other dose modifications may be required based on QTc prolongation, infusion-related reactions, and other tarloxotinib-related toxicity as described in:

- Table 7: Treatment Guidelines for QTcF Prolongation
- Table 8: Treatment Guidelines for Infusion-related Reactions
- Table 9: Treatment Guidelines for Tarloxotinib-related Non-Hematologic Toxicity

Dose level reductions will be in a step-wise fashion. The dose level reductions are presented in Table 6. If a patient requires more than 2 dose level reductions, tarloxotinib will be permanently discontinued.

Table 6: Tarloxotinib Dose Reductions

Dose Level Reduction	Tarloxotinib Dose (mg/m^2)	
	Grade 3 QTc prolongation based on a QTcF ≥ 501 msec	IRR and/or hematologic/ non-hematologic toxicity
1	100	120
2	75	
3	Discontinue tarloxotinib	

IRR = infusion-related reaction; QTc = corrected QT interval; QTcF = corrected QTc interval as calculated according to Fridericia's formula

Hematologic toxicity has not been associated with tarloxotinib administration to date. However, if Grade 3 or 4 neutropenia or thrombocytopenia considered related to tarloxotinib occurs, then the treatment guidelines for non-hematologic toxicity described in Table 9 should be followed. Dose modifications for anemia (any grade) or for Grade 2 or less neutropenia or thrombocytopenia are not required.

If a tarloxotinib-related toxicity results in a treatment delay of more than 3 weeks (withholding more than 2 doses of tarloxotinib), patients will be removed from study treatment unless otherwise approved by the Medical Monitor.

6.7.1 Treatment Guidelines for QTc Prolongation

Immediate medical management of patients will be based on the following:

1. Baseline: A pre-infusion (baseline) ECG will be obtained on all patients, if the automated measurements indicate a QTcF of ≥ 450 msec
   a. The single QTcF will be verified by manually measuring at least 3 complexes within the ECG and determining the average QTcF
   b. All patients must have a pre-infusion QTcF of < 450 msec by either:
      i. Calculation using the automated measurements of the first ECG or
      ii. The manual measurement of a single ECG

   If it is determined that the manually read QTcF ≥ 450 msec, the Medical Monitor should be contacted to discuss the clinical significance of the reading and to determine if it is appropriate to move forward with the infusion.

2. During treatment: Grade 3 QTc prolongation (any QTcF that is ≥ 501 msec OR > 60 msec QTcF increase relative to pre-infusion) will be manually verified by measuring at least 3 complexes with the ECG and determining the average QTcF. If QTcF prolongation is ≥ Grade 3, an ECG may need to be repeated more frequently during a patient's visit, depending on the degree of the prolongation, as indicated in Table 7 and per institutional standards.

Note: Dose modification will be based on the average QTcF using the manual measurements.

If the Investigator has any question regarding the local automated reading, a local cardiologist should be consulted. Treatment guidelines for patients experiencing QTc prolongations are provided in (Table 7).

Patients who experience ≥ Grade 3 QTc prolongation must be assessed by the Investigator (or qualified designee) prior to discharge.

Table 7: Treatment Guidelines for QTc Prolongation

QTc Prolongation	After Tarloxotinib Administration

Grade 1
450 to 480 msec QTcF
	• Cycle 1 and Cycle 2 Day 1
	  ○ May be discharged if the 4-hour (or later) post-infusion QTcF is Grade 1 or lower and asymptomatic
	• After Cycle 2 Day 1
	  ○ Obtain pre-infusion and 2-hour post-infusion ECGs
	  ○ May be discharged if the 2-hour (or later) post-infusion QTcF is ≤ Grade 1 and the patient is asymptomatic
	• Continue the same tarloxotinib dose for subsequent cycles

Grade 2
481 to 500 msec QTcF
	• Cycle 1 and Cycle 2 Day 1
	  ○ May be discharged if the 4-hour (or later) post-infusion QTcF is ≤ Grade 2 and the patient is asymptomatic
	• After Cycle 2 Day 1
	  ○ Obtain pre-infusion and 2-hour post-infusions ECGs
	  ○ May be discharged if the 2-hour or later post-infusion QTcF is ≤ Grade 2 and the patient is asymptomatic
	• Continue the same tarloxotinib dose for subsequent cycles

Grade 3
≥ 501 msec QTcF
	• Obtain ECGs every 15 to 30 minutes until QTcF is ≤ Grade 2 and then obtain ECGs every 1 hour
	• May be discharged home if 2 subsequent measurements (at least 15 minutes apart) after the 4-hour post-infusion QTcF is ≤ Grade 2 and no significant arrhythmias
	• **If QTcF is ≥ 601 msec, permanently discontinue tarloxotinib**
	• If QTcF ≥ 501 msec and ≤ 600 msec
	  ○ Resume tarloxotinib dosing **<u>with dose reduction</u>**
	  ▪ 1st occurrence: reduce to 100 mg/m^2
	  ▪ 2nd occurrence: reduce to 75 mg/m^2
	  ▪ 3rd occurrence: permanently discontinue tarloxotinib
	• Obtain ECGs prior to and hourly (for at least 4 hours) following the next tarloxotinib infusion

Grade 3 > 60 msec increase from pre-infusion QTcF AND ≤ 500 msec QTcF	• Obtain ECGs every 15-30 minutes until QTcF is ≤ Grade 2 and then obtain ECGs every 1 hour • May be discharged home if 2 subsequent measurements (at least 15 minutes apart) after the 4-hour post-infusion QTcF is ≤ Grade 2 and no significant arrhythmias • Obtain ECGs prior to and hourly (for at least 4 hours) following the next tarloxotinib infusion
Grade 4 TdP or polymorphic ventricular tachycardia, signs/symptoms of serious arrhythmia	• Place patient on telemetry and obtain ECGs as clinical indicated • Obtain Cardiologist consult and admit to hospital for extended observation on telemetry • Permanently discontinue tarloxotinib

ECG = electrocardiogram; msec = millisecond; QTcF = corrected QT interval as calculated according to Fridericia's formula; TdP = Torsade de Pointes

Note: If QTcF prolongation is ≥ Grade 3, an ECG may need to be repeated more frequently during the patient's

visit depending on the degree of the prolongation and per institutional standards.

Treatment and retreatment guidelines in this study are based on absolute QTcF observations that vary from the NCI CTCAE. Importantly, dose reductions are not based on the QTcF change from baseline, only the absolute QTcF. For example, if a patient has a change > 60 msec from baseline but has an absolute QTcF ≤ 500 msec, no dose reduction is required.

6.7.2 Treatment Guidelines for Infusion-related Reactions

Treatment and management of infusion-related reactions will be based on the severity and type of symptom(s) experienced. Treatment guidelines for infusion-related reactions are presented in Table 8.

Table 8: Treatment Guidelines for Infusion-Related Reactions

Grade (CTCAE v5.0)	Definition	Treatment Guideline
Grade 1	• Mild transient reaction • Infusion interruption not indicated • Intervention not indicated	• Monitor for at least 2 hours after the end of the infusion • Provide patient instructions and prophylactic medications at discharge as appropriate • Consider adjusting premedication based on symptoms for subsequent infusions
Grade 2	• Therapy or infusion interruption indicated but responds promptly to symptomatic treatment • Prophylactic medications indicated for ≤ 24 hours	• Administration of medications (e.g., anti-histamines, steroids, NSAIDs and IV fluids), as appropriate • Monitor for at least 2 hours after the end of the infusion • Consider adjusting premedication based on symptoms for subsequent infusions
Grade 3	• Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion) • Recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae	• Administration of medications (e.g., anti-histamines, steroids, NSAIDs and IV fluids), as appropriate • Hospitalization for medical care and observation • Reduce tarloxotinib dose to 120 mg/m^2 for subsequent doses*, or consider slowing infusion rate, and/or adjusted premedication after discussion with the Medical Monitor • If Grade 3 infusion reaction recurs after this initial dose reduction, then reduce the tarloxotinib dose to 75 mg/m^2 for subsequent doses*
Grade 4	• Life-threatening consequences • Urgent intervention indicated	• Hospitalization for urgent medical treatment • Discontinue tarloxotinib permanently

CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug
* Dose re-escalation may be permitted following discussion and approval by the Medical Monitor

6.7.3 Treatment Guidelines for Other Non-Hematologic Toxicity

Table 9 provides treatment guidelines for treating tarloxotinib non-hematologic toxicities other than QT prolongation and infusion-related reactions.

Table 9: Treatment Guidelines for Tarloxotinib-Related Non-Hematologic Toxicity

Toxicity (CTCAE v5.0)	Details	Hold Dose	Dose Levels After Recovery to ≤ Grade 2 or Baseline
Grade 2 **Intolerable**	Intolerable skin toxicity or diarrhea	Hold dose until resolution to Grade 0 or 1 or Grade 2 tolerable	If symptoms are intolerable, recurrent, or not controlled by supportive care, hold dose until symptoms improve and reduce to next lower dose level
Grade 2	ALT or AST > 3 x ULN	Hold dose until resolution to < Grade 2 or baseline	150 mg/m^2 (no reduction)
	ALT or AST > 3 x ULN (Grade 2) **AND** a total bilirubin ≥ 2 x ULN (patients without liver metastasis)**	Treatment to be discontinued	Not applicable
Grade 3	Except nausea and vomiting*	Hold dose until resolution to Grade 0 or 1 or Grade 2 tolerable	120 mg/m^2; if recurs, then second reduction to 75 mg/m^2
Grade 4	Life-threatening conditions	Treatment to be discontinued	Not applicable
Grade 4	Except fatigue and non-life-threatening pulmonary embolism that are adequately treated	Hold dose until resolution to Grade 0 or 1	120 mg/m^2; if recurs, then second reduction to 75 mg/m^2

ALT = alanine aminotransferase; ASP = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; ULN = upper limit of normal
* May hold or reduce if nausea/vomiting continues despite optimized anti-emetic treatment
** Tarloxotinib-related toxicity meeting the definition of Hy's Law, tarloxotinib will be discontinued permanently

6.8 Compliance

Investigators are required to conduct the study in compliance with the protocol. Compliance with the protocol will be closely monitored. Important aspects of compliance with this clinical trial include:

- Eligibility,
- Tarloxotinib administration, including:
  - Dose calculation
  - Dose modification
  - Infusion duration
- Performance of protocol-specified assessments,

- ECG monitoring, and
- AE reporting

Protocol deviations are defined as any departure from the protocol or associated instructions and will be monitored. Deviations from the protocol, including violations of inclusion/exclusion criteria, will be assessed as "minor" or "major." Protocol deviations at investigational sites will be discussed with the Investigator and additional training will be provided as needed to secure Investigator compliance.

Study staff will receive additional training as needed to prevent non-compliance.

6.9 Study Visits

Protocol-required assessments scheduled for each study visit are summarized in the Schedule of Events and described below. All assessments with a time point relative to study treatment infusion may be performed in the 5 minutes prior to and following the protocol-specified time. Any assessment that is not able to be collected at the protocol-specified time (e.g., blood sample for pharmacokinetic testing) should be obtained as soon as practicable and the actual date/time of collection recorded.

6.9.1 Screening Period/Baseline Assessments

Patients may be screened anytime during the 28 days prior to Cycle 1 Day 1. Unless otherwise specified, baseline assessments may be done anytime following consent and prior to the first study drug administration. Patients who are determined not to meet eligibility criteria at any time prior to Cycle 1, Day 1 will not receive study drug. The following will be assessed or measured at screening/baseline:

- Informed consent
- Eligibility (including tumor assessment)
- Medical/Disease history
- Smoking history: Smoking history should be documented in the eCRF page as "never", "former" (with quit date), or "current" (document pack years).
- Demographics
- Physical examination
- Weight
- ECOG
- Vital signs
- ECG (12-lead)
- Hematology panel
- Serum chemistry panel

- Urinalysis
- Pregnancy test
  - Serum pregnancy test within 3 to 7 days of Cycle 1 Day 1
- Tumor tissue
  - FFPE block from newly obtained biopsy or archive tissue of at least 8 to 10 slides

    Note: Adequacy must be confirmed by local pathologist.
- Concomitant medications
  - Record all concomitant medications use after 14 days prior to Cycle 1 Day 1
  - Special attention should be accorded to medications that are known to cause prolongation of QTc or deplete potassium
- Conduct baseline radiographic tumor assessment
  - Perform according to institutional practice; include CT or MRI of the chest and abdomen, brain scan, and bone scan. The baseline radiographic tumor assessment is required within 28 days prior to the first dose of tarloxotinib. Brain and bone scans do not need to be repeated for patients with no brain or bone metastases at baseline. A recently completed negative positron emissions tomography (PET) scan can be substituted for the baseline bone scan.

6.9.2 Treatment Period

The following will be assessed or measured at the indicated study days:

Day 1

- Complete physical examination
- ECOG (Cycle 1)
- Weight
- Vital signs
  - Pre-infusion
  - End of infusion (EOI)
  - 30, 60, and 90 minutes after EOI (± 10 minutes)
- ECG (12-lead)
  - Cycle 1
    - Pre-infusion
    - EOI
    - 1, 2, 3, and 4 hours after EOI (± 10 minutes)
    - Hourly thereafter as needed (see Section 6.9.2.1)
  - Cycle 2
    - Pre-infusion

        - EOI
        - 1, 2, 3, and 4 hours after EOI (± 10 minutes)
        - Hourly thereafter as needed (see Section 6.9.2.1)
    - Cycles 3+
        - Pre-infusion
        - 2 hours after EOI (± 10 minutes)
        - 4 hours after EOI (patients with QTcF ≥ 501 msec) (± 10 minutes)
        - Hourly thereafter as needed (see Section 6.9.2.1)
- Hematology panel
- Serum chemistry panel
- Serum potassium (Cycles 1 and 2 only)
    - EOI
    - 3 hours after EOI (± 10 minutes)
- Urinalysis
- Pregnancy test
    - Urine (dipstick allowed)
- PK samples (Cycles 1 and 2 only)
    - Pre-infusion (± 5 minutes)
    - EOI (± 5 minutes)
    - 3 hours after EOI (± 10 minutes)
    - 7 hours after EOI (in a subset of patients on Cycle 1 Day 1 only) (± 10 minutes)
- Blood sample for biomarkers (e.g., ctDNA) (Cycles 1 and 2)
- Ensure that all electrolytes are within normal ranges
- Potassium supplementation, if applicable (See Table 5)
- Premedication, as applicable per local institutional guideline
- Tarloxotinib infusion (at least 1 hour in duration)
- Concomitant medications
- Assess AEs

Days 8, 15, and 22

- Vital signs
    - Pre-infusion
    - EOI
    - 30, 60, and 90 minutes after EOI (± 10 minutes)
- ECG (12-lead)

- Cycle 1
  - Pre-infusion
  - EOI
  - 1, 2, 3, and 4 hours after EOI (± 10 minutes)
  - Hourly thereafter as needed (see Section 6.9.2.1)
- Cycles 2+
  - Pre-infusion
  - 2 hours after EOI (± 10 minutes)
  - 4 hours after EOI (patients with ≥ Grade 3 QTcF prolongation) (± 10 minutes)
  - Hourly thereafter as needed (see Section 6.9.2.1)

- Serum chemistry panel
- Urinalysis (Cycle 1 only)
- Optional tumor biopsy
  - Day 15 after EOI (preferred) or Day 16 (within 24 hours of any EOI)
  - Plasma samples for PK and biomarkers should be obtained as close to the time of biopsy as possible
- Ensure that all electrolytes are within normal ranges
- Potassium supplementation, if applicable (See Table 5)
- Premedication, as applicable per local institutional guideline
- Tarloxotinib infusion (at least 1 hour in duration)
- Concomitant medications
- Assess AEs

Note: Pre-infusion assessments scheduled for Day 1 of Cycles 2 and later cycles are considered Day 29 of the prior cycle. If any patient is not proceeding to an additional cycle, the assessments scheduled for the EOT should be performed within ± 7 days of their last dose of tarloxotinib.

Every 8 weeks (± 5 days) From Cycle 1 Day 1

- Radiographic tumor assessments
  - The first post-baseline radiographic tumor assessment will occur 8 weeks after the Cycle 1 Day 1 visit. The same imaging modality used for baseline imaging (i.e., CT or MRI) must be used for subsequent radiographic tumor assessments.

6.9.2.1 Electrocardiogram Guidance for QT Prolongation During the Treatment Period

In the event of QTcF prolongation (≥ 501 msec or > 60 msec increase compared to pre-infusion), repeat ECG every 15 to 30 minutes until resolved to Grade 2 (481 to 500 msec) or lower (≤480 msec) and then obtain ECGs every hour. For patients who have had a Grade 3 event of

QTcF prolongation at a previous infusion ECGs should be conducted hourly for the 4 hours following the subsequent infusion.

6.9.3 End-of-Treatment Visit

The EOT should be completed within ± 7 days of the last dose of tarloxotinib. The following will be assessed or measured at EOT:

- Complete physical examination
- Weight
- Vital signs
- ECG (12-lead)
- Hematology panel
- Serum chemistry panel
- Pregnancy test
- Urine (dipstick acceptable)
- Blood sample for biomarkers (e.g., ctDNA)
- Concomitant medications
- Assess AEs
- Record the date and reason for the decision to discontinue study treatment

6.9.4 Safety Follow-up Visit

All patients will return to the investigational site 30 days (± 7 days) following the last tarloxotinib infusion for the Safety Follow-up Visit. At this visit, the following will be assessed or measured:

- Physical examination
- Weight
- Vital signs
- ECG (12-lead)
- Hematology panel
- Serum chemistry panel
- Urinalysis
- Assess AEs

6.10 Concomitant Medications and Treatments

All medications (prescription and over-the-counter) and blood products taken within 14 days of Cycle 1 Day 1 until the EOT will be recorded. The reason(s) for treatment, dose, and dates of treatment will be recorded. In addition, concomitant medications used to treat AEs occurring up to 30 days after the last dose of tarloxotinib will be recorded.

6.10.1 Prohibited Medications

Concomitant medications and therapies excluded during the conduct of this trial include:

- Any other anticancer treatment including non-palliative radiation, chemotherapy, monoclonal antibodies, or TKIs
- Hormonal therapy for cancer

Note: Female patients who have been on hormone replacement therapy for menopausal symptoms for a period of at least 2 months will not be excluded from the study provided the planned hormone replacement therapy regimen remains largely unchanged during the conduct of the study

- Other tumor-targeted therapies
- Limited-field palliative radiotherapy to non-target lesions and bone-targeted agents, such as zoledronic acid and denosumab, are permitted.
    - Tarloxotinib should be delayed during radiotherapy and resumed upon completion of radiotherapy, if deemed appropriate by the treating physician after discussion with the Medical Monitor.
- Medications that prolong QT interval and have a risk of TdP (See Appendix B)

Patients should avoid all herbal remedies during study treatment; however, if herbal remedies are used, they should be documented as a concomitant medication. Patients and study staff should be instructed to notify all care providers that they are participating in a clinical study that has identified prohibited medications.

7. ASSESSMENT OF EFFICACY

Tumor assessment and imaging will be performed according to institutional practice and will include CT or MRI of the chest and abdomen, brain scan, and bone scan at baseline. The baseline radiographic tumor assessment is required within 28 days prior to the first dose of tarloxotinib. Brain and bone scans do not need to be repeated for patients with no brain or bone metastases at baseline. Recently completed negative positron emissions tomography (PET) scans can be substituted for baseline bone scans. Subsequent radiographic tumor assessments will be every 8 weeks (±5 days) with respect to Cycle 1 Day 1, until unequivocal PD is documented. The same imaging modality used for baseline imaging (i.e., CT or MRI) must be used for subsequent tumor assessments in each patient. In accordance with RECIST v1.1, response (PR and CR) must be confirmed by a second tumor assessment at least 8 weeks after the initial observed response. The scheduling of subsequent tumor assessments may be adjusted based on the date of the most recent imaging. Investigators are instructed to ensure that original

images (or high-quality copies) of all baseline and on-study scans are filed and available for transmission to the Sponsor (or designee) for a future possible central reading.

Efficacy assessment will be according to the local Investigator.

7.1 Primary Efficacy: Objective Response

The primary efficacy variable, ORR, is defined as a CR or PR according to RECIST v1.1 recorded from baseline until disease progression or death due to any cause.

7.2 Secondary Efficacy

Secondary efficacy variables include:

- BOR as measured by CR, PR, and SD
- DOR as measured from the date of first response to date of disease progression or death
- DCR based on patients who had CR or PR or SD for at least 2 cycles (8 weeks)
- PFS as measured from the date of first study drug dose to the date of the first objective documentation of radiographic disease progression or death due to any cause
- OS as measured from the date of first study drug dose to the date of death by any cause

8. ASSESSMENT OF SAFETY AND EXPLORATORY VARIABLES

8.1 Adverse Events

Investigators will collect information related to AEs will be collected throughout this clinical trial. The terms and definitions are consistent with the US DHHS guidance (2012).

All AEs occurring in all patients will be collected following exposure to study treatment (treatment emergent) until approximately 30 days after the last study treatment. Changes in the patient's medical condition that occur prior to the first exposure to study treatment will be reported as medical history. At each post-treatment visits, patients will be asked about any possible AEs in a non-leading manner. An example of a non-leading method of eliciting AE information is "*Have there been any changes in your health since you were here last*?" Patients should also be asked about the severity and/or persistence of any AEs that were ongoing at the time of their last visit.

All AEs will be followed until stabilization or resolution.

8.1.1 Adverse Events Definitions

8.1.1.1 Adverse Events (21 CFR 312.32(a))

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality. An AE can arise with any use of the drug (e.g., off-label use, use in

combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

8.1.1.2 Suspected Adverse Reaction (21 CFR 312.32(a))

Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

8.1.1.3 Unexpected (21 CFR 312.32(a))

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator's Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

8.1.1.4 Serious Adverse Event (21 CFR 312.32(a))

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- Life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect.

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

8.1.1.5 Serious Unexpected Suspected Adverse Reaction

A suspected adverse reaction that is both serious and unexpected will be reported in an expedited manner.

Rain Therapeutics (or designee) will report all serious unexpected suspected adverse reactions (serious, related, and unexpected AEs) to the regulatory agencies in the countries where this study is conducted per local country requirements.

- Regulatory agencies will be notified (e.g., by telephone, facsimile transmission, or in writing) of all fatal and/or life-threatening suspected adverse drug reactions as soon as possible but no later than 7 calendar days after first knowledge by the Sponsor that a case qualifies, followed by as complete a report as possible within 8 additional calendar days.

- Serious, unexpected suspected adverse reactions that are not fatal or life-threatening must be filed as soon as possible but no later than 15 calendar days after first knowledge by the Sponsor that the case meets the minimum criteria for expedited reporting.

8.2 Adverse Events Reporting

8.2.1 Adverse Event Term

AEs must be reported using standard medical terminology. The use of abbreviations (standard and nonstandard) should be avoided to help ensure a clear understanding of the event. An example of a standard abbreviation that may have several meanings is "MI" which could mean "myocardial infarction" or "mitral insufficiency." All AE terms will be coded using a standardized dictionary (i.e., Medical Dictionary for Regulatory Activities [MedDRA®]). Generally, when reporting a well-known and understood condition, it is preferable to report the overall diagnosis rather that the individual signs and symptoms; the exception to this rule in this study is when the patient experiences an infusion reaction (i.e., infusion-related reaction). The term "intermittent" should be avoided as the duration and incidence of events helps in understanding the safety profile of the study drug.

8.2.2 Adverse Event Severity

AEs will be reported at the highest experienced. AE severity will be graded according to NCI CTCAE v5.0. A copy of the document will be provided to investigational sites and an electronic version is available at:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Events not listed in NCI CTCAE will be graded according to the criteria described in Table 10.

Table 10: Severity Grading Guideline for Adverse Events Not Listed in NCI CTCAE

Adverse Events Not Listed in NCI CTCAE v5.0	
Grade	**Description**
1	Mild; Asymptomatic or mild symptoms; Clinical or diagnostic observations only; Intervention not indicated
2	Moderate; Minimal, local or noninvasive intervention indicated; Limiting age-appropriate instrumental activities of daily living*
3	Severe or medically significant but not immediately life-threatening; Hospitalization or prolongation of hospitalization indicated; Disabling; Limiting self-care activities of daily living**
4	Life-threatening consequences; Urgent intervention indicated
5	Death related to adverse event

Adapted from NCI CTCAE v5.0
NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events
*Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care activities of daily living refer to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.
Note: A semicolon indicates "or" within the description of the grade.

8.2.3 Adverse Event Duration

The start date (the date that the event was first noticed) and the end date (the date that the event had completely resolved or returned to baseline) will be recorded. If the exact date is not known, the best estimate should be reported.

All AEs will be followed until stabilization or resolution.

8.2.4 Adverse Event Causality

Where the determination of the relationship of the AE to study drug rests on medical judgment, the determination must be made with the appropriate involvement of the Investigator, or, if the Investigator is not a physician, a designated sub-investigator who is a physician.

Using the following criteria, Investigators will assess whether there is a reasonable possibility that the study drug caused or contributed to the AE.

Related

- The time sequence between the onset of the AE and study drug administration is consistent with the event being related to study drug; and/or

- There is a possible biologic mechanism for study drug causing or contributing to the AE; and the AE may or may not be attributed to concurrent/underlying illness, other drugs, or procedures.

Not Related

- Another cause of the AE is most likely; and/or
- The time sequence between the onset of the AE and study drug administration is inconsistent with a causal relationship; and/or
- A causal relationship is considered biologically unlikely.

8.3 Serious Adverse Events Reporting

Suspected adverse reactions that meet the definition of serious (see Section 8.1.1.5) require accelerated reporting.

To enable Rain Therapeutics to meet the expedited reporting requirements, Investigators must report all SAEs regardless of causality immediately (within 24 hours of learning of the event). SAEs will be reported by submitting a Serious Adverse Events Report to:

RainDrugSafety@rainthera.com

An event that results in hospitalization or prolongs an existing hospitalization will not be considered an SAE, if the only reason for that hospitalization or prolongation is:

- Administration of study treatment
- Administration of study procedures
- Placement of permanent intravenous catheter
- Hospice placement due to PD

8.4 Reporting Infusion-related Reactions

Infusion-related reactions (IRRs) are defined as “a disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.” The incidence and severity or IRRs will be collected in the eCRF designed to collected tarloxotinib infusion details; individual signs and symptoms of IRRs will be reported as AEs. Investigators will indicate which reported AEs were part of an IRR.

Table 11: Severity Grading Guideline for Infusion-Related Reactions

Infusion-Related Reactions	
Grade	**Description**
1	Mild transient reaction; infusion interruption not indicated; intervention not indicated
2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, intravenous fluids); prophylactic medications indicated for ≤ 24 hours
3	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae
4	Life-threatening consequences; Urgent intervention indicated
5	Death

Adapted from National Cancer Institute Common Terminology Criteria for Adverse Events v5.0
Note: A semicolon indicates "or" within the description of the grade.

8.5 Reporting QTc Prolongation

QT prolongation is not unexpected but it is an AE of special interest (AESI). Grade 3 AESIs require expedited reporting to the Sponsor. ECGs will be obtained throughout the study and will be read locally at the investigational sites. Grade 3 QTc prolongation (absolute QTcF of ≥ 501 msec or QTcF increase of > 60 msec relative to pre-infusion) or Grade 4 QTc prolongation will be reported as an AESI.

Any apparent Grade 3 AESIs should be verified by manually measuring at least 3 complexes within the ECG and determining the average QTcF.

AESIs will be reported by submitting an AESI Report to:

RAIN701@ncgs.com

All events of Grade 3 QTc prolongation (absolute QTcF of ≥ 501 msec or QTcF increase of > 60 msec relative to pre-infusion) or Grade 4 QTc prolongation will be reported as an AESI unless the event met the criteria of serious (see Section 8.1.1.4) in which case it will be reported as an SAE.

Table 12: NCI CTCAE Grading of ECG QTc Prolongation (Medical Dictionary of Regulatory Activities Code: 10014383)

ECG QTc Prolongation NCI CTCAE Grade				
1	**2**	**3**	**4**	**5**
Average QTc 450 to 480 msec	Average QTc 481 to 500 msec	Average QTc ≥ 501 msec OR > 60 msec change from baseline*	Torsade de Pointes OR polymorphic ventricular tachycardia OR signs/symptoms of serious arrhythmia	Not applicable

Adapted from NCI CTCAE v5.0

ECG = electrocardiogram; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; QTc = corrected QT interval; QTcF = corrected QTc interval as calculated according to Fridericia's formula

Definition of QTc prolongation: A finding of a cardiac dysrhythmia characterized by an abnormally long QTc

* Although a Grade 3 event (≥ 501 msec OR > 60 msec change from baseline) is reportable as an adverse event of special interest, dose reductions are not required for patients with absolute QTcF ≤ 500 msec and a ≤ 60 msec QTcF change from baseline.

8.6 Reporting Disease Progression and Death

PD, also referred to a disease progression, and death due to disease progression are study endpoints and information related to these events will collected in eCRFs specifically designed to collect these data. These events will not be reported as AE/SAEs unless the Investigator feels that these are accelerated, atypical, or related to study treatment. Deaths occurring within the 30 days after the last study treatment will be recorded. Any death that the Investigator feels is related to study treatment must be reported to the Sponsor as an SAE within 1 business day of first becoming aware of the death. Deaths occurring more than 30 days after study completion that are not considered related to study treatment may be reported cumulatively on a quarterly basis. Reports of all deaths must be communicated as soon as possible to the appropriate IRB/IEC and/or reported in accordance with local laws and regulations.

If an autopsy is performed, a copy of the report will be requested and provided to the Sponsor, if available.

8.7 Electrocardiogram Monitoring

Standard 12-lead ECGs will be performed locally using a calibrated digital ECG machine capable of providing automated measurements. All ECG tracings will be acquired with the patient in the supine position after the patient has been resting for at least approximately 5 minutes. ECG tracings will be measured and interpreted locally by a cardiologist or other qualified health care professional in accordance with institutional standard of care.

Immediate medical management of patients will be based on the automated reading obtained at the investigational site (all clinically significant ECG readings should be manually verified by a qualified individual). If the Investigator has any question regarding the local automated read, a local cardiologist should be consulted.

For patients with QT prolongation during tarloxotinib infusion, ECGs may need to be conducted more frequently than indicated in the Schedule of Events, depending on the degree of prolongation (see Section 6.9.2.1).

Rain will review all reported ECG measurements at least quarterly.

8.8 Vital Sign Assessments

The following vital signs will be assessed after the patient has been sitting for approximately 5 minutes. Vital signs will be obtained at each visit and prior to and following the start of each tarloxotinib infusion. Vital signs to be measured include:

- Blood pressure (systolic and diastolic; mmHg)
- Heart rate (beats per minute)
- Body temperature (°C)
- Respiration rate (breaths per minute)

8.9 Clinical Laboratory Assessments

Clinical laboratory assessments will be performed by each institution's local laboratory. The following laboratory variables (Table 13) will be collected in accordance with the Schedule of Events. All clinically significant unscheduled laboratory results will be recorded and all clinically significant laboratory results (scheduled and unscheduled) obtained during the study period will be reported as AEs (e.g., ≥ Grade 2 AST, ALT, or serum bilirubin).

Table 13: Clinical Laboratory Assessments

Serum Chemistry:	Sodium Potassium Chloride Bicarbonate Calcium Magnesium Phosphorous Glucose Blood urea nitrogen	Creatinine Bilirubin Aspartate aminotransferase increased Alanine aminotransferase increased Alkaline phosphatase Albumin Total protein
Hematology:	Hematocrit Hemoglobin White blood cell count with differential (reported as absolute counts) • Total neutrophils • Lymphocytes • Monocytes • Eosinophils • Basophils Platelet count	
Urinalysis:	Protein Glucose Ketones Urobilinogen Occult blood Microscopic sediment evaluation, as clinically indicated	
Pregnancy Test:	In women with childbearing potential only: serum β-human chorionic gonadotropin pregnancy test, urine, or urine dipstick	

8.10 Pregnancy Testing and Contraception

Patients who are WOCBP will have a serum pregnancy test performed within the 3 to 7 days prior to Cycle 1 Day 1 and a urine pregnancy test performed on Day 1 (pre-infusion) of all cycles and at EOT. Additional pregnancy testing may be performed according to institutional practice.

Patients who are WOCBP and male patients whose partners are WOCBP will be counseled on the importance of avoiding pregnancy during the study and must agree to the use of at least 1 highly effective method of contraception, in the opinion of the Investigator. WOCBP must use a highly effective method of contraception during the study and for at least 90 days after the last dose of study treatment. Male patients must use a condom and refrain from sperm donation during the study and for at least 30 days after the last dose of study treatment. All patients will be instructed to report any suspected pregnancies in themselves or their partner up to 90 days after the last infusion.

8.11 Physical Examinations

Complete physical examinations, including a review of all body systems, will be performed at the Screening Visit, Day 1 of all cycles, and the EOT as shown in the Schedule of Events. Clinically significant findings observed during physical examination will be reported as medical history (pretreatment) or AEs (post-treatment).

8.12 Eastern Cooperative Oncology Group

All patients will be assessed at Cycle 1 Day 1 using the ECOG Performance Status Scale. An ECOG performance score of 0 to 1 is required for study entry but is not a criterion for retreatment or study treatment discontinuation.

Table 14: ECOG Performance Status Scale

ECOG Performance Status Scale	
Grade	**Description**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, 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

ECOG = Eastern Cooperative Oncology Group
*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655.

8.13 Pharmacokinetics

Blood samples for tarloxotinib and tarloxotinib-E plasma concentrations will be collected prior to and following tarloxotinib infusion on Cycle 1 Day 1 and Cycle 2 Day 1. Serum potassium samples will also be collected after the infusion. Refer to the Laboratory Manual for sample collections, processing, and shipping instructions. All blood samples may be collected within the 5 or 10 minutes (see Schedule of Events) prior to or following the protocol-specified time point. Samples that cannot be collected with the sample collections window should be collected as soon as practicable and the actual date/time of collection reported.

8.14 Tumor Tissue

All patients will have tumor tissue collected at baseline. Tumor tissue may come from archived samples or from a recent pretreatment biopsy. Formalin-fixed paraffin embedded blocks are preferred, but if FFPE tissue is not available patients must have 8 to 10 prepared slides available. Mutation status will be confirmed after enrollment; these results will not be used to determine eligibility.

Tumor samples obtained during screening may also be used to determine levels of the reductase, STEAP4, which is responsible for generating the unstable intermediate species from the prodrug tarloxotinib to the pharmacologically active tarloxotinib-E under hypoxic conditions. As a third priority, if there is enough material, the samples will be used to for a hypoxia gene signature, phosphor-EGFR, and detection of EGFR homodimers by proximity ligation assay.

In addition to the above-mentioned tumor sample, an optional tumor tissue sample for measurement of the active metabolite (tarloxotinib-E) and tarloxotinib will collected from consenting patients on Cycle 1 Day 15 after infusion along with a blood sample for PK. If the

biopsy (and associated PK sample) is not able to be performed on Cycle 1 Day 15, it should be collected within the 24 hours after the tarloxotinib infusion or after another infusion day.

Refer to the Laboratory Manual for samples collection, processing, and shipping instructions.

8.15 Biomarker Analysis

Blood samples will be collected for biomarker assessment (e.g., ctDNA) according to the Schedule of Events. Refer to the Laboratory Manual for samples collection, processing, and shipping instructions.

Biomarker assessment may include ctDNA mutation analysis and evaluation of the concordance of EGFR and HER2 mutation identification between blood and tumor tissue.

9. STATISTICS

The primary objective of this study is to evaluate the ORR of tarloxotinib according to RECIST v1.1.

ORR will be estimated with precision using the 95% exact binomial confidence interval (CI) limits. The analyses of time-to-event endpoints (DOR, PFS, and OS) will follow standard methodology by employing Kaplan-Meier and Cox proportional hazard model methodology.

Safety data will be summarized descriptively. AEs will be summarized by severity, seriousness, and relationship to study drug. Laboratory data will be compared to baseline values.

Additional exploratory data analyses will be conducted as appropriate.

Details of the statistical analyses presented below will be provided in the study's statistical analysis plan (SAP). A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol. The SAP will be finalized prior to database lock. Any changes to the methods described in the plan will be described and justified in the final clinical study report.

9.1 Determination of Sample Size

The primary objective of this study is to determine if tarloxotinib provides a clinically significant tumor response to patients in each cohort. This will be investigated by assessing if the true ORR is at least above some desirable target level following therapy with tarloxotinib.

Currently approved EGFR or HER2 TKIs are, in general, ineffective against EGFR or HER2 exon 20 mutations and only associated with ORR of 12% or less (Robichaux 2018). Other treatment options for this population includes docetaxel, however, the ORR is no better than 15% (Hanna 2017).

For all cohorts, a Simon's 2-stage minimax design (Simon 1989) will be used. The null hypothesis that the true response rate is 15% will be tested against a one-sided alternative. In the first stage, 21 patients will be accrued. If there are 3 or fewer responses among these 21 patients, the cohort will be stopped. Otherwise, 22 additional patients may be accrued for a total of

43 patients in each cohort. The null hypothesis will be rejected if 11 or more responses are observed in 43 patients. This design yields a type I error rate of 0.0454 and power of 0.8014 when the true response rate is 31%. The probability of early termination at the end of the first stage is 0.61 if the true response rate is 15% (Ivanova 2012).

9.2 Patient Disposition

9.2.1 Disposition of Patients

An accounting of the study patients will be tabulated. Patients not meeting the eligibility criteria will be identified. Patients not completing the study will be listed along with the reason for their premature discontinuation. Reasons for premature discontinuation will be summarized.

9.2.2 Protocol Deviations

Deviations from the protocol including violations of inclusion/exclusion criteria will be assessed as "minor" or "major" in cooperation with the Sponsor. Deviations will be defined prior to database lock. Handling of major deviations in statistical analyses will be defined in the SAP.

9.2.3 Analysis Sets

The primary efficacy analysis population includes all patients who received at least 1 dose of tarloxotinib. The Safety Population will consist of all patients who received at least 1 dose of tarloxotinib. The Safety Population will be the analysis population for the safety and primary efficacy analyses.

The Per Protocol (PP) Population is defined as patients who did not have a major protocol deviation that may affect interpretation of results. Efficacy will also be analyzed using the PP Population. A detailed specification of the PP Population will be provided prior to the database lock.

All enrolled patients who receive study treatment, have a baseline tumor assessment with documentation of measurable disease, have at least 1 on-study tumor assessment, whether or not this occurs at the specified imaging interval, and have no major protocol violations including inclusion/exclusion criteria or prohibited concomitant medication while on study, will be considered evaluable for response. Patients with a confirmed objective response (CR or PR) per RECIST criteria will be considered responders. Patients without a confirmed objective response, SD, or PD will be considered to be non-responders.

Patients who are treated and removed from the study prior to on-study tumor assessments because of clinical disease progression will be considered non-responders. Patients who are treated and removed from study prior to on-study tumor assessments for reasons other than clinical progression will be considered unevaluable for response and may be replaced. In addition, if a patient is enrolled without central laboratory confirmation of the specific gene alteration, and then is subsequently found not to have the specific gene alteration by central review, this patient will be considered unevaluable for response and may be replaced.

9.3 General Considerations

Efficacy variables will be assessed without adjustment for multiple comparisons.

Continuous data will be summarized by cohort using descriptive statistics (number of patients, number of missing information, mean, median, standard deviation, minimum, and maximum). Categorical data will be summarized by cohort using frequency tables (frequency counts and percentages).

The statistical test for primary efficacy endpoint ORR will be performed by cohort using an exact binomial test for single proportion at the 5% one-sided significance level, unless otherwise stated.

9.4 Baseline Characteristics and Concomitant Medications

Demographic data, medical history, concomitant disease, and concomitant medication will be summarized by means of descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) or frequency tables by cohort.

9.5 Treatment Compliance

Study drug administration will be described in terms of the total number of cycles administered, the median (range) of cycles administered, and dose intensity.

9.6 Efficacy Analyses

9.6.1 Primary Efficacy Analysis

9.6.1.1 Hypothesis to be Tested

The study is designed to test the null hypothesis that the true ORR is 15% versus the alternative hypothesis that the true ORR is 42% for tarloxotinib in each cohort.

9.6.1.2 Statistical Methods

The primary efficacy endpoint is confirmed ORR.

Objective response is defined as a CR or PR according to RECIST v1.1 recorded from baseline until disease progression or death due to any cause. Response assessment will be according to the local Investigator.

A patient will be considered to have achieved an objective response if the patient has a confirmed CR or PR according to RECIST v1.1. Additionally, patients with inadequate data for tumor assessment (e.g., no baseline assessment or no follow-up assessments) will be considered non-evaluable in the ORR analysis.

The ORR in each cohort will be estimated as the number of patients with confirmed objective response (CR or PR) divided by the number of evaluable patients in the respective cohort ("response rate"). The ORR will be summarized by cohort along with the corresponding 2-sided 95% CI. The best response rate will also be summarized similarly.

9.6.2 Secondary Efficacy Analyses

9.6.2.1 Duration of Response

The DOR is defined as the date of first documentation of OR according to RECIST v1.1 to date of disease progression or death to any cause. The DOR will be summarized using the Kaplan-Meier method and displayed graphically when appropriate. Median event times and the corresponding 2-sided 95% CI will be provided.

9.6.2.2 Disease Control Rate

The DCR is defined as CR, PR, or SD for at least 2 cycles (8 weeks) according to RECIST v1.1 recorded in the period between first study drug dose and disease progression or death to any cause.

The DCR for each cohort will be estimated by dividing the number of patients with CR, PR, or SD for at least 2 cycles (8 weeks) by the number of patients enrolled in each cohort. Similar analysis as for ORR will be performed for DCR.

9.6.2.3 Progression-free Survival

The PFS, which is defined as the time from the date of first tarloxotinib dose to the date of the first objective documentation of radiographic disease progression or death due to any cause, whichever occurs first. For the analysis, PFS data will be censored according to Table 15 for patients who are alive with no objective documentation of (radiographic) disease progression by the data cut-off date for PFS analysis.

Table 15: Censoring Rules for Progression-Free Survival

Situation	Date of Censoring
No baseline radiologic assessment	Date of first study drug dose
No post-baseline radiologic assessment (and no death prior to first scheduled radiologic assessment)	Date of first study drug dose
No progression or death on study	Date of last radiologic assessment
Documented progression or death after 2 or more consecutive missing radiologic assessments	Date of last radiologic assessment
New anticancer therapy started prior to progression	Date of last radiologic assessment prior to new anticancer therapy

The PFS will be summarized using the Kaplan-Meier method and displayed graphically when appropriate. Median event times and the corresponding 2-sided 95% CI will be provided.

9.6.2.4 Overall Survival

OS as measured from the date of first tarloxotinib dose to the date of death by any cause. In the absence of confirmation of death, survival time will be censored to last date the patient is known to be alive. The OS will be summarized using the Kaplan-Meier method and displayed graphically when appropriate. Median event times and the corresponding 2-sided 95% CI will be provided.

9.7 Safety Analyses

MedDRA will be used to map the AE verbatim to lowest level term, preferred term, and system organ class for summary purposes. All AEs including the AE verbatim term and the associated AE MedDRA preferred term will be provided in the patient data listings. Incidence of treatment-emergent AEs and use of concomitant medications will be summarized descriptively by cohort and total. Results for clinical laboratory parameters, vital signs, ECGs, and physical examinations will be summarized by cohort and combined and by study visits. Descriptive summary statistics in observed values as well as changes from baseline will be presented. In addition, thresholds of marked laboratory abnormalities based on NCI CTCAE v5.0 will be predefined for specific safety parameters. Incidence of marked laboratory abnormalities and shift tables will be presented.

9.7.1 Cardiac Safety

Electrocardiogram parameters (PR interval, QRS interval, QT interval corrected for heart rate by Fridericia's formula [QTcF] and Bazett's formula [QTcB], and heart rate) will be presented as actual values and as changes from the baseline values by summary statistics (number, mean, standard deviation, median, minimum, and maximum). Each of these will be presented at each scheduled ECG time, along with their 2-sided upper 90% CI, using a mixed effects analysis of variance. The primary statistical model will include the effects of patient and ECG time. The numbers and percentages of patients who meet categorical analyses such as the following criteria at each scheduled ECG time point will be presented.

- Absolute QTc interval:
    - QTc interval < 450
    - QTc interval 451 to 480 msec
    - QTc interval 481 to 500 msec
    - QTc interval ≥ 501 msec
- Change from predose baseline in QTc interval:
    - ≤ 30 msec
    - 31 to 60 msec
    - > 60 msec

The numbers and percentages of patients meeting each criterion will be summarized for each ECG time point, as well as for each patient overall at any time. In addition, a central tendency analysis of the ECG parameters will be performed.

Abnormal ECG findings not present at the predose baseline will be summarized as the number of patients with each finding at 1 or more ECG times. Descriptive waveform morphology changes will be provided. Additional ECG analyses may be conducted and will be provided in a separate SAP.

9.8 Other Analyses

9.8.1 Pharmacokinetic Analyses

Pharmacokinetic samples for tarloxotinib and tarloxotinib-E will be collected for patients on Cycle 1 Day 1 and Cycle 2 Day 1. Exploratory analysis (via graphical displays and/or population PK/pharmacodynamics) will be conducted to examine the relationship of exposure to tarloxotinib and tarloxotinib-E and specific safety parameters including QTc interval and, if possible, to efficacy endpoints (e.g., ORR) and support PK analyses. Details of the planned analyses and the results of these analyses will be described in a separate PK data analysis plan.

9.8.2 Tumor Tissue

Tumor tissue will be analyzed based on the following priority:

1. Archived tumor samples or newly obtained pretreatment samples is mandatory for all patients and will be used for concordance analyses against the test used for patient enrollment. The companion diagnostic platform used for these analyses remains to be determined.

2. Tumor STEAP4 will be analyzed and correlated with disease-outcome parameters to determine the predictive value. This analysis will only be performed if the patient provided consent.

3. Exploratory analyzes of phosphor-EGFR, EGFR proximity ligation assay and a hypoxia gene signature will be performed if the patient provided consent.

An optional tissue sample will be obtained at post-infusion from consenting patients will be analyzed for tarloxotinib and tarloxotinib-E levels.

9.8.3 Biomarker Analyses

Blood samples will be collected for biomarker (e.g., ctDNA mutation) analysis at baseline and at several time points throughout the study. Details of the analysis for biomarker and other ancillary data will be provided in the SAP.

10. QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Data Quality Assurance

The Sponsor or Sponsor's designee will conduct a site visit to verify the qualifications of each Investigator, inspect the site facilities, and inform the Investigator of responsibilities and the procedures for ensuring adequate and correct documentation.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. All information recorded in the electronic data capture (EDC) system for this study must be consistent with the patients' source documentation (i.e., medical records).

10.1.1 Database Management and Quality Control

All data generated by the site personnel will be captured electronically at each study center using an EDC system. Data from external sources (such as laboratory data) will be entered into the database. Once the EDC clinical data have been submitted to the central server at the independent data center, corrections to the data fields will be captured in an audit trail. The reason for change, the name of the person who performed the change, together with the time and date will be logged to provide an audit trail.

If additional corrections are needed, the responsible monitor or data manager will raise a query in the EDC application. The appropriate staff at the study site will answer queries sent to the Investigator. The name of the staff member responding to the query and time and date stamp will be captured to provide an audit trail. Once all source data verification is complete and all queries are closed, the monitor will freeze the EDC.

The specific procedures to be used for data entry and query resolution using the EDC system will be provided to study sites in a training manual. In addition, site personnel will receive training on the EDC system.

11. ETHICS

11.1 Informed Consent

Before each patient is admitted to the study, written informed consent will be obtained from the patient according to the regulatory and legal requirements of the participating country. This consent form must be dated and retained by the Investigator as part of the study records. The Investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. The terms of the consent and when it was obtained must also be documented in the EDC system.

Patients may elect to provide optional tumor or plasma samples for DNA biomarker analysis and correlative studies. These samples will be collected only if the patient provides additional consent.

If a protocol amendment is required, the informed consent form may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and approved by the appropriate IEC/IRB and signed by all patients subsequently enrolled in the study as well as those currently enrolled in the study.

11.2 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor or Sponsor's designee must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate).

Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients with appropriate instructions.

11.3 Duration of the Study

The total study duration is estimated to be 36 months, including approximately 24 months for accrual and approximately 12 months for follow-up after the last patient is enrolled. Patients are expected to receive up to 10 cycles of treatment. The end of the study is defined as the last patient visit or contact, including telephone contacts, for collection of any study-related data.

11.4 Premature Termination of the Study

If the Investigator, the Sponsor, or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to patients if the study continues, the study may be terminated after appropriate consultation between the relevant parties. The study may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study
- Failure to enroll patients at an acceptable rate
- A decision on the part of the Sponsor to suspend or discontinue development of the drug

11.5 Confidentiality

All goods, materials, information (oral or written) and unpublished documentation provided to the Investigator (or any company acting on their behalf), inclusive of this protocol, the patient eCRFs, and the Tarloxotinib Investigator's Brochure are the exclusive property of the Sponsor. Documents and information provided to the Investigator by the Sponsor may not be given or disclosed by the Investigator or by any person within his authority in part or in totality to any unauthorized person without the prior written formal consent of the Sponsor.

It is specified that the submission of this protocol and other necessary documentation to the IRB or IEC is expressly permitted, the IRB or IEC members having the same obligation of confidentiality.

The Investigator shall consider as confidential and shall take all necessary measures to ensure that there is no breach of confidentiality in respect of all information accumulated, acquired or deduced during the trial, other than that information to be disclosed to a third party mandated by applicable law.

Any language relating to these issues appearing in the Clinical Trial Agreement will supersede that which is outlined in this section.

The anonymity of participating patients must be maintained. Patients will be identified in the EDC system and other documents submitted to the Sponsor or Sponsor's designee by their

patient number, initials, and/or birth date, not by name. Documents not to be submitted to the Sponsor or Sponsor's designee that identify the patient (e.g., the signed informed consent) must be maintained in confidence by the Investigator.

12. DATA HANDLING AND RECORD KEEPING

12.1 Case Report Forms and Source Documentation

All data obtained during this study should be entered in the EDC system promptly. All source documents from which EDC entries are derived should be placed in the patient's medical records. Measurements for which source documents are usually available include laboratory assessments, ECG recordings, CT scans, MRI, and X-rays. EDC entries may be checked against source documents at the study site or remotely by the Sponsor or Sponsor's designee site monitor. After review by the site monitor, completed EDC entries will be uploaded and forwarded to the Sponsor (or designee). Instances of missing or uninterpretable data will be discussed with the Investigator for resolution.

The specific procedures to be used for data entry and query resolution using the EDC system will be provided to study sites in a training manual. In addition, site personnel will receive training on the EDC system.

12.1.1 Data Collection

The investigators (and appropriately authorized staff) will be given access to an online web-based EDC) system which is 21 CFR Part 11 compliant. This system is specifically designed for the collection of the clinical data in electronic format. Access and right to the EDC system will be carefully controlled and configured according to everyone's role throughout the study. In general, only the Investigator and authorized staff will be able to enter data and make corrections in the eCRFs.

The eCRF should be completed for each patient included in the study and should reflect the latest observations on the patients participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or immediately after the patient's visit or assessment. The Investigator must verify that all data entries in the eCRF are accurate and correct.

Computerized data-check programs and manual checks will identify any clinical data discrepancies for resolution. Corresponding queries will be loaded into the system and the site will be informed about new issues to be resolved on-line. All discrepancies will be solved on-line directly by the Investigator or by authorized staff. Off-line edit checks will be done to examine relationships over time and across panels to facilitate quality data.

After completion, the Investigator will be required to electronically sign off the clinical data.

Data about all study drug dispensed or administered to the patient and any dosage changes will be tracked on the eCRF.

12.2 Access to Source Data

During the study, a monitor will make site visits or conduct remote monitoring to review protocol compliance, compare EDC entries and individual patient's medical records, and ensure that the study is being conducted according to pertinent regulatory requirements. EDC entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

Checking of the EDC entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Moreover, Regulatory Authorities of certain countries, IRBs, IECs, and/or the Sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures the Sponsor (or designee) the necessary access at all times.

12.3 Data Processing

All data will be entered by site personnel into the EDC system. The data-review and data-handling document, to be developed during the initiation phase of the study, will include specifications for consistency and plausibility checks on data and will also include data-handling rules for obvious data errors. Query/correction sheets for unresolved queries will be sent to the study monitors for resolution with the Investigator. The database will be updated based on signed corrections.

Concomitant medications will be coded using the WHODrug Global, which employs the Anatomical Therapeutic Chemical classification system. Medical history, current medical conditions, and AEs will be coded using MedDRA terminology. The versions of the coding dictionaries will be provided in the clinical study report.

12.4 Archiving Study Records

Per 21 CFR 312.62(c), investigators shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application 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 2 years after the investigation is discontinued and FDA is notified. However, documents may be retained for a longer period if required by the applicable legal requirements.

Rain Therapeutics will maintain archive copies of all records for a period of no less than 25 years.

13. PUBLICATION POLICY

By signing the study protocol, the Investigator agrees with the use of results of the study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, Regulatory Authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

An Investigator shall not publish any data (poster, abstract, paper, etc.) without discussion with and approval by the Sponsor.

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APPENDIX A: PACKAGING, LABELING, AND STORAGE OF STUDY DRUG

Study drug will be bulk packaged by the Sponsor according to all local legal requirements. Study drug will be bulk labeled in accordance with applicable regulatory requirements. Consult the Pharmacy Manual for additional details.

Tarloxotinib will be supplied frozen (–20°C ± 5°C) in 20-mL vials containing a minimum of 100 mg tarloxotinib in at least 10 mL of a sterile, preservative-free solution containing 40% 2-hydroxypropyl-beta-cyclodextrin, 20 mM citrate, disclosing minimally the product name, strength, lot number, route of administration, required storage conditions, Sponsor's name, manufacturers name and address, and precautionary labeling as required by US federal law and/or international and local laws.

Storage

Tarloxotinib must be stored in a secure area with limited access under controlled conditions at -20°C ± 5°C.

Dose Preparation

Tarloxotinib vials are stored at -20°C ± 5°C and are thawed at room temperature prior to use. Complete thawing at room temperature could take up to 2 hours. Once thawed, tarloxotinib vials should be diluted into 5% Dextrose in Water (D5W) within 12 hours. D5W for dilution of tarloxotinib will be obtained from commercial source and will be stored at room temperature. The final tarloxotinib concentration for the prepared tarloxotinib/D5W solution should be no less than 0.15 mg/mL and no more than 1 mg/mL.

Method of Administration

Once diluted in D5W for infusion, tarloxotinib is stable at room temperature exposed to light for up to 24 hours. Tarloxotinib should be administered as a 1-hour IV infusion, through a 0.2-µm in-line filter.

Drug Accountability

The Investigator is responsible for the control of drugs under investigation. Adequate records of the receipt and disposition of all tarloxotinib shipped to the site must be maintained. Records will include dates, lots received, quantities received, quantities dispensed, quantities damaged (if applicable), storage conditions, and the identification codes of the patients who received tarloxotinib. The individual administering the tarloxotinib or designee will write the study number, patient number, lot number, number of vials, date, and start/stop times of each administration, and the destruction of all tarloxotinib on the Drug Accountability Record, as appropriate. The Investigator is responsible for returning or destroying all unused study drug to the Sponsor or designee and must verify that no remaining supplies are in the Investigator's possession at the end of the study, unless otherwise instructed by the Sponsor. Further instructions can be found in the Pharmacy Manual.

APPENDIX B: QT-PROLONGING DRUGS WITH A KNOWN RISK FOR TORSADE DE POINTES

It is the responsibility of each Investigator to check this list periodically for new additions.

Please refer to the following website for the most recent information:

https://crediblemeds.org/pdftemp/pdf/CombinedList.pdf

Antiarrhythmics
- Amiodarone (Cordarone, Pacerone)
- Bepridil (Vascor)
- Disopyramide (Norpace)
- Dofetilide (Tikosyn)
- Dronedarone (Multaq)
- Flecainide (Tambocor)
- Hydroquinidine (Serecor)
- Ibutilide (Corvert)
- Nifekalant (Shinbit)
- Procainamide (Pronestyl, Procan)
- Quinidine (Cardioquin, Quinaglute)
- Sotalol (Betapace)

Antibiotics
- Azithromycin (Zithromax)
- Ciprofloxacin (Cipro, Otiprio, Ciloxan)
- Clarithromycin (Biaxin)
- Erythromycin (Erythrocin, EES)
- Gatifloxacin (Tequin)
- Grepafloxacin (Raxar)
- Levofloxacin (Levaquin, Tavanic)
- Moxifloxacin (Avelox)
- Pentamidine (NebuPent, Pentam)
- Roxithromycin (Rulide)
- Sparfloxacin (Zagam)

Antidepressant
- Citalopram (Celexa)
- Escitalopram (Cipralex)

Anti-emetics
- Chlorpromazine (Thorazine, Largactil, Megaphen)
- Domperidone (Motilium)
- Droperidol (Inapsine)
- Ondansetron (Zofran)

Anticancer
- Aclarubicin (Aclacin)
- Oxiplatin (Eloxatin)
- Vandetanib (Caprelsa)

Antifungal
- Fluconazole (Diflucan, Trican)
- Pentamidine (Pentam)

Antihistamine
- Astemizole (Hismanal)
- Terfenadine (Seldane)

Anticholesterolemic
- Probucol (Lorelco)

Antimalarials
- Chloroquine (Aralen)
- Halofantrine (Halfan)
- Hydroxychloroquine (Plaquenil)

Antipsychotics
- Chlorpromazine (Thorazine)
- Chlorprothixene (Truxal)
- Haloperidol (Haldol)
- Levomepromazine (Nosinan, Levoprome)
- Levosulpiride (Lesuride, Eliva)
- Mesoridazine (Serentil)
- Pimozide (Orap)
- Sulpiride (Dogmatil)
- Sultopride (Barnetil, Barnotil, Topral)
- Thioridazine (Mellaril)

Gastrointestinal Stimulant
- Cisapride (Propulsid)

Opiate Agonists
- Levomethadyl acetate (Orlaam)
- Methadone (Dolophine, Methadose)

Other

- Anagrelide (Agrylin)
- Arsenic trioxide (Trisenox)
- Cesium chloride
- Cocaine
- Cilostazol (Pletal)
- Donepezil (Aricept)
- Ibogaine
- Papaverine hydrochloride (intracoronary)
- Propofol (Diprivan)Sevoflurane (Ultane)
- Terlipressin (Teripress, Glypressin)
- Terodiline (Micturin)

DECLARATION OF THE INVESTIGATOR

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Tarloxotinib Investigator's Brochure, electronic data capture system, and other scientific data. I have read and understood and agree to abide by all the conditions and instructions contained in this protocol and agree to:

- Conduct the study in accordance with the relevant, current protocol and will only make changes in a protocol after notifying the Sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- Personally, conduct or supervise the described investigation.
- Inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and IRB)/IEC review and approval in 21 CFR Part 56 are met.
- Report to the Sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64. I have read and understand the information in the protocol and Tarloxotinib Investigator's Brochure, including the potential risks and side effects of the drug.
- Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- Maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
- Ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

Responsible Investigator

_____ _____
Signature Date

_____
Name (Printed)

_____
Title (Printed)