Brigatinib Before Brain Irradiation Trial (B3i Trial): A Phase II Trial of Brigatinib Alone for Brain Metastases from ALK+ Lung Cancer

Protocol Number: 19-2862

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Funded by: Takeda

PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
V.2	03/02/2021	Addition of risk to sun exposure. Clarification of study visit windows, SAE/AE reporting language, and follow up language. General protocol clarifications.	Changes made due to brigatinib memo from Takeda.

Version	Date	Description of Change	Brief Rationale
V.3	09/01/2021	Changed PI, Clarified AE/SAE reporting language	
V.4	9/14/2021	Changed PI	Temporary PI change due to PI going on leave.
V.5	TBD	Changed PI	PI has returned from leave.

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STATEMENT OF COMPLIANCE

This is an investigator-initiated study. The principal investigator (PI), Chad Rusthoven, MD is conducting the study and acting as the sponsor. As the sponsor-investigator, both the legal/ethical obligations of a PI and those of a sponsor will be followed.

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by applicable United States (US) laws and applications, including but not limited to United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812), as applicable.

The PI will assure that no changes to the protocol will take place without documented approval from the Institutional Review Board (IRB). All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Sponsor-Principal Investigator: _____
Print/Type Name

Signature: _____ **Date:** _____

Site Principal Investigator: _____
Print/Type Name

Signature: _____ **Date:** _____

LIST OF ABBREVIATIONS

ACRONYM	DESCRIPTION
AE	Adverse event
ALK	Anaplastic lymphoma kinase
BM	Brain metastases
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CMP	Comprehensive metabolic panel
CMP	Clinical monitoring plan
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CSF	Cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P40 enzymes
DCR	Disease Control Rate
DSMC	Data and Safety Monitoring Committee
ECOG-PS	Eastern Cooperative Oncology Group – Performance Status
EORTC	European Organization for Research and Treatment of Cancer
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
IIT	Investigator-Initiated Trial
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
MI	Myocardial Infarction
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCCTG	North Central Cancer Treatment Group
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
OHRP	Office of Human Research Protection
ORR	Objective response rates
PCI	Percutaneous Coronary Intervention
PD	Progressive Disease
PET/CT	Positron emission tomography-computed tomography
PI	Principal Investigator
PR	Partial Response
QLQ	Quality of Life Questionnaire
QOL	Quality of life
RANO	Response Assessment in Neuro-Oncology Criteria

ACRONYM	DESCRIPTION
RECIST	Response Evaluation in Solid Tumors Criteria
RT	Radiation therapy
RTOG	Radiation therapy Oncology Group
SAE	Serious Adverse Event
SD	Stable disease
SRS	Stereotactic radiosurgery
T2/FLAIR	T2 Weighted fluid attenuated inversion recovery
TKI	Tyrosine kinase inhibitor
UAP	Unanticipated Problem
UCCC	University of Colorado Cancer Center
UCD	University of Colorado Denver
WBRT	Whole-brain radiotherapy

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol Title:

Brigatinib Before Brain Irradiation Trial (B3i Trial): A Phase II Trial of Brigatinib Alone for Brain Metastases from ALK+ Lung Cancer

Objectives:

- ***Primary Objective:***
  1. To evaluate if CNS control is acceptable with a strategy of brigatinib alone for patients with ALK+ lung cancer with brain metastases

- ***Secondary Objectives:***
  1. To evaluate time until progression with brigatinib alone
  2. To evaluate overall survival with a strategy of brigatinib alone
  3. To evaluate the best CNS objective response rates (ORR) with brigatinib alone
  4. To evaluate the time until the administration of WBRT with brigatinib alone
  5. To evaluate longitudinal changes in quality of life with brigatinib alone

Endpoint:

- ***Primary Endpoint:***
  1. Disease Control Rate (DCR) of brain metastases at 3 months (13-week MRI ±7 days) where DCR is defined as complete response (CR), partial response (PR), or stable disease (SD) as defined by the RANO-BM criteria.

- ***Secondary Endpoints:***
  1a. Time until any CNS progressive disease (PD) by RANO-BM criteria and rates at follow up intervals (up to 24 months from Day 1).
  1b. Time until any local PD (ie, in brain lesions identified at the time of enrollment) by RANO-BM criteria and rates at follow up intervals (up to 24 months from Day 1).
  1c. Time until any distant brain PD (ie, new brain lesions that were not present at the time of enrollment) by RANO-BM criteria and rates at follow up intervals (up to 24 months from Day 1).
  1d. Time until progression at any site using RANO-BM for intracranial disease and RECIST for extracranial disease and rates at follow up intervals (up to 24 months from Day 1).

2a. Time until death from any cause and rates at follow up intervals (up to 24 months from Day 1).
2b. Time until brain metastases-specific mortality, defined as intracranial progression as a component of cause of death and rates at follow up intervals (up to 24 months from Day 1).
3. Cumulative rate of best responses individually for complete response (CR), partial response (PR), stable disease (SD), by RANO-BM criteria
4. Time until the administration of whole brain-radiotherapy (WBRT) and rates at follow up intervals (up to 24 months from Day 1).
5. Quality of life will be assessed using standardized QOL metrics (EORTC QLQ C30/BN 20)

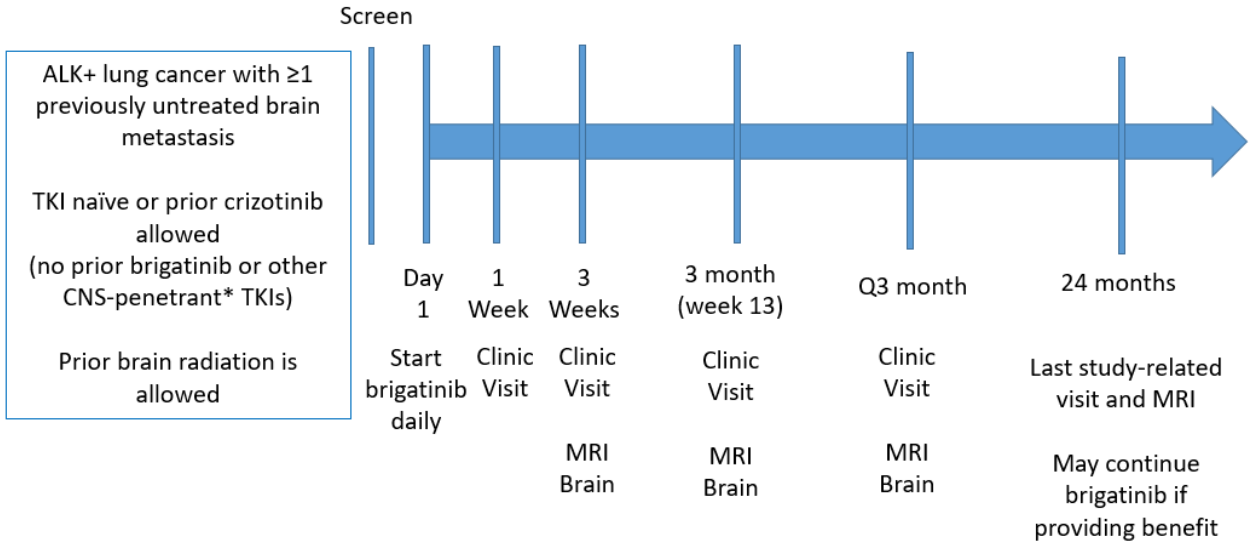
- ***Exploratory:***
  1. Analysis of blood at baseline and at progression to correlate blood-based markers with clinical outcomes.
  2. To characterize corticosteroids administration before and after brigatinib initiation

Population:

- **Sample size**
  - Maximum number of participants that can be enrolled is 35 (allow for screen failures)
  - Minimum number of participants to be enrolled 19 (number of participants needed to answer scientific question/aims)
- ***Gender*** Male and Female
- ***Age Range*** 18-100 years
- ***Demographic group****:* Patients with brain metastases from ALK+ lung cancer without prior treatment with brigatinib
- ***General health status:*** ECOG ≤2
- ***Geographic location:*** United States

Phase:	II
Participating Sites:	University of Colorado, Mayo Rochester, City of Hope Los Angeles
Description of Study Intervention:	Brigatinib, an oral tyrosine kinase inhibitor (TKI) targeting anaplastic lymphoma kinase (ALK)
Study Duration:	4 years
Participant Duration:	2 years

1.2 STUDY SCHEMA



*Patients with prior exposure to brigatinib, alectinib, lorlatinib, and ceritinib are excluded.

1.3 SCHEDULE OF EVENTS

	Screen/ Enroll	Year 1							Year 2 (Week)				End of Treatment	Survival Follow Up
		Day		Week										
Procedures	**≤28 days Day 1**	**Day 1**	**Day 8[c]**	**3[c]**	**13[d]**	**26[e]**	**39[e]**	**52[e]**	**65[e]**	**78[e]**	**91[e]**	**104[e]**	**Termination[j]**	**Every 6 months for up to 2 years from Day 1[f]**
Informed Consent/Review Eligibility	X													
Medical History	X													
MRI Brain	X			X	X	X	X	X	X	X	X	X	X	
QOL Assessments[b]		X		X	X	X	X	X	X	X	X	X	X	
Clinic Visit (complete physical exam)	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy Test (WOCBP only)[g]	X													
Concomitant Meds (including corticosteroids agent and dose)	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Labs (CBC, CMP, CPK, Lipase, Amylase)	X	X	X	X	X	X	X	X	X	X	X	X	X	
Research Blood for cfDNA	X												X	
RECIST 1.1/RANO-BM	X			X	X	X	X	X	X	X	X	X	X	
Systemic Imaging (CT C/A±P or PET/CT)	X'				X	X	X	X	X	X	X	X	X	
Brigatinib Administration[a]		X	X	X	X	X	X	X	X	X	X	X		
CNS Radiation for Brain Metastases Progression (as indicated per PI/Sub-I)													X[i]	
Vitals Collection (BP, spO_2 and HR)	X	X	X	X	X	X	X	X	X	X	X	X	X	
Survival and Disease Status, Current Therapy														X

3-month intervals are defined as 13 weeks (52 weeks per 12 months / 4)

[a] All patients will be started on brigatinib 90 mg daily for 7 days, before escalating to 180 mg daily thereafter as tolerated
[b] EORTC QLQ-C30 and BN20 brain-specific questionnaire
[c] Day 8 and Week 3 procedures have a window of ± 4 days from Day 1
[d] Week 13 procedures have a window of ± 7 days
[e] All time points 26 weeks and onwards inclusive have a window of ± 14 days
[f] For patients removed from study treatment prior to 24 months (Week 104), survival follow-up will be done every 6 months (±14 days from Termination Visit) for up to 24 months from Day 1, or until death or patient withdrawal of consent; this includes for patients who develop CNS progression while on study
[g] Pregnancy Test (for WOCBP only) should also be performed prior to any radiation therapy subsequent to enrollment including radiation for brain or extracranial disease according to SOC.
[h] Baseline neurologic symptoms should be scored per Cox, James D., et al "Toxicity criteria of the radiation therapy oncology group (RTOG) and the European organization for research and treatment of cancer (EORTC)." *International Journal of Radiation Oncology• Biology• Physics* 31.5 (1995): 1341-1346. Only patients with neurologic symptoms from their brain metastases that are grade 0, 1, 2 are eligible for inclusion; patients with grade 3 and 4 neurologic symptoms are excluded (see section 5). Scale: Grade 0 (no neurologic symptoms), Grade 1 (Fully functional status (i.e., able to work) with minor neurological findings, no medication needed), Grade 2 (Neurological findings present sufficient to require home care/nursing assistance may be required/medications including steroids/antiseizure agents may be required), Grade 3 (Neurological findings requiring hospitalization for initial management), Grade 4 (Serious neurological impairment that includes paralysis, coma, or seizures > 3 per week despite medication/hospitalization required)
[i] CNS salvage radiation therapy will be done in the event of brain metastases progression, per treating investigator
[j] For patients discontinuing study treatment prior to Week 104, termination visit assessments (other than CNS salvage therapy, if required) are to occur within 30 days of last dose of study drug. If patient continues on study treatment until Week 104, the study termination visit is to occur at Week 104 (month 24) and patients may transition to SOC brigatinib at that time, if still receiving clinical benefit.
[k] Baseline systemic imaging (CT or PET/CT only) performed per standard of care within 6 weeks (42 days) of Day 1 will be permitted

2 INTRODUCTION

2.1 STUDY RATIONALE

Patients with metastatic non-small cell lung cancer (NSCLC) with anaplastic lymphoma kinase (ALK) mutations that can be targeted with oral tyrosine kinase inhibitors (TKIs) have an excellent prognosis compared to historic data on NSCLC patients without targetable mutations. Brain metastases (BM) are common in patients with ALK+ lung cancer and BM have historically been treated with radiation therapy either to the entire brain with whole-brain radiotherapy (WBRT) or focally with stereotactic radiosurgery (SRS). Radiation therapy (RT) is effective for the control of brain metastases, but can be associated with toxicity to cognitive function and quality of life. Newer generation of TKIs targeting ALK, including brigatinib, have demonstrated increased CNS penetration and activity in the treatment brain metastases. This raises the possibility of a new paradigm in the treatment of ALK+ NSCLC brain metastases involving brigatinib alone and reserving radiation therapy to the brain as a salvage therapy option for subsequent CNS progression. However, there have not been dedicated trials designed to prospectively evaluate a strategy of brigatinib alone for brain metastases.

In this single-arm phase II trial, patients with ALK+ brain metastases who are either TKI naïve or have had prior crizotinib, but without prior treatment with brigatinib or other CNS-penetrant TKIs (e.g., alectinib, lorlatinib, and ceritinib), will be treated with brigatinib alone in the setting of close clinical follow up and brain magnetic resonance imaging (MRI) surveillance to maximize safety and allow for early intervention with radiation therapy in the event any CNS progression occurs. If brigatinib alone can offer high rates of CNS disease control in this setting, this data could contribute to a change in paradigm in the treatment of BM in ALK+ NSCLC that would allow more patients to delay or avoid the potential sequelae of CNS RT.

2.2 BACKGROUND

Brain metastases (BM) are a significant problem for patients with non-small cell lung (NSCLC) driven by anaplastic lymphoma kinase (ALK) gene rearrangements. Up to 30-40% of ALK NSCLC patients will present with BM at diagnosis and over 70% will ultimately develop BM (Rusthoven 2016). Crizotinib, a first-generation ALK inhibitor has demonstrated relatively poor CNS penetration and limited CNS activity (Costa 2015). As a result, historically, ALK+ NSCLC patients treated with crizotinib who developed BM were treated with early administration of CNS radiotherapy (RT) as the standard of care.

CNS RT is effective at treating BM but can significantly affect quality-of-life (QOL) and cognitive function. In the EORTC 22952-26001 trial, the use of WBRT was associated with inferior global QOL at 9 months and inferior cognition at 1 year compared to radiosurgery alone (Soffieti 2011). In the NCCTG-N0574, WBRT was associated with an objective decrease in cognition at 3 months, which persisted for 1 year in long term survivors (Brown 2016).

Brigatinib is a next-generation TKI with FDA approval for the treatment of metastatic ALK NSCLC. Brigatinib has notably demonstrated promising central nervous system (CNS) activity in the treatment and prevention of BM. In a multicenter phase II trial, brigatinib provided an intracranial objective response of 67% in crizotinib-refractory patients with measurable BM at enrollment (Kim 2017). In a phase 3 trial comparing brigatinib to a crizotinib, the intracranial response rate for measurable BM at enrollment was 78% with brigatinib vs 29% with crizotinib (Camidge 2018). The observation of high intracranial ORRs with brigatinib raises the possibility of a new paradigm for the treatment of patients with ALK+ NSCLC brain metastases with drug alone and reserving CNS RT for patients who subsequently develop CNS progression.

Prospective investigations of CNS RT de-intensification strategies are particularly important for ALK+ NSCLC, where patients are often younger at diagnosis and experience prolonged median survival of >4 years after the identification of brain metastases, which is more than long enough to manifest potential cognitive sequelae from CNS RT. For example, in a multi-institutional study of ALK+ NSCLC treated in the crizotinib era, the median OS was 49.5 months post BM; 50% required ≥2 courses of RT, 25% required ≥3 courses of RT, and 50% required WBRT (Johung 2016).

Given the impressive CNS response rates with brigatinib in subgroup analyses of patients with brain metastases treated on prior prospective trials, there is now strong rationale and justification for prospective trials dedicated to the evaluation of a strategy of brigatinib alone, for patients with ALK+ NSCLC brain metastases, reserving CNS RT for CNS progression. In particular, clinicians considering brigatinib alone for ALK+ patients with BM will require prospective data demonstrating the safety and efficacy of brigatinib alone in this setting. Short-term outcomes, such as CNS disease control at 3 months, are important in order to demonstrate that a strategy of brigatinib will not result in harm or missed opportunities to offer effective salvage therapies. Here we propose a prospective phase II trial of brigatinib alone for patients with BM. If, as we hypothesize, brigatinib can offer high rates of CNS disease in this setting, this data could contribute to a change in paradigm in the treatment of BM in ALK+ NSCLC that would allow more patients to delay or avoid the potential sequelae of CNS RT.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

This study involves the treatment of patients with BM from ALK+ NSCLC with brigatinib alone and close clinical and MRI surveillance (delaying CNS RT until potential CNS progression, if that were to occur in the future). The primary risk is the potential for higher rates of CNS progression, which is the focus of the trial and the primary endpoint of the study. BM can cause neurologic symptoms, anxiety, require treatments, and may be potentially life threatening in some cases. For this reason, the study involves close clinical follow up and MRI surveillance, to allow early interventions if CNS progression were to occur in patients treated on the trial.

Additional risks are related to the side effect profile of the drug brigatinib. Brigatinib is an FDA approved standard therapy in the first and subsequent lines for patients with metastatic ALK+ NSCLC according to the contemporary NCCN non-small cell lung cancer guidelines. The side effect profile of brigatinib is detailed in subsequent sections of the protocol. In patients who develop CNS progression and require CNS RT, the standard risks associated with CNS RT including fatigue, hair loss, headaches, nausea, and small risks of seizure, radiation necrosis, and focal neurologic deficits apply. It is important to note that CNS RT is considered the gold standard treatment for brain metastases, endorsed by the contemporary NCCN CNS tumor guidelines (v2.2019) and the above risks are considered standard side effects with radiation in this setting that are applicable to patients treated on or off protocol.

2.3.2 KNOWN POTENTIAL BENEFITS

This study involves the treatment of patients who have BM with brigatinib alone (delaying CNS RT until potential CNS progression, if that were to occur in the future). The benefit patients in this arm may achieve is the effective treatment of their BM with a single modality (brigatinib alone) while avoiding or delaying the need for CNS RT. CNS RT can be associated with a negative impact on QOL and cognition, as well as logistical stress and anxiety.

2.3.3 ASSESSMENT OF POTENTIAL BENEFITS

The risks to participants are reasonable in relation to the anticipated benefits to participants and/or society, and in relation to the importance of the knowledge that may reasonably be expected to result, thereby falling in favor of performing the study:

- To Participant: Patients enrolling on this trial may benefit from a single-modality approach (i.e., brigatinib alone without CNS radiation) for the treatment of their disease while avoiding the potential toxicities of CNS radiation
- To Society: Investigations into treatment strategies that can potentially reduce toxicity and the number of modalities used to treat an illness are important to society and have the potential to reduce toxicities, dependency, and health care associated costs and to improve the quality of life for patients and care givers.
- Justify the importance of the knowledge gained: If a treatment strategy of brigatinib alone for patients with ALK+ NSCLC brain metastases demonstrates acceptable CNS disease control, this study has the potential to improve patient QOL and to potentially reduce health care costs in this population. Conversely, if a treatment strategy of brigatinib alone results in unacceptable CNS disease control rates, this would affirm the historic standard of care of combining systemic therapy with CNS RT to treat brain metastases.

3 OBECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To evaluate if CNS control is acceptable with a strategy of brigatinib alone for patients with ALK+ lung cancer brain metastases	Disease Control Rate (DCR) of brain metastases at 3 months (13-week MRI ±7 days), where DCR is defined as complete response (CR), partial response (PR), or stable disease (SD) as defined by the RANO-BM criteria.	It is critical to confirm the short-term safety and efficacy of a treatment approach involving brigatinib alone without CNS RT
Secondary		
1. To evaluate time until progression with brigatinib alone	**1a.** Time until any CNS progressive disease (PD) by RANO-BM criteria and rates at follow up intervals (up to 24 months from Day 1). **1b.** Time until any local PD (i.e., in brain lesions identified at the time of enrollment) by RANO-BM criteria and rates at follow up intervals (up to 24 months from Day 1).	It is important to evaluate the specific elements of disease control (including local and distant control, as well as CNS and extracranial control) with a strategy of brigatinib alone.

	1c. Time until any distant brain PD (i.e., new brain lesions that were not present at the time of enrollment) by RANO-BM criteria and rates at follow up intervals (up to 24 months from Day 1). **1d.** Time until progression at any site using RANO-BM for intracranial disease and RECIST for extracranial disease and rates at follow up intervals (up to 24 months from Day 1).	
2. To evaluate overall survival with a strategy of brigatinib alone	**2a.** Time until death from any cause and rates at follow up intervals (up to 24 months from Day 1). **2b.** Time until brain metastases-specific mortality, defined as intracranial progression as a component of cause of death and rates at follow up intervals (up to 24 months from Day 1).	It is important to describe the overall survival with a strategy of brigatinib alone.
3. To evaluate the best CNS objective response rates (ORR) with brigatinib alone	**3.** Cumulative rate of best responses individually for complete response (CR), partial response (PR), stable disease (SD), by RANO-BM criteria	It is important to describe the rates of responses in existing brain lesions with a strategy brigatinib alone.
4. To evaluate the time until the administration of WBRT with brigatinib alone	**4.** Time until the administration of whole brain-radiotherapy (WBRT) and rates at follow up intervals (up to 24 months from Day 1).	It is important to characterize the time until WBRT with a strategy brigatinib alone, as WBRT is associated with known toxicities.
5. To evaluate longitudinal changes in quality of life with brigatinib alone	**5.** Quality of life will be assessed using standardized QOL metrics (EORTC QLQ C30/BN 20)	It is important to characterize the longitudinal QOL achieved with a strategy of brigatinib alone.
Exploratory		
1. Analysis of blood at baseline and at progression to correlate with clinical outcomes.	**1.** Evaluation of cfDNA and/or other blood-based markers at baseline and progression to correlate with clinical outcomes including disease recurrence, survival, and quality of life	Evaluations of cfDNA can offer important insights into prognostic and predictive biomarkers for patients with metastatic ALK+ NSCLC with brain metastases.
2. To characterize corticosteroids	**2.** Quantification of the agent and dosage of corticosteroids at each study assessment	It is important to quantify the effect of brigatinib on corticosteroid requirements

administration before and after brigatinib initiation		because corticosteroids can be associated with symptoms and negative effects on quality of life

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a single arm phase-II study including patients with ALK+ NSCLC and brain metastases, who are either neurologically asymptomatic or have only mild neurologic symptoms (RTOG acute neurologic morbidity score 0-2) from their brain metastases, who are TKI naïve or have had prior exposure to crizotinib, but who are naïve to brigatinib and other ALK TKIs including alectinib, lorlatinib, and ceritinib. At screening and enrollment, patients will have a history and physical exam, CTCAE symptoms assessment, and brief QOL questionnaires.

At day 1, all patients will be started on brigatinib 90 mg daily for 7 days, before escalating to 180 mg daily thereafter as tolerated.

At day 8, patients will be seen for a scheduled clinic visit. Each clinic visit will include toxicity assessment and physical exam. Day 8 procedures have an allowable window of ±4 days. Brief QOL questionnaires will be administered at baseline (Day 1), at 3 weeks (Day 21), and at 3 months (week 13) and subsequent visits every 3 months.

At 3 weeks (Day 21), patients will be seen for scheduled clinic visits and a scheduled surveillance brain MRI. Week 3 procedures have an allowable window of ± 4 days. Subsequently, patients will have scheduled clinic visits and surveillance brain MRIs at 3 months post enrollment (week 13) and at 3 month intervals for year 1 and 2 (ie, at week 26, 39, 52, 65, 78, 104).

Patients who develop CNS progression during the study will be offered palliative radiation for their brain metastases and their disease status will be recorded as CNS progression event.

Patients who experience disease progression per RECIST 1.1 or RANO BM may continue to be treated with brigatinib if, in the opinion of the treating investigator, they continue to experience clinical benefit. Note, this is an accepted treatment strategy per the contemporary NCCN NSCLC guidelines. In this case, patients will be removed from study treatment and will be followed for survival for up to 24 months from Day 1, but may continue to receive brigatinib per standard of care.

If patients do not experience disease progression, they will complete the study treatment at 24 months. Patients continuing to benefit from brigatinib in the opinion of the treating physician may remain on the drug after 24 months per standard of care.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Brigatinib has demonstrated promising ORRs for patients with existing BM in subgroup analyses of prospective phase 2 and 3 trials, as well as prevention of new BM. In a multicenter phase II trial, brigatinib provided an intracranial objective response of 67% in crizotinib-refractory patients with measurable BM at enrollment (Kim 2017). In a phase 3 trial comparing brigatinib to a crizotinib, the intracranial response rate for measurable BM at enrollment was 78% with brigatinib vs 29% with crizotinib (Camidge 2018). However, these trials were not designed to evaluate the role brigatinib alone in patients with brain metastases and many of the patients included in these subset analyses received brain radiation therapy for the brain metastases. The current trial proposal is dedicated specifically to the evaluation of brigatinib alone in patients with brain metastases with a primary endpoint to evaluate whether this approach results in acceptable CNS control.

4.3 JUSTIFICATION FOR DOSE

The dose selected is the standard FDA approved doses for brigatinib. All patients will be started on brigatinib 90 mg daily for 7 days, before escalating to 180 mg daily thereafter.

4.4 END OF STUDY DEFINITION

Individuals will be followed for 2 years from Day 1, or until death or patient withdrawal of consent; this includes patients who develop CNS progression while on study. Participants are free to withdraw from participation in the study at any time upon request. Patients who continue to benefit from brigatinib in the opinion of the treating physician may stay on brigatinib beyond 2 years per standard of care. The study will conclude when the final patient on study reaches 2 years of follow up, or is removed from the study.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all the following criteria:

1. Provision to sign and date the consent form.
2. Stated willingness to comply with all study procedures and be available for the duration of the study.
3. Ability to take and retain oral medications.
4. Be a male or female aged ≥18 years.
5. Patients with ALK+ lung cancer with evidence of ≥1 previously untreated brain metastases on brain MRI. Prior therapy (radiation or surgery) for brain metastases is allowed, similar to other prospective trials of systemic therapy alone for BM (e.g., Tawbi et al, NEJM, 379.8 (2018): 722-730). However, patients must have ≥1 previously untreated at the time of enrollment.
6. Patients may be ALK TKI naïve OR have had prior crizotinib therapy.
7. Patients may be included if they are asymptomatic from their brain metastases (RTOG/EORTC grade 0) or if they have mild symptoms from their brain metastases not to exceed RTOG/ EORTC grade 1 or 2 (Grade 1: Fully functional status (i.e. able to work) with minor neurological findings, no medication needed; Grade 2: Neurological findings present sufficient to require home care / nursing assistance may be required / medications including steroids/anti-seizure agents may be required) (Cox, James D., et al "Toxicity criteria of the radiation therapy oncology group (RTOG) and the European organization for research and treatment of cancer (EORTC)." *International Journal of Radiation Oncology• Biology• Physics* 31.5 (1995): 1341-1346). See table below for acute CNS symptom grading.

Grade 0	Grade 1	Grade 2	Grade 3 (excluded)	Grade 4 (excluded)
No neurologic symptoms	Fully functional status (i.e., able to work) with minor neurological findings, no medication needed	Neurological findings present sufficient to require home care/ nursing assistance may be required/medications including steroids/ antiseizure agents may be required	Neurological findings requiring hospitalization for initial management	Serious neurological impairment that includes paralysis, coma, or seizures > 3 per week despite medication/ hospitalization required

8. Neurologically symptomatic patients must not require immediate surgical or radiation therapy for their symptoms, as decided by an investigator.
9. Have an Eastern Cooperative Oncology Group (ECOG) performance status ≤2.
10. Have adequate organ function, as determined by
    - ALT/AST ≤2.5 × upper limit of normal (ULN); ≤5 × ULN is acceptable if liver metastases are present
    - Total serum bilirubin ≤1.5 × ULN (<3.0×ULN for patients with Gilbert syndrome)
    - Estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m2, using the modification of diet in renal disease (MDRD) equation
    - Serum lipase/amylase ≤1.5 × ULN
    - Absolute neutrophil count (ANC) ≥1.5 × 10^9/L
    - Platelet count ≥75 × 10^9/L
    - Hemoglobin ≥9 g/dL
11. For females of childbearing potential, have a negative pregnancy test documented prior to initiating brigatinib.
12. For female and male patients who are fertile, agree to use 2 effective methods of contraception with their sexual partners from the time of signing the informed consent through 4 months after the last dose of study drug, or agree to completely abstain from heterosexual intercourse. Brigatinib may decrease effectiveness of hormonal contraceptives, therefore, women are recommended to use non-hormonal methods of contraception. Highly effective non-hormonal birth control for women of child bearing potential with male partners includes:
    - Sexual abstinence (no sexual intercourse)
    - Intrauterine device (IUD) or intrauterine system (IUS)

- Bilateral tubal ligation (both tubes tied)
- Vasectomized partner

13. Male patients, even if surgically sterilized (i.e., status post-vasectomy) must agree to 1 of the following:
    - Practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug, or completely abstain from heterosexual intercourse.
14. Patient is willing and able to comply with avoiding prolonged sun exposure while taking brigatinib, and for at least 5 days after discontinuation of treatment.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Patients who have received prior brigatinib therapy or other CNS-penetrant ALK TKIs, including alectinib, lorlatinib, or ceritinib.
2. RTOG/EORTC Acute CNS symptoms, grade 3 and 4 (Grade 3: Neurological findings requiring hospitalization for initial management; Grade 4: Serious neurological impairment that includes paralysis, coma, or seizures > 3 per week despite medication / hospitalization required).
3. Be pregnant, planning a pregnancy, or breastfeeding.
4. Have clinically significant, uncontrolled cardiovascular disease per investigator, specifically including, but not restricted to:
    a. Myocardial infarction (MI) within 6 months prior to the first dose of study drug
    b. Unstable angina within 6 months prior to first dose of study drug
    c. Clinically significant congestive heart failure (CHF) within 6 months prior to first dose of study drug
    d. History of clinically significant atrial or ventricular arrhythmia (including clinically significant bradyarrhythmia), as determined by the treating physician
    e. Cerebrovascular accident or transient ischemic attack within 6 months prior to first dose of study drug
5. Have uncontrolled hypertension per the investigator. Patients with persistent hypertension of systolic ≥140 or diastolic ≥90 mm Hg should be under treatment on study entry to control blood pressure.
6. Have a history or the presence at baseline of pulmonary interstitial disease, drug-related pneumonitis, or radiation pneumonitis.

7. Have an ongoing or active infection, including, but not limited to, the requirement for intravenous (IV) antibiotics.
8. Have a known history of human immunodeficiency virus (HIV) infection. Testing is not required in the absence of history.
9. Have a known or suspected hypersensitivity to brigatinib or its excipients.
10. Additional systemic therapies for the treatment of lung cancer may not be taken concomitantly with brigatinib (eg, TKIs, immunotherapy, chemotherapy). No washout period is required for prior therapy.
11. Have malabsorption syndrome or other GI illness that could affect oral absorption of brigatinib.
12. Have any condition or illness that, in the opinion of the investigator, would compromise patient safety or interfere with the evaluation of brigatinib.
13. Received systemic treatment with strong cytochrome p-450 (cyp)3a inhibitors, strong cyp3a inducers, or moderate cyp3a inducers within 14 days before enrollment.
14. Had major surgery within 30 days of the first dose of brigatinib. Minor surgical procedures such as catheter placement or minimally invasive biopsies are allowed.
15. Have been diagnosed with another primary malignancy other than NSCLC, except for adequately treated nonmelanoma skin cancer or cervical cancer in situ; definitively treated nonmetastatic prostate cancer; or patients with another primary malignancy who are definitively relapse-free with at least 3 years elapsed since the diagnosis of the other primary malignancy.

5.3 LIFESTYLE CONSIDERATIONS

Lifestyle considerations are similar to patients treated with metastatic ALK+ NSCLC in other settings. Patients should contact their physicians immediately if they develop new or worsening neurologic symptoms or side effects suspected to be related to brigatinib therapy.

5.4 SCREEN FAILURES

Patients who have signed informed consent and subsequently fail to meet the inclusion and/or exclusion criteria are defined as screen failures. Once the investigator determines that screening will not continue for a patient, and the patient will not be enrolled in the study, the screen failure should be documented. Patients who screen fail may later be re-screened with prior sponsor-investigator approval.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Patient and physician interest in enrollment is expected to be high given the strong clinical rationale to support a strategy of brigatinib alone with close clinical and MRI surveillance as a potential strategy to avoid the toxicity of CNS RT. We anticipate that retention rates will be high given that the follow-up requirements are similar to the standard of care with the exception of the 1-week clinic visit and 3-week clinic visit and brain MRI. These additional follow up requirements are considered appropriate to ensure the safety of the brigatinib alone approach. All other clinic visits and follow up MRIs are considered to be consistent with the standard-of-care.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

All patients will be started on brigatinib 90 mg daily for 7 days, before escalating to 180 mg daily thereafter.

The clinical follow-up and imaging requirements are similar to the standard of care with the exception of the 1-week clinic visit and 3-week clinic visit and brain MRI. These additional follow-up requirements are considered appropriate to ensure the safety of the brigatinib alone approach.

Patients who develop CNS progression will be treated with standard of care CNS RT, as prescribed by a board-certified radiation oncologist. CNS RT may entail stereotactic radiosurgery (SRS), WBRT, or partial brain radiotherapy, as appropriate in the opinion of the radiation oncologist. For guidance on radiation techniques and doses, adherence to the NCCN CNS tumor guidelines for brain metastases section (www.ncccn.org) is recommended.

6.1.2 DOSING AND ADMINISTRATION

The recommended dosing regimen for brigatinib is 90 mg orally once daily for the first 7 days. If 90 mg is tolerated per investigator during the first 7 days, increase the dose to 180 mg orally once daily.

If brigatinib is interrupted for 14 days or longer for reasons other than adverse reactions, resume treatment at 90 mg once daily for 7 days before increasing to the previously tolerated dose. Interruptions due to treatment related AEs should be managed as per section 6.1.2.2 and 6.1.2.3 below.

Brigatinib may be taken with or without food. Instruct patients to swallow tablets whole. Do not crush or chew tablets. If a dose of brigatinib is missed or vomiting occurs after taking a dose, do not administer an additional dose and take the next dose of brigatinib at the scheduled time.

6.1.2.1 RECOMMENDED BRIGATINIB DOSE REDUCTION LEVELS

Table 1: Recommended Brigatinib Dose Reduction Levels

Starting Dose	**Dose Reduction Levels**				
	First	**Second**	**Third**	**Fourth**	**Fifth**
90mg QD	60mg QD	Permanently discontinue	Not applicable	Not applicable	Not applicable
180mg QD	120mg QD	90mg QD	60mg QD	Permanently discontinue	Not applicable

6.1.2.2 DOSE MODIFICATIONS FOR PNEUMONITIS

Pneumonitis and interstitial lung disease are known side effects of TKIs used in NSCLC, generally occurring later in the course of therapy. Crizotinib has been associated with severe, life-threatening, or fatal treatment-related pneumonitis in clinical trials with a frequency of 4 in 255 (1.6%) patients. Other TKIs used in the treatment of NSCLC have similar adverse reactions. In the ALTA trial, brigatinib was associated with pneumonitis in 3.7% of patients in the 90 mg group (90 mg once daily) and 9.1% of patients in the 90 → 180 mg group (180 mg once daily with 7-day lead-in at 90 mg once daily). Adverse reactions consistent with possible ILD/pneumonitis occurred early (within 9 days of initiation of brigatinib; median onset was 2 days) in 6.4% of patients, with Grade 3 to 4 reactions occurring in 2.7%.

Drug-related pneumonitis may be associated with signs and symptoms such as dyspnea, hypoxia, cough, hemoptysis, and fever as well as radiologic evidence of parenchymal or interstitial changes. The diagnosis of pneumonitis and determination of causal relationship to the drug is

often confounded by the underlying disease (especially lymphangitic carcinomatosis) and other factors such as lung infection and radiation effect due to non-specific signs and symptoms as well as similar radiological appearance. Pneumonitis should be suspected when such signs and symptoms develop or in asymptomatic patients when a new ground glass opacity or interstitial infiltration is noted in imaging studies. If a patient is considered to have the potential diagnosis of drug-related pneumonitis, physical examination, assessment of oxygen saturation, evaluation for infectious etiologies, and thoracentesis, bronchoscopy, or open lung biopsy should be considered to reach a diagnosis. If the causality is at least possibly related to the study drug, management of pneumonitis, including dose interruption and potential discontinuation, as presented in during first 7 days of treatment prior to escalation to 180 mg QD) and after escalation to 180 mg QD), is required.

BRIGATINIB DOSE MODIFICATION RECOMMENDATIONS FOR TREATMENT-RELATED PNEUMONITIS OCCURRING PRIOR TO DOSE ESCALATION TO 180 MG QD (IE, FIRST 7 DAYS OF TREATMENT):

Toxicity Grade (CTCAE v4.03)	**Recommended Action**
Grade 1	Withhold the dose until pneumonitis returns to grade 0 (baseline), then resume at 90 mg and do not escalate. If pneumonitis recurs, permanently discontinue treatment.*
Grade 2	Withhold the dose until pneumonitis returns to Grade 0, then resume at 60 mg and do not escalate.* If pneumonitis recurs, permanently discontinue treatment.*
Grade 3	Permanently discontinue treatment.*
Grade 4	Permanently discontinue treatment.*

*Or in select cases per investigator discretion and discussion with Lead PI, consider continued use/shallower dose escalation as per Camidge et al, JTO 2019

BRIGATINIB DOSE MODIFICATION RECOMMENDATIONS FOR TREATMENT-RELATED PNEUMONITIS OCCURRING AFTER DOSE ESCALATION TO 180 MG QD:

Toxicity Grade (CTCAE v4.03)	**Recommended Action**
Grade 1	Withhold the dose until pneumonitis returns to grade 0 (baseline), then resume at the same dose. If pneumonitis recurs, permanently discontinue treatment.*
Grade 2	Withhold the dose until pneumonitis returns to Grade 0. Resume at 120 mg QD.* If pneumonitis recurs, permanently discontinue treatment.*
Grade 3	Permanently discontinue treatment.*
Grade 4	Permanently discontinue treatment.*

*Or in select cases per investigator discretion and discussion with Lead PI, consider continued use/shallower dose escalation as per Camidge et al, JTO 2019

6.1.2.3 DOSE MODIFICATION RECOMMENDATION TABLE FOR TREATMENT-RELATED ADVERSE EVENTS (EXCLUDING PNEUMONITIS)

Table 2: Brigatinib Dose Modification Recommendations for Treatment-Related Adverse Events (excluding pneumonitis)

Adverse Reaction	**Severity***	**Dose Modification**
Hypertension	Grade 3 hypertension (SBP greater than or equal to 160 mmHg or DBP greater than or equal to 100 mmHg, medical intervention indicated, more than one anti-hypertensive drug, or more intensive therapy than previously used indicated)	• Withhold brigatinib until hypertension has recovered to Grade 1 or less (SBP less than 140 mmHg and DBP less than 90 mmHg), then resume brigatinib at same dose. • Recurrence: withhold brigatinib until recovery to Grade 1 or less, and resume at next lower dose (Table 1) or permanently discontinue treatment.
	Grade 4 hypertension (life-threatening consequences, urgent intervention indicated)	• Withhold brigatinib until recovery to Grade 1 or less(SBP less than 140 mmHg and DBP less than 90 mmHg), and resume at next lower dose (Table 1) or permanently discontinue treatment. • Recurrence of Grade 4 hypertension: permanently discontinue brigatinib.
Bradycardia (HR less than 60 bpm)	Symptomatic bradycardia	• Withhold brigatinib until recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above. • If a concomitant medication known to cause bradycardia is identified and

Adverse Reaction	Severity*	Dose Modification
		discontinued or dose-adjusted, resume brigatinib at same dose upon recovery to asymptomatic bradycardia or to resting heart rate of 60 bpm or above. • If no concomitant medication known to cause bradycardia is identified, or if contributing concomitant medications are not discontinued or dose-adjusted, resume brigatinib at next lower dose (Table 1) upon recovery to asymptomatic bradycardia or to resting heart rate of 60 bpm or above.
	Bradycardia with life-threatening consequences, urgent intervention indicated	• Permanently discontinue brigatinib if no contributing concomitant medication is identified. • If contributing concomitant medication is identified and discontinued or dose-adjusted, resume brigatinib at next lower dose (Table 1) upon recovery to asymptomatic bradycardia or to a resting heart rate of 60 bpm or above, with frequent monitoring as clinically indicated. • Recurrence: permanently discontinue brigatinib.
Visual Disturbance	Grade 2 or 3 visual disturbance	Withhold brigatinib until recovery to Grade 1 or baseline, then resume at the next lower dose (Table 1)

Adverse Reaction	**Severity***	**Dose Modification**
	Grade 4 visual disturbance	Permanently discontinue brigatinib
Creatine Phosphokinase (CPK) Elevation	Grade 3 CPK elevation (greater than 5.0 × ULN)	• Withhold brigatinib until recovery to Grade 1 or less (less than or equal to 2.5 × ULN) or to baseline, then resume brigatinib at same dose. • If Grade 3 elevation of CPK recurs, brigatinib should be withheld until recovery to Grade 1 or less (less than or equal to 2.5 × ULN) or to baseline, then resume at the next lower dose level per Table 1.
	Grade 4 CPK elevation (greater than 10.0 × ULN)	• Withhold brigatinib until recovery to Grade 1 or less (less than or equal to 2.5 × ULN) or to baseline, then resume brigatinib at next lower dose (Table 1). • If Grade 4 elevation of CPK recurs, permanently discontinue brigatinib
Lipase/Amylase Elevation	Grade 3 lipase or amylase elevation (greater than 2.0 × ULN)	• Withhold brigatinib until recovery to Grade 1 or less (less than or equal to 1.5 × ULN) or to baseline, then resume brigatinib at same dose. • If Grade 3 elevation of lipase and amylase reoccurs, brigatinib should be withheld until recovery to Grade 1 or less (less than or equal to 1.5 × ULN) or to baseline, then resume at the next lower dose level per Table 1.

Adverse Reaction	**Severity***	**Dose Modification**
	Grade 4 lipase or amylase elevation (greater than 5.0 × ULN)	• Withhold brigatinib until recovery to Grade 1 or less (less than or equal to 1.5 × ULN) or to baseline, then resume brigatinib at next lower dose (Table 1). • If Grade 4 elevation of lipase/amylase recurs, permanently discontinue brigatinib
Hyperglycemia	Grade 3 (greater than 250 mg/mL or 13.9 mmol/L) or greater	If adequate hyperglycemic control cannot be achieved with optimal medical management, withhold brigatinib until adequate hyperglycemic control is achieved and consider reduction to the next lower dose (Table 1) or permanently discontinue brigatinib..
Other	Grade 3	• Withhold brigatinib until recovery to baseline, then resume at same dose. • Recurrence: withhold brigatinib until recovery to baseline, then resume at next lower dose or discontinue brigatinib (Table 1).
	Grade 4	• First occurrence: either withhold brigatinib until recovery to baseline and resume at next lower dose (Table 1) or permanently discontinue. • Permanently discontinue brigatinib for recurrence.
bpm = beats per minute; DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure; ULN = upper limit of normal		

Adverse Reaction	Severity*	Dose Modification
*Graded per National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI CTCAE v4). Asymptomatic lab abnormalities may be excluded pending discussion with the lead PI. Hypertension grading should be based on persistent blood pressure readings on optimal therapy, rather than specific drug use for the therapy		

6.1.2.4 MANAGEMENT OF ADDITIONAL SELECTED TREATMENT-RELATED ADVERSE EVENTS

HYPERTENSION

Blood pressure should be monitored and recorded at each visit. Hypertension detected by at least 2 blood pressure measurements should be graded according to NCI CTCAE, v4.03, which defines hypertension as a disorder characterized by a pathological increase in blood pressure: a repeated elevation in the blood pressure exceeding 140 mmHg for systolic and over 90 mmHg for diastolic. For patients who either develop hypertension or experience worsening hypertension during treatment with study drug, at the discretion of the investigator, antihypertensive medication should be initiated or optimized to achieve target blood pressure before interruption or dose reduction of the study drug. If hypertension is persistent despite adequate antihypertensive therapy—including titration of antihypertensive medication or introduction of additional antihypertensive medications—or if grade 4 hypertension develops, dose interruption and reduction is recommended according to the tables above.

BRADYCARDIA

Heart rate should be monitored and recorded at each visit. Brigatinib should be avoided in combination with other agents known to cause bradycardia (e.g., beta-blockers, nondihydropyridine calcium channel blockers, clonidine and digoxin) to the extent possible. For symptomatic bradycardia, dose interruption and reduction is recommended according to the tables above.

PHOTOSENSITIVITY

Photosensitivity to sunlight has occurred in patients treated with brigatinib. Patients should be advised to avoid prolonged sun exposure and tanning beds while taking brigatinib, and for at least 5 days after discontinuation of treatment. When outdoors, patients should be advised to

wear a hat and protective clothing, and to use a broad-spectrum UVA/UVB sunscreen and lip balm (SPF at least 30) to help protect against potential sunburn. For severe photosensitivity reactions (≥ Grade 3), brigatinib should be withheld until recovery to baseline. The dose should be modified accordingly.

NAUSEA AND EMESIS

Nausea should be treated with standard-of-care anti-emetics. Prophylactic anti-emetics may be used.

DIARRHEA

For grade 1 diarrhea, symptomatic care such as loperamide (Imodium®, McNEIL-PPC, Inc.) may be given, or no intervention may be undertaken, according to the investigator's clinical judgment. For grade 2 diarrhea, administer loperamide at 4 mg, then 2 mg every 2 to 4 hours until the patient is symptom-free for 12 hours. No dose modification is necessary unless the patient does not tolerate brigatinib or the symptom recurs. For grade ≥3 despite loperamide, treatment will be withheld until recovery to grade ≤1. Secondary prophylaxis in patients who have experienced diarrhea with brigatinib treatment is allowed. Other medications and supportive care may be added according to the institution's standard of care.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Brigatinib tablets will be provided by, Takeda Pharmaceuticals.

The appropriate study personnel will maintain records of study drug receipt and dispensing.

Patients are to be instructed on proper storage, accountability, and administration of brigatinib.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Brigatinib drug product is supplied as film-coated tablets containing 30 mg of brigatinib active pharmaceutical ingredient. Other ingredients are typical pharmaceutical excipients (lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, colloidal silica, and magnesium stearate). The tablet coating is composed of typical pharmaceutical grade coating components (talc, polyethylene glycol, polyvinyl alcohol, and titanium dioxide). The drug product is

manufactured under current Good Manufacturing Practice in accordance with approved procedures. Brigatinib will be supplied in white high-density polyethylene bottles with induction sealed caps or blister packs. Bottle or blister pack labels will bear the appropriate label text as required by governing regulatory agencies. At a minimum, such text will include product name, product strength, number of tablets, and lot number.

6.2.3 PRODUCT STORAGE AND STABILITY

Brigatinib tablets should be stored in accordance with the storage instructions on the label. The recommended storage condition for brigatinib is under 30°C. Do not refrigerate or freeze.

6.2.4 PREPARATION

The study pharmacist or designee at the site will be responsible for handling and dispensing brigatinib and completing associated documentary paperwork. Supplies are shipped to the investigative site at appropriate intervals, depending on patient accrual. The site must use an appropriate dispensing log/accountability form provided by the sponsor or an acceptable substitute used by the site. Each time study medication is dispensed for a patient, the following information must be recorded: the patient's initials, the patient's study number, drug product strength (e.g., 30 mg), quantity dispensed with the corresponding lot number, date of dispensation, and the initials of the person dispensing the drug. These logs are to be maintained by the study pharmacist in the pharmacy throughout the duration of the study and will be periodically verified by a representative of the sponsor.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This is a prospective, unblinded single arm phase 2 trial.

6.4 STUDY INTERVENTION COMPLIANCE

At clinic visits, patients will be asked by an investigator or coordinator about drug compliance and responses will be documented in the patient's chart. Unused study drug will be returned to the Investigational Pharmacy upon completion of each treatment cycle.

6.5 PROHIBITED THERAPY

At enrollment, additional systemic therapies for the treatment of lung cancer may not be taken concomitantly with brigatinib (eg, TKIs, immunotherapy, chemotherapy), but there will not be a

required washout period for prior systemic therapies, with the exception of systemic treatment with strong cytochrome p-450 (cyp)3a inhibitors, strong cyp3a inducers, or moderate cyp3a inducers, which are not permitted within 14 days of study enrollment (refer to current brigatinib IB version for comprehensive list).

Patients may be switched to regimens containing these therapies by the treating physician if brigatinib is discontinued due to progressive disease or brigatinib intolerance by the patient. Disease progression and the associated changes in therapy will be recorded, the patient will be removed from study treatment, and they will continue to be followed for survival (for up to 24 months from Day 1).

Use of alternative or herbal therapy while on study treatment is only allowed if no known interactions with the study medication exist and must be documented and approved by the sponsor.

6.6 CONCOMITANT THERAPY

Corticosteroids for the treatment of cancer-related symptoms from brain metastases or extracranial disease are allowed. Prophylactic corticosteroids in the absence of symptoms are discouraged. Corticosteroid agent, dose, frequency, and duration recommendations are at the discretion of the treating physician.

Medications taken and considered by the treating physician to be related to the patient's cancer will be recorded in the eCRF from first dose of study drug through 30 days after the last dose.

Brigatinib should be avoided in combination with other agents known to cause bradycardia (e.g., beta-blockers, nondihydropyridine calcium channel blockers, clonidine and digoxin) to the extent possible.

Potential drug interactions:
In vitro studies with human liver microsomes indicate that cytochrome P450 (CYP) 2C8 and CYP3A4 are involved in the human metabolism of brigatinib. Medications and dietary (grapefruit-containing products) or herbal products (St John's Wort) that are strong inhibitors or inducers of CYPs, in particular, CYP2C8 or CYP3A4, should be avoided. Brigatinib is not a reversible inhibitor of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5, with IC50 values of >70 μM. Brigatinib is also

not a metabolism-dependent or a time-dependent inhibitor of the CYPs tested. Hence, drug-drug interactions (DDIs) due to inhibition of CYPs by brigatinib are unlikely.

The list of drugs that interact with CYP450 enzymes (notably, CYP2C8 and CYP3A4, 5, and 7) can be found online at http://medicine.iupui.edu/clinpharm/ddis/table.aspx [Accessed: October 6, 2019]. Drugs listed should be avoided if possible. Note: The website should be used as a guideline and is not necessarily comprehensive. It is the investigator's responsibility to ensure that any drugs under consideration have not been newly identified as CYP inhibitors.

For reference, FDA label information for brigatinib may also be found at: *https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208772lbl.pdf*

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION (STOPPING RULES)

The Sponsor-Investigator has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM STUDY

Participants are free to withdraw from participation in the study at any time upon request. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the Sponsor-Investigator determines may jeopardize the patient's safety if he or she continues in the study.
- Sponsor-Investigator determines it is in the best interest of the patient.
- Patient non-compliance with study procedures as determined by investigator
- Lost to follow-up (see section 7.3).

Patients must discontinue study treatment if they experience any of the following:

- Intolerable toxicity as determined by the investigator.
- Progression of disease requiring an alternate therapy, in the opinion of investigator

- Pregnancy.
- Patient withdrawal of consent or decision to discontinue participation.

At the time of withdrawal, all study procedures outlined for the End of Treatment visit should be completed. Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study or study drug discontinuation should be documented on the appropriate eCRF.

7.3 LOST TO FOLLOW-UP

A subject will be considered lost to follow-up if he or she fails to return for ≥ 3 scheduled visits and is unable to be contacted by the study staff.

The following actions must be taken if a subject fails to return to clinic for a required study visit:

- Site will attempt to contact the subject and reschedule the missed visit and advise subject on importance of maintaining assigned visit schedule
- Before a subject is deemed lost to follow-up, study staff will make three documented attempts to contact the subject. Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

8.1.1 CNS SURVEILLANCE:

Patients will have surveillance brain MRIs at week 3 (± 4 days), 3 months (13 weeks ±7 days), then every 3 months (±14 days). CNS disease status will be graded (complete response, partial response, stable disease, progressive disease) per the modified RANO-BM criteria (Lin, et al *The lancet oncology* 16.6 (2015): e270-e278). Per modified RANO-BM, brain lesions with a unidimensional diameter of ≥5mm are evaluable as measurable lesions.

	Complete Response	**Partial Response**	**Stable Disease**	**Progressive Disease**
Target lesion	None	≥30% decrease in sum longest distance relative to baseline	<30% decrease relative to baseline but <20% increase in sum longest	≥20% increase in sum longest distance relative to nadir*

	Complete Response	Partial Response	Stable Disease	Progressive Disease
			distance relative to nadir	
Non-target lesions	None	Stable or improved	Stable or improved	Unequivocal progressive disease*
New lesion (s)†	None	None	None	Present*
Corticosteroids	None	Stable or decreased	Stable or decreased	Not applicable‡
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse*
Requirements for response	All	All	All	Any

* Progression occurs when this criterion is met.
† A new lesion is one that was not present on prior scans and is visible in minimum two projections. If a new lesion is equivocal, for example because of its small size, continued therapy can be considered, and follow-up assessment will clarify if the new lesion is new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan showing the new lesion. For immunotherapy-based approaches, new lesions alone to do not define progression.
‡ Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

TARGET LESIONS

COMPLETE RESPONSE:

Disappearance of all CNS target lesions sustained for at least 4 weeks; with no new lesions, no use of corticosteroids, and patient is stable or improved clinically.

PARTIAL RESPONSE:

At least a 30% decrease in the sum longest diameter of CNS target lesions, taking as reference the baseline sum longest diameter sustained for at least 4 weeks; no new lesions; stable to decreased corticosteroid dose; stable or improved clinically.

PROGRESSIVE DISEASE:

At least a 20% increase in the sum longest diameter of CNS target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, at least one lesion must increase by an absolute value of 5 mm or more to be considered progression.

STABLE DISEASE:

Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter while on study.

NON-TARGET LESIONS

Non-target lesions should be assessed qualitatively at each of the imaging time points specified in the protocol.

COMPLETE RESPONSE:
Requires all of the following: disappearance of all enhancing CNS non-target lesions, no new CNS lesions.

NON-COMPLETE RESPONSE OR NON-PROGRESSIVE DISEASE:
Persistence of one or more non-target CNS lesion or lesions.

PROGRESSIVE DISEASE:
Any of the following: unequivocal progression of existing enhancing non-target CNS lesions, new lesion(s) (except while on immunotherapy-based treatment), or unequivocal progression of existing tumor-related non-enhancing (T2/FLAIR) CNS lesions.

8.1.2 EXTRACRANIAL SURVEILLANCE

Patients will have surveillance imaging of the body at 3 months (13 weeks ± 7 days) and then every 3 months (± 14 days) for 2 years or as required for standard of care by the investigator. At the discretion of the investigator, the patient may have a computed tomography (CT) scan of the chest/abdomen, with or without the pelvis OR a positron emission tomography–computed tomography (PET/CT) scan. Extracranial disease status will be graded per standard RECIST 1.1 criteria (Eisenhauer et al. "New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)." *European journal of cancer* 45.2 (2009): 228-247.)

8.1.3 QUALITY OF LIFE (QOL) ASSESSMENTS.

QOL will be assessed using the EORTC QLQ-C30 and BN20 brain-specific questionnaire. The EORTC QLQ-C30 is one of the most frequently used questionnaires in cancer patients, and the BN20 is a supplemental questionnaire specifically developed for use with the QLQ-C30 in patients with brain cancer. Both tools have robust psychometric properties resulting from rigorous testing, development, and external validity, and have been used in numerous of oncology trials (Efficace 2002). Specific to PCI, the QLQ-C30 and BN20 have been used in the RTOG PCI trials (RTOG 0212 and 0214) (Gondi 2013), the EORTC 08993-22993 PCI trial (Slotman 2007), and the Intergroup PCI trial (Le Pechoux 2011). The questionnaires are translated and validated in over 80 languages. Use of the questionnaires requires no monetary charge in the non-commercial setting. Together, the questionnaires typically take under 5 minutes to complete, and collection is planned at baseline and with each planned clinical surveillance visit (with the exception of Day 8).

8.2 SAFETY AND OTHER ASSESSMENTS

Adverse events will be assessed at scheduled clinical follow up visits or any intervening time when new adverse events are reported by enrolled patients.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means untoward or unfavorable medical occurrence considered to be related to a study intervention or treatment in humans.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Serious adverse event or **serious suspected adverse reaction**. An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

The adverse event severity grading scale for the NCI CTCAE (v4.03) will be used for assessing adverse event severity. The following table will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE (v4.03).

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated

Grade	Severity
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated
5	Death related to adverse event

NCI CTCAE National Cancer Institute Common Terminology Criteria for Adverse Events. Note: Based on the most recent version of NCI CTCAE (v4.03), which can be found at: *http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm*

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

Only adverse events directly related to study treatment or procedures will be recorded. All serious adverse events, both related and not related, will be reported per section 8.3.6. If there is any doubt as to whether a clinical observation is related or not related to the study treatment or procedures, the event should be reported as related.

To help assess, the following guidelines will be used.

- **Related** – The AE is known to occur with the study procedures, there is a reasonable possibility that a study procedure caused the AE, or there is a temporal relationship between the study procedure and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study procedures and the AE.
- **Not Related** – There is not a reasonable possibility that the study procedure caused the event, there is no temporal relationship between the study procedure and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

Expectedness will only be documented for SAEs. An SAE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All study intervention-related AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, date of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and date of resolution/stabilization of the event. All study drug or intervention-related AEs and SAEs, as well as unrelated SAEs occurring while on study must be documented appropriately. All study intervention-related AEs and SAEs, as well as unrelated SAEs will be followed to adequate resolution per investigator (e.g., to grade 1 or baseline) during the study treatment period for up to 2 years from Day 1. After the study treatment period of 2 years from Day 1, AEs will be managed by the treating physicians per standard of care.

Any medical condition that is present at the time the participant is screened up through the patient's first dose of study treatment will be considered as baseline medical history and will not be reported as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Investigators will record all reportable events with start dates occurring any time after the first dose of study medication until 30 days after the last day of study treatment. SAEs will be followed until resolution or stabilization. At each study visit, the investigator will inquire about the occurrence of AE/ SAEs since the last visit.

8.3.5 ADVERSE EVENT REPORTING

The investigator must record related non-serious adverse events and report to DSMC and IRB according to timetable for reporting specified in section 10.1.6.

Adverse Events may be spontaneously identified by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding attributed as related to the study treatment or intervention is considered to be an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

All Adverse Events which are serious must be reported per section 8.3.6 to Takeda Pharmacovigilance (or designee), sponsor-investigator, and the University of Colorado DSMC from the first dose of brigatinib up to and including 30 days after administration of the last dose of brigatinib. In addition, new primary malignancies that occur during the follow-up periods must be reported, regardless of causality to study regimen, for a minimum of three years after the last dose of the investigational product, starting from the first dose of study drug. All new cases of primary malignancy must be reported to Takeda Pharmacovigilance (or designee).

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial and the attribution is determined to be related to the study intervention (e.g., surgery was performed earlier or later than planned). All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness (es).

Since this is an investigator-initiated study, the principal investigator Chad Rusthoven, MD, also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the sponsor- investigator's EC or IRB.

Regardless of expectedness or causality, all events meeting SAE criteria must be reported in English to Takeda Pharmacovigilance or designee, to the sponsor-investigator, and to the University of Colorado DSMC (see additional SAE reporting instructions in section 8.3.6):

Fatal and Life-Threatening SAEs within 24 hours of the sponsor-investigator's observation or awareness of the event

All other serious (non-fatal/non life threatening) events within 24 hours of the sponsor-investigator's observation or awareness of the event

US and Canada

Toll-Free Fax #: 1-800-963-6290

E-mail: *takedaoncocases@cognizant.com*

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The investigator must record all serious adverse events and report to DSMC and IRB according to timetable for reporting specified in section 10.1.4.

All SAEs will be reported using the FDA 3500A Mandatory MedWatch report form. SAE form can be found at:
http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

To submit an SAE, email as follows within **24 hours of becoming aware of the event:**

To:	Chad.Rusthoven@cuanschutz.edu
	cpdm.iit@cuanschutz.edu
	DSMC@cuanschutz.edu
	takedaoncocases@cognizant.com
Subject:	19-2862 SAE Report Form
Attach:	SAE form completed and signed by the Investigator

Follow-up of unresolved serious adverse events

Any SAEs that are unresolved at the time of the initial report submission should be followed up by the investigator for as long as medically indicated, and an updated SAE report submitted at the time new information regarding the event becomes available.

8.3.7 PRODUCT COMPLAINTS OR MEDICATION ERRORS (INCLUDING OVERDOSE)

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact Takeda

Pharmacovigilance or designee (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Takeda Quality representative.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. While overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Investigators must record all medication errors (including overdose) on the appropriate CRF form. Individuals who identify a potential medication error situation should immediately contact Takeda (see below) and report the event.

For Product Complaints or Medication Errors (Including Overdose), contact Takeda Pharmacovigilance

Phone: 1-844-ONC-TKDA (1-844-662-8532)

Email: *MedInfoUS@takeda.com.*

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Takeda Pharmacovigilance

8.3.8 REPORTING OF PREGNANCY

While a pregnancy test will be performed on female participants of childbearing potential as part of the screening process to ensure no pregnant patients are enrolled, all participants of childbearing potential will be counseled to utilize appropriate contraception. If a pregnancy does occur in a female patient on trial, the pregnancy will be reported as an SAE. The outcome of all pregnancies of female study subjects (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the participant was discontinued from the study treatment. Should pregnancy occur during a participant's trial participation, the participant will be immediately discontinued from the study treatment and followed-up per trial protocol.

If a pregnancy occurs, the following must be documented in the SAE report:

- Relevant family history
- Previous pregnancies (overall number, deliveries, spontaneous miscarriages, etc.)

- Current pregnancy (last menstrual period, expected delivery date, any amniocentesis, chorionic villus sampling, in-vitro fertilization)
- Outcome of pregnancy (i.e. full term, premature birth, spontaneous miscarriage, elective termination. If premature birth, specify gestational age in weeks. If elective abortion, specify any medical reason)
- Details of birth (i.e. DOB, weight, sex, healthy baby, sick baby, congenital anomaly/birth defect, still birth, multiple births, sickness manifestations, etc.)
- Any complications, infections, illness during pregnancy

8.3.8.1 PROCEDURES FOR REPORTING DRUG EXPOSURE DURING PREGNANCY AND BIRTH EVENTS

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must fax a completed MedWatch Form to the Takeda Pharmacovigilance or designee immediately (see Section 8.3). The pregnancy must be followed for the final pregnancy outcome (i.e., delivery, still birth, miscarriage) and Takeda Pharmacovigilance or designee will request this information from the sponsor-investigator.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor-investigator must also immediately fax a completed Pregnancy Form to the Takeda Pharmacovigilance or designee. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Pregnancy Reporting Form:

US FDA MedWatch 3500A:
http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UAP)

The Office of Human Research Protection (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

This study will use the OHRP definition of UAP.

8.4.2 REPORTING OF UNANTICIPATED PROBLEMS

Incidents or events that meet the OHRP criteria for UAPs require the creation and completion of a UAP report. It is the Site PI's responsibility to report UAPs to their IRB. The Lead PI is responsible for reporting the UAP to the IRB and the UCCC DSMC. The UAP report will include the following information:

- Protocol-identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents a UAP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UAP.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):
  Disease Control Rate (DCR) of brain metastases at 3 months (13-week MRI), where DCR is defined as complete response (CR), partial response (PR), or stable disease (SD) as defined by the RANO-BM criteria. The primary analysis will test the following hypotheses:

  H_0: $p \leq 0.60$

  H_1: $p \geq 0.90$

where *p* represents the proportion of patients who meet the DCR criteria.

- Secondary Efficacy Endpoint(s):
  1a. Time until any CNS progressive disease (PD) by RANO-BM criteria
  1b. Time until any local PD (ie, in brain lesions identified at the time of enrollment) by RANO-BM criteria
  1c. Time until any distant brain PD (ie, new brain lesions that were not present at the time of enrollment) by RANO-BM criteria
  1d. Time until progression at any site using RANO-BM for intracranial disease and RECIST for extracranial disease
  2a. Time until death from any cause
  2b. Time until brain metastases-specific mortality, defined as intracranial progression as a component of cause of death
  3. Cumulative rate of best responses for complete response (CR), partial response (PR), stable disease (SD), by RANO-BM criteria
  4. Time until the administration of whole brain-radiotherapy (WBRT)
  5. Quality of life will be assessed using standardized QOL metrics (EORTC QLQ C30/BN 20)

- Exploratory Endpoint(s):

1. Quantification of corticosteroid agent and dose at screening and at each clinical assessment

9.2 SAMPLE SIZE DETERMINATION

The goal of this single arm phase 2 trial is to demonstrate specifically the short-term safety and efficacy of a strategy of brigatinib alone for patients with asymptomatic or mildly symptomatic brain metastases. Using contemporary prospective data on brigatinib (Camidge, et al. "Exploratory Analysis of Brigatinib Activity in Patients with Anaplastic Lymphoma Kinase-Positive Non–Small-Cell Lung Cancer and Brain Metastases in Two Clinical Trials" Journal of Clinical Oncology (2018): JCO-2017), our alternate hypothesis (H_1) is that brigatinib alone will result in a CNS disease control rate (DCR) of 90% at 3 months in this population. An upper 1-sided 1-sample exact binomial test with 19 analyzable patients will have 88.5% power to detect a difference between the null hypothesis (H_0) of 60% or less DCR and H_1, assuming a type-1 error rate of 0.025. Assuming a 20% dropout rate, it is expected that 23 patients would need to be enrolled to yield 19 evaluable patients (i.e. completers).

9.3 POPULATION FOR ANALYSES

This is a modified intent-to-treat analysis. Patients who enroll and initiate brigatinib and undergo the 3-month (13-week) brain MRI assessment will be analyzed for the study primary endpoint. Secondary endpoints related to safety, tolerability or duration of therapy/progression will be conducted on all who start brigatinib.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Standard statistical conventions will be used, such as statistical hypotheses will be tested controlling the type 1 error rate at 0.05 for 2-sided tests and at 0.025 for 1-sided tests, and p-values less than 0.05 will be considered significant. When confidence intervals are reported 95% confidence intervals will be used. In addition to the formal statistical tests of the primary and secondary endpoints, descriptive summary statistics will be produced. All analyses will be performed by a biostatistician in the University of Colorado Cancer Center Biostatistics Core. The full analysis data set includes all patients who are enrolled onto the trial. The safety data set includes all patients who receive at least one treatment of brigatinib. SAS® software 9.4 M5 (SAS Institute Inc., Cary, NC, USA) or later will be used for the statistical analyses of the study.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary efficacy endpoint is 3-month Disease Control Rate (DCR) of brain metastases (based on the 13-week MRI), where DCR is defined as complete response (CR), partial response (PR), or stable disease (SD) as defined by the RECIST 1.1 criteria and brain metastases are defined per RANO-BM criteria. A 1-sided 1-sample exact binomial test will be performed to test the null hypothesis (H0) that $p \leq 0.60$, where p represents the proportion of patients who meet the DCR criteria. With 19 evaluable patients, the test will have 88.5% power to detect an alternative hypothesis value of $p \geq 0.90$ when the type 1 error rate is controlled at 0.025. In addition to the hypothesis test, the proportion of patients meeting the 3-month DCR definition will be summarized using the sample proportion and a 95% exact confidence interval.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary endpoints include several time-to-event endpoints: 4 measuring time-to-progression (time-to-CNS PD, time-to-local PD, time-to-distant brain PD, and time until PD at any site), 2 measuring time-to-death (overall and metastases-specific mortality), as well as time-to-administration of WBRT. All time-to-event endpoints will be analyzed using Kaplan-Meier product-limit methods and summarized graphically using Kaplan-Meier survival plots. In

addition, secondary endpoints will be summarized descriptively, including the rates of events, progressive disease, and survival at the follow up intervals (up to24 months from Day 1). Cumulative rates of best CNS objective response with be described. For QOL, scores from the QLQ-C30 and BN20 will be normalized to 0-100 scales, changes from baseline of $\geqslant$10 points will be considered clinically meaningful, and cumulative changes at each assessment with be described and time-to-event outcomes for declines in QOL will be summarized graphically using Kaplan-Meier and cumulative incidence plots.

9.4.4 SAFETY ANALYSES

Safety will be measured via the CTCAE Version 4.03 criteria and the rate and type of adverse event (AE) will be compared to historical controls and assessed for any increased risk. Listings will be produced of all study-related AEs, which will be reviewed by the study PI. Additionally, any serious adverse event (SAE) will be reported within 24 hours to the study PI who will investigate the attribution of the SAE to the experimental treatment and only continue the study if the experimental treatment is considered safe.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Subject baseline characteristics will be summarized using descriptive statistics. Quantitative variables will be summarized using both measures of the center and spread as well as quantiles of each variable's distribution (e.g. Mean, SD, Minimum, Q_1, Median, Q_3, and Maximum). Qualitative variables will be summarized using counts and percentages.

9.4.6 PLANNED INTERIM ANALYSES

This study is designed to enroll approximately 23 patients in order to yield 19 evaluable patients. Given this relatively small sample size, there are no planned interim analyses for efficacy or futility. After 19 evaluable patients have completed a 3-month brain MRI (allowing for analysis of the primary endpoint of DCR of brain metastases at 3 months), an initial analysis of the primary endpoint and short-term data on secondary endpoints may be performed.

9.4.6.1 SUB-GROUP ANALYSES

Subgroup analyses will be conducted as necessary in order to inform the sensible design of follow-up studies to this trial. The purpose of such subgroup analyses will be to investigate

which subgroups demonstrated favorable response rates to the experimental treatment of brigatinib.

9.4.7 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Listings will be created from all study data, grouped by domain (e.g. demographics, adverse events, lab values, outcome data, etc.).

9.4.8 EXPLORATORY ANALYSES

Blood will be collected at baseline and at progression. For exploratory analyses, circulating free (cf) DNA levels and/or other blood-based markers will be correlated with measured study endpoints including overall survival, disease progression, and quality of life.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent process will be initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families.

Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their

comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study.

The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 CONFIDENTIALITY AND PRIVACY

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor-investigator(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor-investigator, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Colorado Cancer. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the University of Colorado Cancer Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the University of Colorado Cancer Center.

10.1.3 FUTURE USE OF STORED SPECIMENS OR DATA

- **Intended Use:** Samples and data collected under this protocol may be used to study blood-based markers associated with clinical outcomes on brigatinib therapy. No germline genetic testing will be performed.
- **Storage:** Access to stored samples will be limited using freezers stored in badge-protected research areas. The freezer also has a lock to prevent tampering. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.
- **Tracking:** Data will be tracked using REDCap and OnCore.
- **Disposition at completion of the study**: All stored samples will be sent to the Pathology Shared Resources. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

Data collected for this study will be analyzed and stored at the University of Colorado Cancer Center. After the study is completed, the de-identified, archived data will be transmitted to and stored at the Pathology Shared Resource for use by other researchers including those outside of the study. Permission to transmit data to the Pathology Shared Resource will be included in the informed consent.

With the participant's approval and as approved by local IRBs, de-identified biological samples will be stored at the Pathology Shared Resource with the same goal as the sharing of data with the Pathology Shared Resource. These samples could be used for research into the causes of NSCLC, its complications and other conditions for which individuals with NSCLC are at increased risk, and to improve treatment. The Pathology Shared Resource will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the masking of the identity of the participant.

During the conduct of the study, and individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage will not be possible after the study is completed.

When the study is completed, access to study data and/ or samples will be provided through the Pathology Shared Resource.

10.1.4 SAFETY OVERSIGHT

The sponsor investigator will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial including any specimens collected, executing the data and safety monitoring (DSM) plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and study participant safety for all clinical studies at the CU Cancer Center, which is the coordinating institution of this trial. A summary of the DSMC's activities is as follows:

- Conduct of internal audits
- Ongoing review of all serious adverse events (SAEs) and unanticipated problems (UAPs)
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs and UAPs are reported to the DSMC, IRB and the sponsor investigator per protocol. All SAEs and UAPs are to be reported to the DSMC within 7 (for fatal or life-threatening events) or 15 (non-life-threatening events) calendar days of the sponsor investigator receiving notification of the occurrence.

Each subject's treatment outcomes will be discussed by the site PI and appropriate staff at regularly scheduled meetings. Data regarding number of subjects, significant toxicities, dose modifications, and treatment responses will be discussed and documented in the meeting's minutes.

The sponsor investigator is responsible for organizing and conducting regularly scheduled teleconferences with all participating sites. The sponsor investigator will also be responsible for including data from all the participating sites to include the minutes from these regularly scheduled teleconferences between the sponsor investigator and the sites within the overall trial's DSM progress report.
The sponsor investigator will provide a DSM progress report to the CU Cancer Center DSMC on a recurring basis (either every six or twelve months based on DSMC vote). The DSM report will include a protocol summary, current enrollment numbers, summary of toxicity data to include

specific SAEs, UAPs and AEs, any dose modifications, all protocol deviations, and protocol amendments. The DSM report submitted to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted. Results and recommendations from the review of this progress report by the DSMC will then be provided to the sponsor investigator in a DSMC review letter. The sponsor investigator is then responsible for ensuring this letter is submitted to the site's IRB of record at the time of IRB continuing

http://www.ucdenver.edu/academics/colleges/medicalschool/centers/cancercenter/clinicaltrials/DSMC/Pages/DSMC.aspx

10.1.5 CLINICAL MONITORING

Clinical site monitoring will be conducted to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/ amendment(s), with GCP, and with applicable regulatory requirement(s).

Monitoring for this study will be performed by a CU Cancer Center Clinical Monitor in accordance with the clinical monitoring plan (CMP), incorporated herein by reference. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of the monitoring reports.

10.1.6 QUALITY ASSURANCE AND QUALITY CONTROL

Quality Control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/ resolution.

Following written SOPs, the study monitor will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial-related sites, source data/ documents, and reports for the purpose of monitoring and auditing by the DSMC audit team, and inspection by local and regulatory authorities.

10.1.7 DATA HANDLING AND RECORD KEEPING

10.1.7.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.7.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of an investigational marketing application and until there are no pending or contemplated marketing applications or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations or institutional policies. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the PI when these documents no longer need to be retained.

10.1.8 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or SOP requirements. The noncompliance may be either on the part of the participant, the

investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. These practices are consistent with ICH E6, sections:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3.
- 5.1 Quality Assurance and Quality Control, section 5.1.1.
- 5.20 Noncompliance, sections 5.20.1 and 5.20.2.

It is the responsibility of the study team to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents, and reported to DSMC and COMIRB. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/ study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the -SOP and/or study procedures manual.

10.1.9 PUBLICATION AND DATA SHARING POLICY

This study will ensure that the public has access to the published results of this research.

As required, either for publication (the ICMJE or other publication policy), or according to U.S. regulations (Section 801 of the Food and Drug Administration Amendments Act of 2007) this clinical trial will be registered in a public trials registry including ClinicalTrials.gov, which is sponsored by the National Library of Medicine, and the NCI CTRP Registry for cancer clinical trials.

10.1.10 CONFLICT OF INTEREST POLICY

Independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed.by the University of Colorado Denver's (UCD) Office of Regulatory Compliance Conflict of Interest and Commitment Management (COIC) program. Persons with a perceived conflict of interest will have such conflicts managed in a way that is appropriate to their participation in the trial. Conflict of Interest management plans are project-specific and are reviewed at least annually. UCD has integrated the institutional conflict of interest management program with its existing program.

11 REFERENCES

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