NCT #: 05313009

MUSC CTO #: 103408

A PHASE 1B TRIAL OF TARLOXOTINIB AND SOTORASIB IN PATIENTS WITH KRAS G12C MUTATIONS

PRINCIPAL INVESTIGATOR:
Mariam Alexander, MD PhD
Medical University of South Carolina
86 Jonathan Lucas St
Charleston, SC 29425
Phone: 843/792-4271
FAX: 843/876-1963
E-mail: alexanma@musc.edu

STATISTICIAN:
Elizabeth G. Hill, Ph.D.
Medical University of South Carolina
86 Jonathan Lucas St
Charleston, SC 29425
Phone: 843/876-1115
FAX: 843/876-1963
E-mail: hille@musc.edu

CO-INVESTIGATOR:
John Wrangle, MD MPH
Medical University of South Carolina
86 Jonathan Lucas St
Charleston, SC 29425
Phone: 843/792-7786
FAX: 843/876-1963
E-mail: wrangle@musc.edu

COORDINATING OFFICE: **Sponsor-Investigator Support Unit**
Hollings Cancer Center Clinical Trials Office
1 South Park Circle, Bldg. 1, Suite 503
Charleston, SC 29407
Phone: 843-792-9321
Fax: 843-876-1962

PROTOCOL VERSION HISTORY
Version 1 dated August 17, 2021
Version 2 dated October 6, 2021
Version 3 dated February 27, 2023

SYNOPSIS

Study Number	103408
Sponsor	Rain Therapeutics
Phase	Phase IB
Objectives	Primary Objectives - To evaluate the RP2D, safety, and tolerability of tarloxotinib in combination with sotorasib in patients with *KRAS G12C* mutated advanced non-small cell lung cancer (NSCLC) -To evaluate the tumor objective response rate (ORR) assessed by RECIST 1.1 criteria of the combination of tarloxotinib with sotorasib Secondary Objectives To evaluate other measures of efficacy of the combination of tarloxotinib with sotorasib in patient with *KRAS G12C* mutated advanced NSCLC
Study Design	This is a Phase IB dose expansion trial with safety lead-in evaluating the safety, clinical activity/efficacy of the combination of tarloxotinib and sotorasib in patients with KRAS G12C mutation who have progressed on any small molecule targeting *KRAS G12C* mutant Non-Small Cell lung cancer.
Treatment	Sotorasib 960 mg PO daily + tarloxotinib IV weekly at the combination RP2D determined in the safety lead-in Treatment cycle: Day 1, 8, 15, 22 of every 28-day cycle Tumor assessment every 8 weeks
Eligibility	**Inclusion** *1)* Histologically confirmed diagnosis of squamous or non-squamous NSCLC with *KRAS* G12C mutation 2) Unresectable or metastatic disease 3) No available treatment with curative intent 4) Must have previously received treatment with a platinum-containing chemotherapy regimen. Additional prior therapies for metastatic KRAS G12C mutated NSCLC are also permitted. 5) Must have previously received at least one month trial of sotorasib or a therapy targeting *KRAS* G12C mutation with documented progression. If sotorasib dose from prior therapy was reduced for toxicity, patients that meet the above criteria are expected to receive study treatment at the reduced dose. 6) Must have measurable or evaluable disease as defined by RECIST 1.1 7) Age >18 years 8) Life expectancy of at least 3 months 9) Recovery from adverse effect of prior therapy at the time of enrollment 10) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 11) Laboratory values within the screening period: a) Absolute neutrophile count > 1000/mm3 b) Platelet count > 100,000 /mm3 c) Hemoglobin > 8 in the absence of transfusions for at least 2 weeks d) Total bilirubin < 1.5 x upper limit of normal (or < 3 x ULN if associated with liver metastases or Gilbert's disease) e) Aspartate transaminase (AST) or alanine transaminase (ALT) < 3 x ULN (or < 5x ULN if associated with liver metastases f) Creatinine clearance (CrCl) > 60 mL/min calculated by CKD-EPI or MDRD 12) Women of child-bearing potential agrees to use contraception while participating in the study and for a period of 6 months following termination of study treatment 13) Completed informed consent process

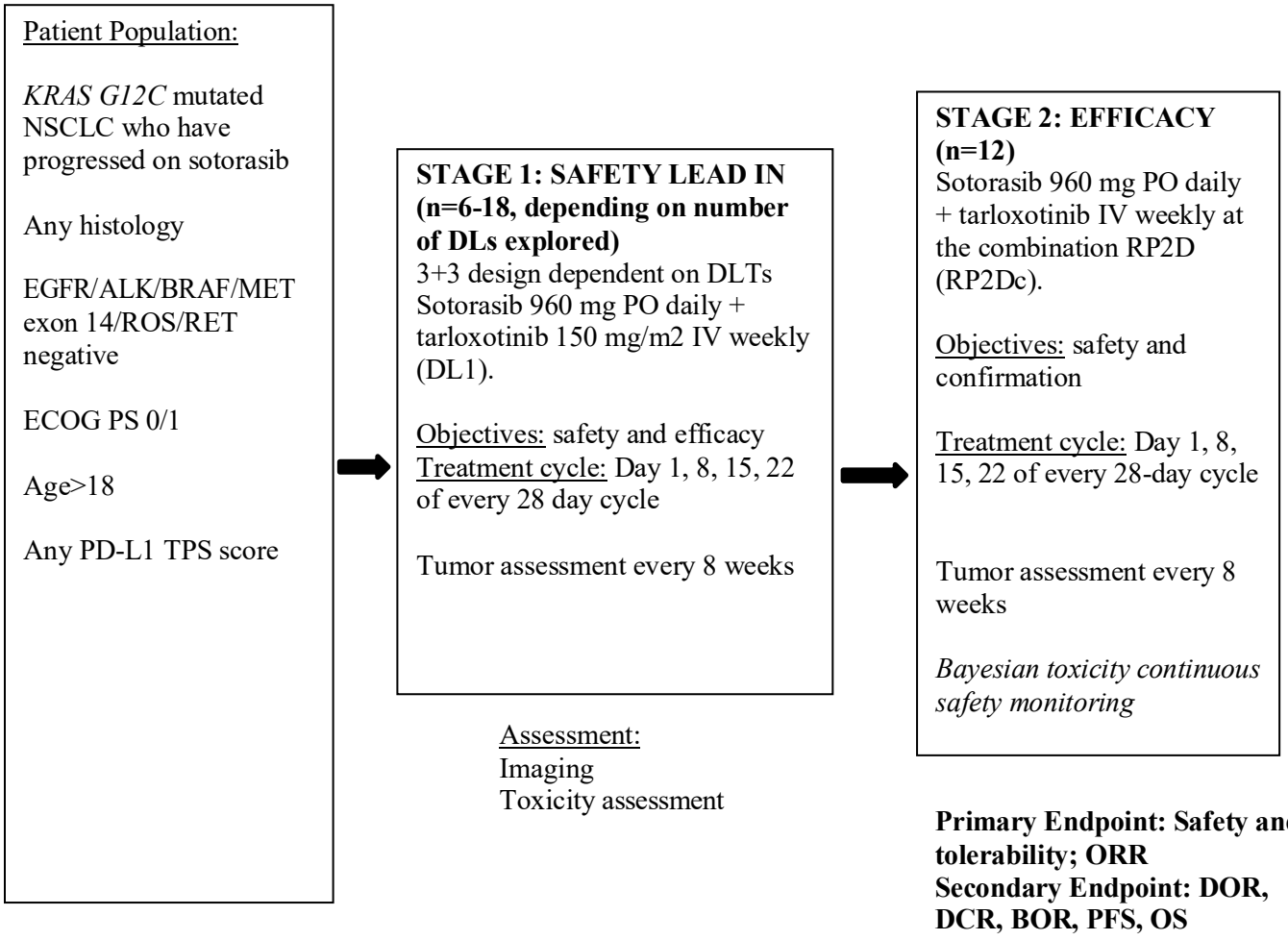
	14) Willing to comply with clinical trial instructions and requirements. **Exclusion** 1) Active, untreated brain metastases. Patients are eligible if brain metastases are previously treated and asymptomatic. Patients must be neurologically stable and on a stable or tapering dose of corticosteroids for at least 2 weeks prior to C1D1. 2) History of intestinal disease or major gastric surgery likely to alter absorption of study treatment or inability to swallow pills 3) Congestive heart failure > NYHA Class 3 4) QTc > 480 milliseconds or family history of Long QT syndrome 5) Ongoing need for a medication with a known risk of Torsades de Pointes that cannot be switched to alternative treatment prior to study entry. 6) Pregnancy or breast feeding 7) Has other known non-KRAS G12C activating oncogene-driver mutations, including but not limited to: ALK, ROS1, RET, BRAF, NTRK1/2/3, MET, EGFR 8) Previously have received anti-EGFR or anti-HER2 TKIs 9) Previously have received anti-EGFR or anti-HER2 monoclonal antibodies 10) Clinically active or symptomatic interstitial lung disease 11) Known concurrently 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. 12) Infection requiring systemic treatment within 7 days prior to cycle 1 day1. 13) Patients with known hypersensitivity to either tarloxotinib, sotorasib, or any of the ingredients.
Criteria for Efficacy Evaluation	Objective response (OR = CR+PR) measured by CT and assessed per RECIST 1.1. Complete response (CR) and Partial response (PR) require confirmatory CT repeat assessment at least 4 weeks after the first detection of response
Criteria for Safety Evaluation	Dose-limiting toxicities, treatment-emergent adverse events, treatment-related adverse events, clinically significant changes in vital signs, electrocardiograms, laboratory tests
Statistical Methods	**Analysis Populations** The following analysis sets will be defined for this study. The **safety analysis set** comprises all enrolled patients who receive any quantity of study treatment, regardless of eligibility. The safety evaluation will be performed based on the first dose of study treatment a patient receives, regardless of the patient's cohort assignment. The safety analysis set will be used for all dosing/exposure and safety analyses.

	The **DLT-evaluable population (*safety lead-in only*)** comprises patients who have either completed the DLT-observation period (1 cycle, 28 days) and received at least 75% of planned doses of the tarloxotinib and sotorasib combination in cycle 1 or have discontinued study treatment or study participation before completing cycle 1 due to a DLT. The **intention to treat (ITT) analysis set** comprises all patients in the safety analysis set eligible for study inclusion and who meet the inclusion criteria for dose expansion, including eligible safety lead-in patients treated at the combination RP2D. This analysis set will be used for all efficacy analyses. **Safety lead-in** A minimum of 6 patients and as many as 18 patients will be enrolled in a safety lead-in cohort to evaluate the safety of the combination of tarloxotinib and sotorasib. Sotorasib will be held at a fixed dose of 960 mg QD (the approved dose) while the starting dose of tarloxotinib will be the monotherapy RP2D equal to 150mg/m^2 QW (dose level 1 [DL1]). Following a 3+3 algorithm, an initial 3 patients will be enrolled at DL1. If 0 or 1 of 3 patients experience a DLT, an additional 3 patients will be enrolled to DL1. DL1 will be declared the combination RP2D ($RP2D_c$) if at most 1 of 6 patients treated at DL1 experience a DLT. Alternatively, if there are 2 or more DLTs observed at DL1, 3 patients will be enrolled at DL -1 and the 3+3 rules repeated for safety evaluation. The $RP2D_c$ will be the highest DL at which at most 1 patient of 6 experiences a DLT. If DL -2 is considered too toxic, additional dose levels below DL -2 may be evaluated for safety. **Dose expansion** Once the tarloxotinib $RP2D_c$ is reached, an expansion cohort of up to 12 patients will be enrolled to evaluate the safety of the combination of tarloxotinib and sotorasib. Eligible safety lead-in patients treated at the $RP2D_c$ will be included in the expansion cohort.

TABLE OF CONTENTS

1 SCHEMA

This is a Phase IB dose expansion trial with safety lead-in evaluating the safety, clinical activity/efficacy of the combination of tarloxotinib and sotorasib in patients with KRAS G12C mutation who have progressed on any small molecule targeting *KRAS G12C* mutant Non-Small Cell lung cancer.



3+3 design to de-escalate tarloxotinib dosing based on DLTs

Dose level	Sotorasib	Tarloxotinib
-2	960 mg PO daily	75 mg/m2 IV weekly
-1	960 mg PO daily	100 mg/m2 IV weekly
0 (full dose)	960 mg PO daily	150 mg/m2 IV weekly

2 OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVE

Objectives	Endpoints
To evaluate the RP2D, safety, and tolerability of tarloxotinib in combination with sotorasib in patients with *KRAS G12C* mutated advanced non-small cell lung cancer (NSCLC).	Dose-limiting toxicities, treatment-emergent adverse events, treatment-related adverse events, clinically significant changes in vital signs, electrocardiograms, laboratory tests
To evaluate the tumor objective response rate (ORR) assessed by RECIST 1.1 criteria of the combination of tarloxotinib with sotorasib	Objective response (OR = CR+PR) measured by CT and assessed per RECIST 1.1. Complete response (CR) and Partial response (PR) require confirmatory CT repeat assessment at least 4 weeks after the first detection of response

2.2 SECONDARY OBJECTIVES

Objectives	Endpoints
To evaluate other measures of efficacy of the combination of tarloxotinib with sotorasib in patient with *KRAS G12C* mutated advanced NSCLC	- Duration of response (DOR) as measured from the date of first response to date of disease progression or death - Disease control rate (DCR)based on patient who had CR or PR or Stable disease (SD) for at least 2 cycles (8 weeks) - Best overall response (BOR) - Progression free survival (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 - Overall survival (OS) as measured from the date of first study drug dose to the date of death by any cause

3 BACKGROUND

3.1 STUDY RATIONALE

3.1.1 Introduction

KRAS acts as a key protein in transducing signals from cell surface receptors, such as receptor tyrosine kinases (RTKs) into cells to initiate a network of cytoplasmic and nuclear signaling cascades that mediate key processes, such as cell cycle entry and cell survival that regulate

normal tissue homeostasis(1). Due to the central importance of KRAS in mediating critical cellular processes, there are significant interconnected signaling feedback pathways that protect normal cells from uncontrolled proliferation and cell death. These signaling feedback pathways are also activated by tumor cells upon inhibition of mutated *KRAS*, which may result in intrinsic or acquired resistance to small molecule *KRAS G12C* inhibitors. Pre-clinical studies in non-small cell lung cancer (NSCLC) have shown that a key pathway that may be activated upon KRAS inhibition is the upstream ERBB RTKs, which provides the rationale for dual *KRAS* and ERBB blockade in overcoming resistance mechanisms in *KRAS* mutated NSCLC(2).

3.1.2 Non-small cell lung cancer

Lung cancer is the second most common cancer and the leading cause of cancer death in the United States. There were approximately 247,270 new cases of lung cancer that occurred in 2020 (3). Prior studies have reported that lung cancer resulted in more deaths than breast cancer, prostate cancer, colorectal cancer, and leukemia combined in men ≥40 years old and women ≥60 years old. The past decade has seen a revolution of new advances in the management of non-small cell lung cancer (NSCLC) with remarkable progresses in screening, diagnosis, and treatment. The advances in systemic treatment have been driven primarily by the development of molecularly targeted therapeutics, immune-checkpoint inhibitors and anti-angiogenic agents, all of which have transformed this field with significantly improved patient outcomes. Despite these advances, most patients with advanced NSCLC have incurable disease, particularly after failure of a platinum-based chemotherapy regimen and check point inhibitors.

3.1.3 KRAS G12C mutated lung cancer

One of the earliest identified molecular drivers of NSCLC is the GTPase transductor protein called KRAS. It is a member of the RAS family of oncogenes and at the apex of multiple signaling pathways central to tumor cell proliferation. KRAS mutant lung cancers have worse outcomes in both early stage and advanced metastatic settings, illustrating the critical need for novel agents targeting KRAS-driven NSCLC. *KRAS G12C* mutations are present in ~15% of lung adenocarcinomas and 0-8% of other cancers(2). The missense mutation at codon 12 interferes with the GTPase, activating protein mediated GTP hydrolysis and shifting the equilibrium between the signaling-competent KRAS-GTP and signaling incompetent KRAS-GDP in favor of the GTP bound state. This process links upstream cell surface receptors such as the ERBB family (EGFR, HER-2, HER-3, HER-4) to downstream pathways such as RAF/MEK/ERK and PI3K/AKT/mTOR which leads to uncontrolled cell proliferation and survival.

Attempts to identify small molecular inhibitors of KRAS have been unsuccessful for many years as there was a lack of a clearly defined deep pocket in the structure of RAS outside of the nucleotide binding site and the challenge of targeting the nucleotide binding site due to extraordinarily high affinity of GTP. Recently, several pioneering studies have identified small molecule cysteine-reactive inhibitors that covalently modify the mutant KRAS G12C protein to reveal an allosteric switch II pocket(4, 5). The induction of the structurally disordered pocket by these small molecule inhibitors converts the GTP preference of naïve KRAS G12C to the inactive GDP bound state, impairing its interaction with downstream effectors.

AMG510/Sotorasib was the first KRAS G12C inhibitor to the enter the clinic. A Phase I/II clinical trial involving 129 patients included 59 patients with *KRAS G12C* mutated NSCLC who had progressed on prior standard therapies. Patients were enrolled in dose escalation and expansion cohorts to receive daily sotorasib monotherapy (960 mg PO daily) (6). At a median follow up of 12.2 months, approximately 50% of NSCLC patients demonstrated tumor regression with a confirmed objective response rate (ORR) of 37.1% (95% CI 28.6-46.2%) and a disease control rate (DCR) of 80.6% (95% CI 72.6-87.2%). The median time to objective response was 1.4 months and median duration of response was 10 months, with median progression free survival (PFS) of 6.8 months. The FDA has now accepted a new drug application and granted it a priority review for the treatment of patients with *KRAS G12C* mutant locally advanced or metastatic NSCLC following at least 1 prior systemic treatment, with an expected decision date by August 2021.

Although the results from these early-stage clinical trials showed promise, ~50% of KRAS G12C mutant NSCLC patients failed to respond to therapy and rate of relapse is high calling for the need for novel combinations to overcome intrinsic and acquired resistance mechanisms in this subset of patients.

3.1.4 Rationale for the combination of KRAS G12C inhibitors with pan-ERBB inhibition

It was previously thought that constitutively active oncogenic KRAS induces growth factor independence. However, recent evidence has suggested that specific *KRAS* mutant isoforms such as *KRAS G12C* may be regulated by upstream activation of several receptor tyrosine kinases. Lito *et. al.* demonstrated that concurrent EGFR and G12C inhibition potentiated growth inhibition in two different *KRAS G12C* mutant NSCLC cell lines(7). The pattern of RTK dependence appears to vary between *KRAS G12C* mutant cancer but numerous RTKs are involved in the adaptive feedback mechanism to G12C inhibition. This may be mediated through an adaptive RAS pathway activation. Misale *et. al.*, identified several RTK inhibitors exhibiting strong synergies with G12 inhibitors(8). Umelo *et. al.* examined RTK dependent cell lines to provide evidence that in a group of mutant *KRAS G12C* NSCLC lines, HER2 and HER3 are major upstream signaling activators(9). They examined several NSCLC lines to shows that EGF or NRG1 beta stimulation can strongly enhance the amount of active RAS in cells harboring oncogenic KRAS G12C, which suggest that some KRAS mutant cancers retain sensitivity to upstream stimuli emanating from extracellular signaling via the ERBB pathway. Silencing oncogenic KRAS in EGFR/HER dependent cells reduced cellular growth and induced a modest apoptotic signal. The depletion of KRAS expression by mutant specific siRNA was accompanied by a reduction in AKT phosphorylation in the ERBB dependent subset and activation of STAT3, which suggests a feedback loop via STAT3 that re-establishes oncogenic signaling thereby compensating for the loss of AKT survival signals. Pan ERBB inhibition in these *KRAS G12C* mutated NSCLC lines resulted in a potent suppression of growth and inhibition of receptor signaling and downstream signaling effectors. Thus, sole silencing of oncogenic KRAS may not be an effective therapeutic strategy in KRAS-addicted cancers since upstream events and feedback loops are likely to attenuate or annul the effects of the therapeutic intervention. These pre-clinical studies provide a solid ground to evaluate the use of pan-ERBB inhibitors in combination with *KRAS G12C* inhibitors in patients with KRAS mutant lung tumors.

3.1.5 Tarloxotinib

Tarloxotinib is a recently discovered novel prodrug that releases a potent, irreversible pan-ERBB (EGFR, HER2 and HER4) TKI. It is designed to be inactive under normal oxygen conditions but undergoes fragmentations under low oxygen conditions (hypoxia) to release the potent irreversible active metabolite (tarloxotinib-E) that has activity against both normal and mutant versions of the ERBB family(10). Selective production of tarloxotinib-E under hypoxic conditions generates a therapeutic window where it is selectively activated in hypoxic tumor regions to deliver higher drug delivery to tumor tissue. This reduces systemic exposure which avoids on-target EGFR related toxicities than standard EGFR TKI. In a mouse xenograft model of a human derived EGFR exon 20 insertion, intra-tumoral tarloxotinib-E levels were 20 time higher than skin and 50 times higher than plasma demonstrating selective tumor conversion. This strategy broadens the therapeutic window leading to improved efficacy, while reducing toxicity. Multiple pre-clinical studies have further demonstrated the efficacy of tarloxotinib compared to standard EGFR inhibitors(11).
Phase I clinical trials to determine the MTD and DLTs of tarloxotinib, enrolled 27 patients with locally advanced or metastatic solid tumors(12). Of the patients that received tarloxotinib as a weekly 1-hour infusion, 6 patients received the drug at the recommended Phase 2 dose of 150 mg/m2 with good tolerance.

3.1.6 Combination of Sotorasib with Tarloxotinib

The combination of tarloxotinib with sotorasib is poised to provide highly specific tumor inhibition while targeting the vertical KRAS signaling pathway with minimal toxicity. The combination is unlikely to result in clinically relevant drug-drug interaction (DDI) based on absorption, metabolism, elimination or protein-binding. Tarloxotinib is intravenously administered while sotorasib is a small molecule that is administered orally; no absorption interactions are expected.

Table 2 provides a comparison of the toxicity noted in Phase I/II clinical trials of these two drugs. The safety profile is expected to be generally non-overlapping with the exception of gastrointestinal adverse events that include nausea and diarrhea.

3.1.7 Comparison of Toxicity reported in the individual Phase I/II studies of Sotorasib and Tarloxotinib

Adverse events	Tarloxotinib (n=23)		Sotorasib (n=129)	
	Any grade	>G3	Any grade	>G3
QTc prolongation	60.9%	34.8%	-	-
Rash acneiform	43.5%	4.3%	-	-
Diarrhea	21.7%	4.3%	29.5%	2.3%
Nausea	21.7%	0%	20.9%	1.6%
Fatigue	33.3%	0%	23.3%	2.3%

Vomiting	-	-	17.8%	3.9%
Abdominal pain	-	-	17.8%	3.1%
Dyspnea	-	-	16.3%	2.3%
Cough	-	-	15.5%	0%
Back pain	-	-	14.7%	1.6%
Decreased appetite	-	-	14.7%	1%
Headache	-	-	14.0%	0%
AST elevation	-	-	13.2%	2.3%
anemia	-	-	13.2%	4.7%
dizziness	-	-	13.2%	0%
ALT elevation	-	-	11.6%	0%
Constipation	-	-	10.9%	0%
Pyrexia	-	-	10/9%	0%
Insomnia	-	-	10.1%	0%
Myalgia	-	-	10.1%	0%
Peripheral edema	-	-	10.1%	0%
Arthralgia	-	-	10.1%	1.6%

4 SUBJECT SELECTION

4.1 INCLUSION CRITERIA

Patients eligible for study participation must meet all the following criteria:

1) Histologically confirmed diagnosis of squamous or non-squamous NSCLC with *KRAS* G12C mutation
2) Unresectable or metastatic disease
3) No available treatment with curative intent
4) Must have previously received treatment with at a platinum-containing chemotherapy regimen. Additional prior therapies for metastatic KRAS G12C mutated NSCLC are also permitted.
5) Must have previously received at least one month trial of sotorasib or a therapy targeting *KRAS* G12C mutation with documented progression. If sotorasib dose from prior therapy was reduced for toxicity, patients that meet the above criteria are expected to receive study treatment at the reduced dose.
6) Must have measurable or evaluable disease as defined by RECIST 1.1
7) Age >18 years

8) Life expectancy of at least 3 months
9) Recovery from adverse effect of prior therapy at the time of enrollment
10) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
11) Laboratory values within the screening period:
    a) Absolute neutrophile count > 1000/mm3
    b) Platelet count > 100,000 /mm3
    c) Hemoglobin > 8 in the absence of transfusions for at least 2 weeks
    d) Total bilirubin < 1.5 x upper limit of normal (or < 3 x ULN if associated with liver metastases or Gilbert's disease)
    e) Aspartate transaminase (AST) or alanine transaminase (ALT) < 3 x ULN (or < 5x ULN if associated with liver metastases
    f) Creatinine clearance (CrCl) > 60 mL/min calculated by CKD-EPI or MDRD
12) Women of child-bearing potential agrees to use contraception while participating in the study and for a period of 6 months following termination of study treatment
13) Completed informed consent process
14) Willing to comply with clinical trial instructions and requirements.

4.2 EXCLUSION CRITERIA

Patients eligible for study participation CANNOT meet any of the following criteria:

1) Active, untreated brain metastases. Patients are eligible if brain metastases are previously treated and asymptomatic. Patients must be neurologically stable and on a stable or tapering dose of corticosteroids for at least 2 weeks prior to C1D1.

2) History of intestinal disease or major gastric surgery likely to alter absorption of study treatment or inability to swallow pills

3) Congestive heart failure > NYHA Class 3

4) QTc > 480 milliseconds or family history of Long QT syndrome

5) Ongoing need for a medication with a known risk of Torsades de Pointes that cannot be switched to alternative treatment prior to study entry.

6) Pregnancy or breast feeding

7) Has known activating non-KRAS G12C oncogene-driver mutations, including but not limited to: ALK, ROS1, RET, BRAF, NTRK1/2/3, MET, EGFR.

8) Previously have received anti-EGFR or anti-HER2 TKIs

9) Previously have received anti-EGFR or anti-HER2 monoclonal antibodies

10) Clinically active or symptomatic interstitial lung disease

11) Known concurrently 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.

12) Infection requiring systemic treatment within 7 days prior to cycle 1 day 1.

13) Patients with known hypersensitivity to either tarloxotinib, sotorasib, or any of the ingredients.

4.3 INCLUSION OF WOMEN AND MINORITIES

Both men and women of all races and ethnic groups are eligible for this trial.

5 SUBJECT REGISTRATION

The Hollings Cancer Center's Sponsor-Investigator Support Unit (SIS Unit) will provide patient registration services for the study. The SIS Unit will conduct a patient eligibility audit review of all eligibility source documents prior to patient registration. These procedures are outlined in the MUSC 103408 Operations Manual. After obtaining signed informed consent and completion of required baseline assessments, eligible subjects will be registered. A unique subject number will be assigned to each patient. The SIS Unit will issue a patient registration confirmation email to the enrolling study team at the time of registration which will include the patient's study ID number.

5.1 SUBJECT RECRUITMENT

Subjects will be recruited from the existing patient population of the Hollings Cancer Center thoracic medical oncology clinics.

5.1.1 INFORMED CONSENT PROCESS

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Informed consent will be obtained by personnel who are qualified by education, training, and experience to perform the task. The Sponsor-Investigator will not use the services of study personnel for whom sanctions have been invoked where there has been scientific misconduct or fraud.
Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. The approved consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

5.1.2 RECRUITMENT METHODS

Subjects will be recruited via internal and external patient referrals to Hollings Cancer Center, multidisciplinary tumor board meetings in which new and ongoing patient cases are reviewed, and the existing patient population of the Principal Investigator and Sub-Investigators.

5.1.3 SETTING

The study will be conducted at Hollings Cancer Center and other potential designated sub-sites to be determined.

6 TREATMENT/STUDY INTERVENTION

6.1 STUDY TREATMENT AND TREATMENT SCHEDULE

This is a traditional safety and efficacy study of Sotorasib and Tarloxotinib for patients with KRAS G12C mutant NSCLC. Treatment will be administered on an outpatient basis.

Sotorasib will be administered at a recommended Phase 2 dose of 960 mg PO daily.

All patients will receive a weekly tarloxotinib infusion at the RP2Dc determined in the safety lead-in portion of the trial administered as a 1-hour IV infusion on Days 1, 8, 15, and 22 of each 28-day cycle until disease progression or unacceptable toxicity. 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.

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. In the safety lead-in portion of the study, an initial 3 patients will be treated at Dose Level 1 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]). The dose level for subsequent patient cohorts will be determined using standard 3+3 dose escalation/de-escalation rules using the dose levels indicated in table below.

3x3 design to de-escalate tarloxotinib dosing based on DLTs

Dose level	Sotorasib	Tarloxotinib
-2	960 mg PO daily	75 mg/m2 IV weekly
-1	960 mg PO daily	100 mg/m2 IV weekly
0 (full dose)	960 mg PO daily	150 mg/m2 IV weekly

6.2 DEFINITION OF DOSE-LIMITING TOXICITY (DLT)

Toxicities will be graded according to the NCI Common Toxicity Criteria scale version 5.0. If multiple toxicities are seen, the presence of DLT should be based on the most severe toxicity grade experienced. DLT will be defined as any of the following events occurring during treatment with study drugs and is deemed possibly, probably or definitely attributable to the study drugs:

- Any Grade 3 or 4 thrombocytopenia, anemia and/or neutropenia.
- Any other non-hematologic Grade 3 or 4 toxicity that is clinically significant, excluding alopecia.
- Any grade 3 nausea, vomiting or diarrhea that persists > 72 hours despite the use of maximal medical intervention and/or prophylaxis as indicated by good clinical practice and the judgment of the investigator.
- Any grade 4 vomiting or diarrhea regardless of duration.
- Failure to recover from toxicities to be eligible for re-treatment within 4 weeks.
- Any death not clearly due to the underlying disease or extraneous causes, and for any toxicity requiring permanent discontinuation of study drug(s).
- Hy's law, defined as: AST or ALT > 3 x the upper limit of normal (ULN) with concurrent increase in total bilirubin > 2 x ULN without evidence of cholestasis or alternative explanations, (e.g., viral hepatitis, disease progression in the liver, etc.)
- Neutropenic fever

6.3 DOSE ESCALATION RULES

Dose escalation/de-escalation in the safety lead-in portion of the trial will follow a standard 3+3 algorithm. Please refer to section 11, Statistical Considerations, for additional details.

6.4 DOSE MODIFICATIONS

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 5.0.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

6.5 TREATMENT AND RETREATMENT CRITERIA

The results of tumor assessments are 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 clinically indicated, 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 Principal Investigator.
  - If other electrolytes (e.g., 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 Principal Investigator and possible dose/schedule modification and/or study treatment discontinuation discussed.

6.5.1 Treatment Beyond Progression

Patients with disease progression may continue to receive the combination of tarloxotinib and sotorasib if, in the opinion of the Treating Investigator, the patient is still benefiting (e.g., asymptomatic systemic progression or local symptomatic progression) following discussion with and approval by the Principal Investigator. In addition, the following criteria must be met:

- Absence of clinical symptoms or signs indicating clinically significant disease progression
- No decline in performance status
- Absence of rapid disease progression or threat to vital organs or critical anatomical sites (e.g., CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention

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 Principal Investigator.

6.5.2 Tarloxotinib Dose Modifications

All patients will receive a weekly tarloxotinib infusion at the RP2Dc determined in the safety lead-in portion of the trial administered as a 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. All patients will begin study treatment 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 below.
Dose level reductions will be in a step-wise fashion. If a patient requires more than 2 dose level reductions, tarloxotinib will be permanently discontinued.

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 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 Principal Investigator.

Should a dose reduction for sotorasib be required, given the potential for overlapping toxicities and challenges in attributing toxicities to one drug in a combination therapy, a dose reduction in tarloxotinib should also be considered.

Dose level	Sotorasib	Tarloxotinib
0 (full dose)	960 mg PO daily	150 mg/m2 IV weekly
-1	480 mg PO daily	100 mg/m2 IV weekly
-2	240 mg PO daily	75 mg/m2 IV weekly

6.5.3 Treatment Guidelines for QTc Prolongation

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

a. Baseline: A pre-infusion (baseline) ECG will be obtained on all patients, if the automated measurements indicate a QTcF of ≥ 450 msec
b. The single QTcF will be verified by manually measuring at least 3 complexes within the ECG and determining the average QTcF
c. All patients must have a pre-infusion QTcF of < 450 msec by either: Calculation using the automated measurements of the first ECG or the manual measurement of a single ECG
d. If it is determined that the manually read QTcF ≥ 450 msec, the Principal Investigator should be contacted to discuss the clinical significance of the reading and to determine if it is appropriate to move forward with the infusion.
e. 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 this section and per institutional standards.

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

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

6.5.4 Treatment Guidelines for QTc Prolongation

QTc Prolongation	After Tarloxotinib Administration
Grade 1 450 to 480 msec QTcF	• Cycle 1 and Cycle 2 Day 1 o May be discharged if the 4-hour (or later) post-infusion QTcF is Grade 1 or lower and asymptomatic • After Cycle 2 Day 1 o Obtain pre-infusion and 2-hour post-infusion ECGs o 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 o 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 o Obtain pre-infusion and 2-hour post-infusions ECGs o 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 o Resume tarloxotinib dosing **with dose reduction** ▪ 1st occurrence: reduce to 100 mg/m2 ▪ 2nd occurrence: reduce to 75 mg/m2 ▪ 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.

6.5.5 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 the table below.

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	• Interrupt tarloxotinib infusion • 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 • After symptoms resolve to baseline, resume future tarloxotinib infusions to 50% of the initial infusion rate

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	• Interrupt tarloxotinib infusion • 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/m2 for subsequent doses*, and/or adjusted premedication after discussion with the Principal Investigator • If Grade 3 infusion reaction recurs after this initial dose reduction, then reduce the tarloxotinib dose to 75 mg/m2 for subsequent doses • After symptoms resolve to baseline, resume future tarloxotinib infusions to 50% of the initial infusion rate
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 Principal Investigator

6.5.6 Treatment Guidelines for Other Non-Hematologic Toxicity

The table below provides treatment guidelines for treating tarloxotinib non-hematologic toxicities other than QT prolongation and infusion-related reactions.

Toxicity (CTCAE v5.0)	**Details**	**Hold Dose**	**Dose Levels After Recovery to ≤ Grade 2 or Baseline**
Grade 2	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/m2 (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	Nausea and vomiting*	Hold dose until resolution to Grade 0 or 1 or Grade 2 tolerable	120 mg/m2; if recurs, then second reduction to 75 mg/m2
Grade 4	Pulmonary embolism that is adequately treated	Hold dose until resolution to Grade 0 or 1	120 mg/m2; if recurs, then second reduction to 75 mg/m2
Grade 4	All other life-threatening conditions	Treatment to be discontinued	Not applicable

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

6.5.7 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 monitoring.

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.

7 DRUG INFORMATION

Tarloxotinib will be administered intravenously once weekly. Sotorasib will be self-administered orally by subjects daily.

7.1 TARLOXOTINIB

7.1.1 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.

7.1.2 Tarloxotinib Dose Calculation

All patients will receive a weekly tarloxotinib infusion at the RP2Dc determined in the safety lead-in portion of the trial. administered as a 1-hour IV infusion on Days 1, 8, 15, and 22 of each 28-day cycle until disease progression or unacceptable toxicity. 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 x H 0.725) x 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.

7.1.3 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.

7.1.4. 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.

7.1.5 Dose Delays

All dose schedule modifications of > 1 day must be discussed with the Principal Investigator (or designee). Intentional cycle delays of > 1 day (e.g., patient vacation, physician requested "drug holiday") must be approved by the Principal Investigator (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.

7.1.6 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. 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 Principal Investigator should be informed as soon as possible. The infusion should be rescheduled based on Investigator judgment, taking into consideration the patient's safety.

7.1.7 Supportive Care

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.

7.1.8 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:

Potassium Supplementation Guidelines Pre-infusion	
Serum Potassium (mEq/L)	**Potassium Supplementation Strategy**
< 3.5	• Hold tarloxotinib • Administer potassium replacementper 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 replacementper institutional policy (IV and/or PO)

7.2 SOTORASIB

7.2.1 Description

Sotorasib is an inhibitor of the RAS GTPase family. The molecular formula is C30H30F2N6O3, and the molecular weight is 560.6 g/mol. The chemical name of sotorasib is 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-(1M)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-4-[(2S)-2- methyl-4-(prop-2-enoyl)piperazin-1-yl]pyrido[2,3-d]pyrimidin-2(1H)-one.

Sotorasib has pKa values of 8.06 and 4.56. The solubility of sotorasib in the aqueous media decreases over the range pH 1.2 to 6.8 from 1.3 mg/mL to 0.03 mg/mL.

Sotorasib is supplied as film-coated tablets for oral use containing 120 mg. Inactive ingredients in the tablet core are microcrystalline cellulose, lactose monohydrate, croscarmellose sodium,

and magnesium stearate. The film coating material consists of polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide yellow.

7.2.2 Mechanism of Action

Sotorasib is an inhibitor of KRASG12C, a tumor-restricted, mutant-oncogenic form of the RAS GTPase, KRAS. Sotorasib forms an irreversible, covalent bond with the unique cysteine of KRASG12C, locking the protein in an inactive state that prevents downstream signaling without affecting wild-type KRAS. Sotorasib blocked KRAS signaling, inhibited cell growth, and promoted apoptosis only in *KRAS G12C* tumor cell lines. Sotorasib inhibited KRASG12C *in vitro* and *in vivo* with minimal detectable off-target activity. In mouse tumor xenograft models, sotorasib-treatment led to tumor regressions and prolonged survival, and was associated with anti-tumor immunity in *KRAS G12C* models.

7.2.3 Toxicology

Carcinogenicity studies have not been performed with sotorasib.

Sotorasib was not mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay and was not genotoxic in the *in vivo* rat micronucleus and comet assays.

Fertility/early embryonic development studies were not conducted with sotorasib. There were no adverse effects on female or male reproductive organs in general toxicology studies conducted in dogs and rats.

7.2.4 Pharmacology

Sotorasib exposure-response relationships and the time course of the pharmacodynamic response are unknown.

The pharmacokinetics of sotorasib have been characterized in healthy subjects and in patients with KRAS G12C-mutated solid tumors, including NSCLC. Sotorasib exhibited non-linear, time-dependent, pharmacokinetics over the dose range of 180 mg to 960 mg (0.19 to 1 time the approved recommended dosage) once daily with similar systemic exposure (i.e., AUC0-24h and Cmax) across doses at steady-state. Sotorasib systemic exposure was comparable between film-coated tablets and film-coated tablets predispersed in water administered under fasted conditions. Sotorasib plasma concentrations reached steady state within 22 days. No accumulation was observed after repeat LUMAKRAS dosages with a mean accumulation ratio of 0.56 (coefficient of variation (CV): 59%).

Absorption:
The median time to sotorasib peak plasma concentration is 1 hour.

Effect of Food:
When 960 mg LUMAKRAS was administered with a high-fat, high-calorie meal (containing approximately 800 to 1000 calories with 150, 250, and 500 to 600 calories from protein, carbohydrate and fat, respectively) in patients, sotorasib AUC0-24h increased by 25% compared to administration under fasted conditions.

Distribution:
The sotorasib mean volume of distribution (Vd) at steady state is 211 L (CV: 135%). In vitro, sotorasib plasma protein binding is 89%.

Elimination:
The sotorasib mean terminal elimination half-life is 5 hours (standard deviation (SD): 2). At 960 mg LUMAKRAS once daily, the sotorasib steady state apparent clearance is 26.2 L/hr (CV: 76%).

Metabolism:
The main metabolic pathways of sotorasib are non-enzymatic conjugation and oxidative metabolism with CYP3As.

Excretion:
After a single dose of radiolabeled sotorasib, 74% of the dose was recovered in feces (53% unchanged) and 6% (1% unchanged) in urine.

Specific Populations:
No clinically meaningful differences in the pharmacokinetics of sotorasib were observed based on age (28 to 86 years), sex, race (White, Black and Asian), body weight (36.8 to 157.9 kg), line of therapy, ECOG PS (0, 1), mild and moderate renal impairment (eGFR: ≥ 30 mL/min/1.73 m2), or mild hepatic impairment (AST or ALT < 2.5 × ULN or total bilirubin < 1.5 × ULN). The effect of severe renal impairment or moderate to severe hepatic impairment on sotorasib pharmacokinetics has not been studied.

7.2.5 Supplier

Amgen Pharmaceuticals

7.2.6 Sotorasib Dosage and Administration

The recommended dosage of sotorasib is 960 mg (eight 120 mg tablets) orally once daily until disease progression or unacceptable toxicity. Take sotorasib at the same time each day with or without food. Swallow tablets whole. Do not chew, crush or split tablets. On the days of Tarloxotinib infusion, Sotorasib should be taken at the same time as the start of the infusion.

7.2.7 Missed Doses

If a dose of sotorasib is missed by more than 6 hours, take the next dose as prescribed the next day. Do not take 2 doses at the same time to make up for the missed dose. If vomiting occurs after taking sotorasib, do not take an additional dose. Take the next dose as prescribed the next day.

7.2.8 Dose Modifications for Adverse Reactions

Dose level -1	480mg once daily
Dose level -2	240mg once daily

Sotorasib should be discontinued if further dose reduction is indicated below 240mg once daily.

Adverse reaction	**Dosage modification**
Grade 2 AST or ALT elevation with symptoms Grade 3-4 AST or ALT	• Hold sotorasib dosing until recovery to Grade 1 or resolution • Resume sotorasib dosing at the next lower dose level
AST or ALT > 3 x ULN with total bilirubin > 2 x ULN in the absence of alternative causes	• Permanently discontinue sotorasib
Interstital Lung Disease (ILD) or pneumonitis, any grade	• Hold sotorasib dosing if either is suspected • Permanently discontinue sotorasib dosing if either is confirmed
Grade 3 nausea or Grade 3-4 vomiting despite appropriate supportive care (including anti-emetic therapy)	• Hold sotorasib dosing until recovery to Grade 1 or resolution • Resume sotorasib dosing at the next lower dose level

8 CONCOMITANT THERAPY

8.1 PERMITTED MEDICATIONS

All medications (prescription and non-prescription/OTC) and blood products taken within 14 days of Cycle 1 Day 1 until the EOT visit 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.

8.2 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 Torsades de Pointes.

- Acid-Reducing Agents – avoid coadministration with proton pump inhibitors (PPI) and H2 receptor antagonists. If an acid-reducing agent cannot be avoided, adjust administration of sotorasib to be 4 hours before or 10 hours after a local antacid.

- Strong CYP3A4 Inducers: Avoid coadministration with strong CYP3A4 inducers

- CYP3A4 Substrates: Avoid coadministration with CYP3A4 substrates for which minimal concentration changes may lead to therapeutic failures of the substrate. If coadministration cannot be avoided, adjust the substrate dosage in accordance to its prescribing Information.

- P-gp substrates: Avoid coadministration with P-gp substrates for which minimal concentration changes may lead to serious toxicities. If coadministration cannot be avoided, decrease the substrate dosage in accordance with its Prescribing Information.

9 STUDY ASSESSMENTS

9.1 GENERAL GUIDELINES

Prior to any study specific activities, the subject must be aware of the nature of his/her disease and willingly consent to the study after being informed of study procedures, the experimental therapy, possible alternatives, risks and potential benefits.

9.2 STUDY CALENDAR

SCHEDULE OF EVENTS[8]	**SCR**	**C1 D1**	**C1 D8**	**C1 D15**	**C1 D22**	**C2 D1**	**C2 D8**	**C2 D15**	**C2 D22**	**C3+ D1**	**C3+ D8**	**C3+ D15**	**C3+ D22**	**EOT**[6]	**SFU**[6]	**LTFU**
Informed consent	X															
Eligibility review	X															
Medical History	X															
Physical Exam	X	X				X				X				X	X	
ECOG Performance Status	X	X				X				X				X	X	
Vital signs[9]	X													X	X	
Pre-infusion		X	X	X	X	X	X	X	X	X	X	X	X			
30, 60, and 90 mins after EOI		X	X	X	X	X	X	X	X	X	X	X	X			
		X	X	X	X	X	X	X	X	X	X	X	X			
ECG 12-lead	X													X	X	
Pre-infusion		X	X	X	X	X	X	X	X	X	X	X	X			
EOI		X	X	X	X	X										
1h after EOI[1]		X	X	X	X	X				X	X	X	X			
2h after EOI[1]		X	X	X	X	X	X	X	X	X	X	X	X			
3h after EOI[1]		X	X	X	X	X										
4h after EOI[1]		X	X	X	X	X	X	X	X							
CBCD	X	X				X				X				X	X	
CMP [10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Magnesium	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Phosphorous	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum potassium																
EOI		X				X										
3h post EOI		X				X										
Urinalysis	X															
B-HCG[2]	X	X				X								X		
Biomarker samples/ctDNA samples[3]		X				X								X		
Potassium Supplementation[4]		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			
Sotorasib dosing		***Continuous dosing***														
Tumor Assessment[5]	X	*** Every 8 weeks (+/- 5 days) from Cycle 1 Day 1***														
Concomitant Meds	***Every visit***															
Adverse Events Assessment	***Every visit***															
Survival status																X

CT = Computed tomography, ECOG = Eastern Cooperative Oncology Group, EOI = End of Infusion, EOT = End of Treatment, SFU = Safety Follow-up, MRI = Magnetic Resonance Imaging, PET= Positron Emissions Tomography, QTcF = Corrected QT interval as calculated according to Fridericia's formula, SCR = Screening period

[1] For patients with Grade 3 QTcF prolongation (≥ 501 msec or > 60 msec increase compared to pre-infusion), repeat ECG every 15 to 30 mins until resolved to Grade 2 (481 to 500 msec) or lower (≤480 msec) and then obtain ECGs every hour up to 4 hours post infusion, or longer as clinically indicated.
[2] Serum pregnancy test at baseline, then urine pregnancy test, for women of childbearing potential
[3] Collect blood for biomarkers per correlatives manual.
[4] If required. See section 7, potassium supplementation.
[5] Perform radiographic assessments according to institutional practice. Include CT or MRI of the chest and abdomen, and if applicable, brain CT or MRI, bone scan, or PET-CT at screening. The baseline tumor assessment is required within 28 days prior to first dose of tarloxotinib. PET-CT may be substituted for a contrasted CT of the chest and abdomen if tumor measurements are obtained per RECIST 1.1 criteria. The same imaging modality used for baseline imaging must be used for subsequent tumor assessments in each patient.
[6]The EOT visit should be conducted within +/- 7 days of the last dose of tarloxotinib, and the safety follow-up should occur 30 days (+/- 7 days after the last dose of tarloxotinib).
[7]Patients may be followed for survival status every 3 months for up to 6 months after the last patient on study visit (LPV) at the investigator's discretion.
[8]Informed consent, medical history and physical exam/ECOG status to be obtained within 28 days of Cycle 1 Day 1. Baseline labs and ECG are to be obtained within 14 days of Cycle 1 Day 1.
[9] Vital signs should include: Height (at screening only), weight, blood pressure, temperature, respirations, and O^2 saturation.
[10] Liver function testing to be performed every 3 weeks for the first 3 months, then monthly as clinically indicated.

Cycles are 28 days in length. Study visits have a +/- 1 day window to allow for holidays or other rescheduling reasons, to be documented in the research record.

9.3 CRITERIA FOR REMOVAL FROM PROTOCOL TREATMENT

Subjects may discontinue study treatment at any time. Any subject who discontinues treatment will be asked to return to the study center to undergo end of treatment assessments as outlined within Study Calendar (Section 7.2). The primary reason for discontinuation should be recorded. In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Radiographic disease progression
- Clinical disease progression

- Inter-current illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree or require discontinuation of study drugs
- Completion of protocol treatment.
- Unacceptable toxicity
- Death
- Subject may withdraw from the study at any time for any reason.
- Treatment delay for unacceptable duration for any toxicity in the opinion of the investigator
- Concomitant treatment with a prohibited medication
- Subject non-compliance

9.4 DURATION OF FOLLOW UP

Subjects may be followed for survival status every 3 months for up to 6 months after the last patient on study visit (LPV) at the investigator's discretion.

10 DEFINITION OF ENDPOINTS

10.1 PRIMARY EFFICACY ENDPOINT

Objective response (OR = CR+PR) measured by CT and assessed per RECIST 1.1. Complete response (CR) and partial response (PR) require confirmatory CT repeat assessment at least 4 weeks after the first detection of response.

10.2 SECONDARY EFFICACY ENDPOINTS

1) **Duration of response** (DOR) as measured from the date of first response (CR or PR) to date of disease progression (taking as reference for progressive disease the smallest measurements recorded since the treatment started) or death.

2) **Disease control rate** (DCR) based on patient who had CR or PR or Stable disease (SD) for at least 2 cycles (8 weeks).

3) **Best overall response** (BOR) determined from a sequence of responses assessed. Two objective status determinations of CR before progression are required for a BOR of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a BOR of PR. A minimum timeframe of 8 weeks is required for a BOR of SD.

3) **Progression free survival** (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.

4) **Overall survival** (OS) as measured from the date of first study drug dose to the date of death by any cause.

10.3 SAFETY ENDPOINTS

Primary safety endpoints are Dose-limiting toxicities, treatment-emergent adverse events, clinically significant changes in vital signs, electrocardiograms (especially QT), laboratory parameters (hematology, serum chemistry, urinalysis, serum pregnancy test), physical examination results.

10.4 EXPLORATORY ENDPOINTS

1) To evaluate the utility of detection of KRAS G12C mutations in plasma ctDNA to identify the study population.
2) To explore the association between baseline tumor biomarkers, gene alterations and clinical activity.
3) To identify known and possibly new markers of resistance to KRAS G12C inhibition in baseline tumor tissue (if available) including phosphorylated ERK and S6 kinase.
4) To examine mutations in *RAS* and other tumor genes potentially implicated in the resistance to sotorasib using ctDNA.

11 STATISTICAL CONSIDERATIONS

11.1 STUDY DESIGN

Study CTO # 103048 is a potentially multicenter, non-randomized, single cohort phase IB trial evaluating the safety and efficacy of tarloxotinib in combination with sotorasib in NSLC patients with KRAS G12C mutation who have progressed on any small molecule KRAS G12C inhibitor.

Safety lead-in
A minimum of 6 patients and as many as 18 patients will be enrolled in a safety lead-in cohort to evaluate the safety of the combination of tarloxotinib and sotorasib. Sotorasib will be held at a fixed dose of 960 mg QD (the approved dose) while the starting dose of tarloxotinib will be the monotherapy RP2D equal to 150mg/m^2 QW (dose level 1 [DL1]). Following a 3+3 algorithm, an initial 3 patients will be enrolled at DL1. If 0 or 1 of 3 patients experience a DLT, an additional 3 patients will be enrolled to DL1. DL1 will be declared the combination RP2D ($RP2D_c$) if at most 1 of 6 patients treated at DL1 experience a DLT. Alternatively, if there are 2 or more DLTs observed at DL1, 3 patients will be enrolled at DL -1 and the 3+3 rules repeated for safety evaluation. The $RP2D_c$ will be the highest DL at which at most 1 patient of 6 experiences a DLT. If DL -2 is considered too toxic, additional dose levels below DL -2 to be determined may be considered for safety.

Dose expansion
Once the tarloxotinib $RP2D_c$ is reached, an expansion cohort of up to 12 patients will be enrolled to evaluate the safety of the combination of tarloxotinib and sotorasib. Eligible safety lead-in patients treated at the $RP2D_c$ will be included in the expansion cohort.

The combination of tarloxotinib and sotorasib will not be considered promising if there is weak evidence the true objective response rate (ORR) exceeds 20%. Specifically, the trial will be declared negative if Prob (true ORR > 20% | observed no. of responses) < 20%, equivalent to observing at most 1 response in 12 patients. We assume the true ORR follows a beta (0.5, 0.5) prior distribution and, conditional on the true ORR, the number of responses follows a binomial distribution. If at least 2 responses in 12 patients are observed, the combination may be considered promising. Given 1 response in 12 patients, the probability the true ORR exceeds 20% is approximately 16%. Given 2 responses in 12 patients, the probability the true ORR exceeds 20% is approximately 42%.

11.1.1 SAMPLE SIZE DETERMINATION

The sample size of 6 patients in the safety lead-in and 12 patients in the expansion cohort will allow for preliminary assessment of safety and anti-tumor activity at the $RP2D_c$. For primary safety outcomes, the table below shows the probability of observing at least one DLT/DLT-equivalent (DLT-E) for true DLT/DLT-E rates ranging from 10% to 40% for group sample sizes of 6 (safety lead-in cohort) and 12 (expansion cohort). (A DLT-equivalent is any safety event that would have qualified as a DLT had that patient been enrolled in the safety lead-in portion of the study.)

Probability of observing at least 1 DLT/DLT-equivalent events for n = 6 or 12.

	Probability of observing ≥1 DLT/DLT-Es	
True DLT/DLT-E rate	**n=6**	**n=12**
0.05	0.26	0.46
0.10	0.47	0.72
0.15	0.62	0.86
0.20	0.74	0.93
0.25	0.82	0.97
0.30	0.88	0.99

For the 12 patients in the expansion cohort, example incidence rates and corresponding exact 95% binomial confidence intervals (CIs) summarizing safety (e.g., AE or DLT-E rates) or response (e.g., ORR or DCR) are shown in the table below. The values are provided as a reference for estimation rather than as a basis for any decision criteria. The $RP2D_c$ may be revised based on accumulated safety data obtained in expansion.

Estimated incidence rate and exact binomial 95% CI for n = 12.

		95% CI	
No. of Cases	**Estimated Rate**	**Lower Limit**	**Upper Limit**
0	0	0	0.26

1	0.08	0.00	0.38
2	0.17	0.02	0.48
3	0.25	0.05	0.57
4	0.33	0.10	0.65
5	0.42	0.15	0.72
6	0.5	0.21	0.79

11.1.2 POPULATIONS FOR ANALYSES

The following analysis sets will be defined for this study.

The **safety analysis set** comprises all enrolled patients who receive any quantity of study treatment, regardless of eligibility. The safety evaluation will be performed based on the first dose of study treatment a patient receives, regardless of the patient's cohort assignment. The safety analysis set will be used for all dosing/exposure and safety analyses.

The **DLT-evaluable population (*safety lead-in only*)** comprises patients who have either completed the DLT-observation period (1 cycle, 28 days) and received at least 75% of planned doses of the tarloxotinib and sotorasib combination in cycle 1 or have discontinued study treatment or study participation before completing cycle 1 due to a DLT.

The **intention to treat (ITT) analysis set** comprises all patients in the safety analysis set eligible for study inclusion and who meet the inclusion criteria for dose expansion, including eligible safety lead-in patients treated at the $RP2D_c$. This analysis set will be used for all efficacy analyses.

11.2 STATISTICAL ANALYSES

11.2.1 GENERAL APPROACH

Frequencies and percentages will be used to summarize the distributions of categorical variables. Mean, median, range, inter-quartile range and standard deviation will be used to summarize distributions of continuous variables.

11.2.1.1 Participant Disposition

A detailed description of participant disposition will be provided at the end of the study, including a summary of the number and percentage of patients entered into the study, enrolled in the study, and treated, as well as the number and percentage of patients completing the study or discontinuing (overall and by reason for discontinuation).

11.2.1.2 Participant Characteristics

A summary of baseline patient and disease characteristics, historical diagnoses, pre-existing conditions, and prior therapies will be reported using descriptive statistics.

11.2.1.3 Concomitant Therapy

A summary of prior and concomitant medications by dose level (safety lead-in) and cohort (lead-in versus expansion) will be reported.

11.2.1.4 Treatment Compliance

Study treatment compliance will be assessed as the proportion of treatment actually taken relative to what is expected, after accounting for protocol-defined dose adjustments. For oral medications, study treatment taken will be derived from the difference between the total number of capsules/tablets dispensed and returned over the course of the patient's treatment. The number of cycles received, dose omissions, dose reductions, dose delays, and dose intensity will be summarized for all treated patients by dose level (safety lead-in) and cohort (lead-in versus expansion).

11.2.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Objective response rate (ORR), defined as the proportion of patients who achieve a best overall response of CR or PR, is the primary efficacy endpoint. Tumor response will be measured and recorded using RECIST 1.1 guidelines (Eisenhauer et al. 2009). All lesions should be radiologically evaluated using the same method used for baseline evaluation. Any CR or PR will require confirmation at least 4 weeks following initial response observation. Objective response rate will be summarized for the ITT population using frequencies and proportions. A 95% CI for the ORR will be constructed using exact binomial (Clopper-Pearson) methods.

11.2.3 ANALYSIS OF THE SECONDARY EFFICACY ENDPOINT(S)

Disease control rate (DCR) is defined as the proportion of patients who achieve a CR or PR or SD for at least 2 cycles. DCR will be summarized for the ITT population using frequencies and proportions. A 95% CI for the DCR will be constructed using exact binomial (Clopper-Pearson) methods.

Best overall response (BOR) will be determined from a sequence of responses assessed. Two objective status determinations of CR before progression are required for a BOR of CR. Two determinations of PR or better before progression, but not qualifying for a CR, are required for a BOR of PR. A minimum timeframe of 8 weeks is required for a BOR of SD. BOR will be summarized for the ITT population using frequencies and proportions. A 95% CI for BORs of CR, PR, SD or PD will be constructed using exact binomial (Clopper-Pearson) methods.

Duration of response (DOR) will be evaluated only for responders. Duration of response is measured from the date of first confirmed response (CR or PR) to date of first disease progression (taking as reference for progressive disease the smallest measurements recorded since the treatment started) or death. DOR will be summarized graphically using Kaplan-Meier curves. Median DOR and corresponding 95% CI will be reported. For patients who are not known to have died or to have had a progression of disease as of the data-inclusion cut-off date, DOR will be censored at the date of last objective response assessment prior to the date of any subsequent systemic anticancer therapy.

Progression free survival (PFS) is defined as the time from the date of start of treatment to the first date of radiologically documented progressive disease or the date of death due to any cause, whichever occurs first. PFS will be summarized graphically using Kaplan-Meier curves. Median

PFS and corresponding 95% CI will be reported. For patients who are not known to have died or progressed as of the data-inclusion cut-off date, PFS time will be censored at the date of the last objective progression-free disease assessment prior to the date of any subsequent systemic anticancer therapy.

Overall survival (OS) is defined as the time from the date of start of treatment to the date of death due to any cause. OS will be summarized graphically using Kaplan-Meier curves. Median OS and corresponding 95% CI will be reported. For patients who are alive, lost to follow-up, or withdrawn from the study at the time of analysis, OS will be censored at the last date the patient is known to be alive.

11.2.4 SAFETY ANALYSES

All patients in the safety analysis set will be evaluated for safety and toxicity. Adverse events, SAEs and TEAEs will be summarized by System Organ Class (SOC) and by decreasing frequency of Preferred Term within SOC. Safety analyses will include the following summaries:

- AEs, including severity and possible relationship to study drug
- SAEs, including possible relationship to study drug
- AEs leading to dose adjustments
- DLTs and DLT-E events
- Discontinuations from study treatment due to AEs or death
- Treatment-emergent abnormal changes in laboratory values
- Treatment-emergent abnormal changes in vital signs and ECGs

AEs should be reported for 28 days after the last dose of tarloxotinib and/or sotorasib.

11.2.5 EXPLORATORY ANALYSES

The frequency and proportion of patients with specific mutations and alterations will be summarized. Corresponding exact binomial (Clopper-Pearson) 95% confidence intervals will be constructed. The association of specific mutations and alterations with clinical activity will be evaluated using Fisher's exact test for categorical efficacy endpoints and using Cox proportional hazards regression models for time-to-event efficacy endpoints.

11.3 INTERIM ANALYSES

Safety lead-in

Safety and tolerability data will be reviewed on a cohort-by-cohort basis during safety lead-in to determine if an additional cohort of patients should be enrolled at the current DL, if de-escalation is warranted, or if the protocol should be amended to evaluate additional intermediate or lower DLs. The final determination of the $RP2D_c$ will be based on the totality of data including, but not limited to, safety and early signs of anti-tumor activity.

Dose expansion

Interim futility analysis. Given the limited sample size, there will be no futility interim analysis in the dose expansion cohort.

Continuous safety monitoring. Bayesian toxicity monitoring will be used to perform continuous safety monitoring of patients enrolled in the expansion cohort. Specifically, patients enrolled in the expansion cohort will be monitored for incidence of DLT-equivalent (DLT-E) events, defined as any safety event that would have qualified as a DLT had that patient been enrolled in the safety lead-in portion of the study. We assume the true DLT-E rate follows a beta (0.5, 0.5) prior distribution and, conditional on the true DLT-E rate, the number of patients who experience a DLT-E follows a binomial distribution. If Prob (DLT-E rate > 33% | observed no. DLT-Es) > 50%, trial enrollment will be paused. (Note: The observed number of DLT-Es will include DLTs from eligible safety lead-in patients treated at the RP2Dc who are included in the expansion cohort. Bayesian toxicity monitoring parameters were selected to calibrate with the 3+3 de-escalation rules used in the safety lead-in.) If the trial is paused, the safety review committee will review the totality of the safety data and determine whether to continue patient enrollment at the current $RP2D_c$, introduce intermediate or lower dose levels for evaluation, or close the trial to accrual and declare the combination of tarloxotinib and sotorasib too toxic. This monitoring rule has a 13% and 95% probability of pausing if the true DLT-E rate is 10% or 50%, respectively. The table below specifies safety monitoring thresholds.

Bayesian toxicity monitoring boundaries		
No. of patients	**No. of DLT-Es to pause study**	**Observed DLT-E rate**
6	≥2	≥0.33
7-9	≥3	≥0.33
10-11	≥4	≥0.36
12 – expansion cohort fully accrued		

12 CORRELATIVE STUDIES

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 expression of specific mutations and biomarkers in consenting patients.

Blood samples will be collected for biomarker analysis at Cycle 1 Day 1, Cycle 2 Day 1, and end of treatment. Whole blood samples will be collected in two 10 mL cell-free DNA BCT (Streck) blood collection tubes and two 10 mL BD Vacutainer EDTA tubes with total volume of collection no more than 40 mL. Tumor tissue will be collected for retrospective concordance mutation testing and correlation with biomarkers.

13 ADVERSE EVENT REPORTING REQUIREMENTS

13.1 PURPOSE

AE data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AE are reported in a routine manner at scheduled times during a trial. Additionally, certain AEs must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe routine and expedited AEs reporting for this protocol.

Throughout the study, the Investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safety of the drug under investigation.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

13.2 DEFINITION OF ADVERSE EVENT

An AE is defined as any illness, sign or symptom which has appeared or worsened during the course of the study, regardless of causal relationship to the drug under study, experienced by a patient.

All adverse events should be recorded and described in the adverse event database in REDCap. Adverse events also include Grade 3 or 4 abnormal laboratory test results that were not noted in the Screening Phase.

Pre-existing diseases or conditions will not be considered AEs unless there is an increase in the frequency, duration or severity, or a change in the quality, of the disease or condition. Only grade 3 or 4 abnormal lab values that were not noted during the Screening Phase should be recorded; however, any clinical consequences of the abnormality, regardless of grade should be reported as AEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Progression of cancer also will not be considered an AE.

Death should only be entered as the outcome for an AE when the patient’s death is at least probably related to the AE (Note: the causal relationship of the AE to the test article is not to be considered in making this decision). If more than 1 AE is possibly related to the patient's death, the outcome of death should be indicated for each such AE.

13.3 DEFINITION OF SERIOUS ADVERSE EVENT

An SAE is defined by regulatory agencies as one that suggests a significant hazard or side effect, regardless of the investigator or sponsor’s opinion on the relationship to investigational product. This includes, but may not be limited events that result in the following outcomes:

- Death
- Life-threatening. Patient was at substantial risk of dying at the time of the event or use or continued use of the medical product may have resulted in the death of the patient.
- Hospitalization (initial or prolonged). Report hospital admissions or prolongation of hospitalization. Emergency room visits that do not result in admission should be evaluated for one of the other serious outcomes.
- Disability or Permanent Damage. Report is the adverse event resulted in a substantial disruption of a person's ability to conducts normal life functions.
- Congenital anomaly/birth defect. Report if it is suspected that the exposure to the medical product prior to conception or during pregnancy may have resulted in an adverse outcome for the child.
- Other Serious or important medical events. If the event does not fit other outcomes, but may jeopardize the patient and may require intervention to prevent one of the other outcomes.

13.4 DEFINITION OF SEVERITY

Adverse events will be graded according to the revised NCI Common Toxicity Criteria. If toxicities are not defined by the NCI Common Toxicity Criteria v. 4.0, the intensity of each adverse event should be graded as outlined below:

GRADE 1	MILD: Sign or symptom noticeable, but does not interfere with normal daily activities.
GRADE 2	MODERATE: Sign or symptom sufficient to interfere with normal daily activities.
GRADE 3	SEVERE: Sign or symptom is incapacitating, with inability to perform daily activities.
GRADE 4	LIFE-THREATENING: sign or symptom poses immediate risk of death to this patient.

13.5 DEFINITION OF RELATIONSHIP TO STUDY DRUG

The categories for classifying the Investigator's opinion regarding the relationship of an AE to the study drug are listed below.

Definitely related:	An adverse event occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug should be clinically plausible. The event must be definite pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary and feasible.

Possibly related:	An adverse event with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Not related:	An adverse event with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying diseases provide plausible explanations.

13.6 DOCUMENTATION OF ADVERSE EVENTS

The Investigator will monitor and/or ask about or evaluate AEs using non leading questions at each visit or evaluation. The occurrence of all AEs will be documented in the CRF with the following information, where appropriate:

- AE name or term
- When the AE first occurred (start date)
- When the AE stopped (stop date), (or an indication of "ongoing")
- How long the AE persisted (optional)
- Severity of the AE
- Seriousness
- Actions taken
- Outcome
- Investigator opinion regarding the relationship of AE to the study drug(s)

13.7 FOLLOW UP OF PATIENTS WITH ADVERSE EVENTS

The Investigator will follow patients with AEs, even if the patient was withdrawn from the study due to the AE, until the adverse event has:

- resolved
- the patient has returned to baseline state of health,
- the patient is lost to follow-up,
- the event is otherwise explained,
- the Investigator does not expect any further improvement or worsening of the adverse event.

Medically significant AEs considered related to the investigational product by the investigator or the sponsor will be followed until resolved or considered stable.

14 DATA COLLECTION AND MANAGMENT

Electronic and hard copy CRF's will be provided for the recording of data. With the exception of hard copy case report forms utilized for expedited reporting requirements, such as the reporting of SAE's, the remainder of patient data will be collected and submitted via electronic CRFs. All data should be substantiated by clinical source documents organized within a patient research record. ICH Good Clinical Practices are to be followed.

Electronic data for on study and follow-up patient data is submitted via the electronic system called REDCap (Research Electronic Data Capture). REDCap is managed from the Medical University of South Carolina as a consortium partner under their CTSA. REDCap CRF is a secure, Web-based application designed to capture and manage research study data.

The system has been reviewed for 21CFR Part 11 compliance and has been deemed "21CFR 11 Capable." Users of the REDCap system are limited to members of the IRB approved research team who are delegated data management responsibilities, typically the study coordinator and data manager.

15 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

15.1 INFORMED CONSENT

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

15.2 INSTITUTIONAL REVIEW

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46)

16 REFERENCES

1. Kruspig B, Monteverde T, Neidler S, Hock A, Kerr E, Nixon C, et al. The ERBB network facilitates KRAS-driven lung tumorigenesis. Science translational medicine. 2018;10(446).
2. Uras IZ, Moll HP, Casanova E. Targeting KRAS Mutant Non-Small-Cell Lung Cancer: Past, Present and Future. International journal of molecular sciences. 2020;21(12).
3. American Cancer Society http://cancerstatisticscenter.cancer.org. Cancer Statistics Center. Accessed May 24 2020.
4. Janes MR, Zhang J, Li LS, Hansen R, Peters U, Guo X, et al. Targeting KRAS Mutant Cancers with a Covalent G12C-Specific Inhibitor. Cell. 2018;172(3):578-89.e17.
5. Hallin J, Engstrom LD, Hargis L, Calinisan A, Aranda R, Briere DM, et al. The KRAS(G12C) Inhibitor MRTX849 Provides Insight toward Therapeutic Susceptibility of KRAS-Mutant Cancers in Mouse Models and Patients. Cancer discovery. 2020;10(1):54-71.
6. Hong DS, Fakih MG, Strickler JH, Desai J, Durm GA, Shapiro GI, et al. KRAS(G12C) Inhibition with Sotorasib in Advanced Solid Tumors. The New England journal of medicine. 2020;383(13):1207-17.
7. Lito P, Solomon M, Li LS, Hansen R, Rosen N. Allele-specific inhibitors inactivate mutant KRAS G12C by a trapping mechanism. Science (New York, NY). 2016;351(6273):604-8
8. Misale S, Fatherree JP, Cortez E, Li C, Bilton S, Timonina D, et al. KRAS G12C NSCLC Models Are Sensitive to Direct Targeting of KRAS in Combination with PI3K Inhibition. Clinical cancer research : an official journal of the American Association for Cancer Research. 2019;25(2):796-807.
9. Umelo IA, De Wever O, Kronenberger P, Van Deun J, Noor A, Singh K, et al. Combined targeting of EGFR/HER promotes anti-tumor efficacy in subsets of KRAS mutant lung cancer resistant to single EGFR blockade. Oncotarget. 2015;6(24):20132-44.
10. Estrada-Bernal A, Le AT, Doak AE, Tirunagaru VG, Silva S, Bull MR, et al. Tarloxotinib Is a Hypoxia-Activated Pan-HER Kinase Inhibitor Active Against a Broad Range of HER-Family Oncogenes. Clinical cancer research : an official journal of the American Association for Cancer Research. 2020.
11. Suda K, Nishino M, Koga T, Fujino T, Kobayashi Y, Mitsudomi T, et al. Abstract 2200: Potent in vitro activity of Tarloxotinib for EGFR C797S and other mutations refractory to current EGFR tyrosine kinase inhibitors. Cancer research. 2019;79(13 Supplement):2200.
12. Liu1 SV VL, Lee VHF, Zhu VW, Baik CS, Sacher A, McCoach CE, Nguyen D, Li JY, Pacheco JM, Kim C, Burns TF, Schenk EL, Leighl N, Tozzi L, Camidge DR. LBA61 - First analysis of RAIN-701: Study of tarloxotinib in patients with non-small cell lung cancer (NSCLC) EGFR Exon 20 insertion, HER2-activating mutations & other solid tumours with NRG1/ERBB gene fusions. ESMO 2020. 2020.