Protocol #: LCI-GU-URO-CRI-001

TITLE: A PHASE II STUDY OF CRIZOTINIB IN PATIENTS WITH c-MET OR RON-POSITIVE METASTATIC UROTHELIAL CANCER

LAY TITLE: CRIZOTINIB FOR PATIENTS WITH METASTATIC UROTHELIAL CANCER.

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Investigational drug:
Xalkori (crizotinib)

The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Confidential

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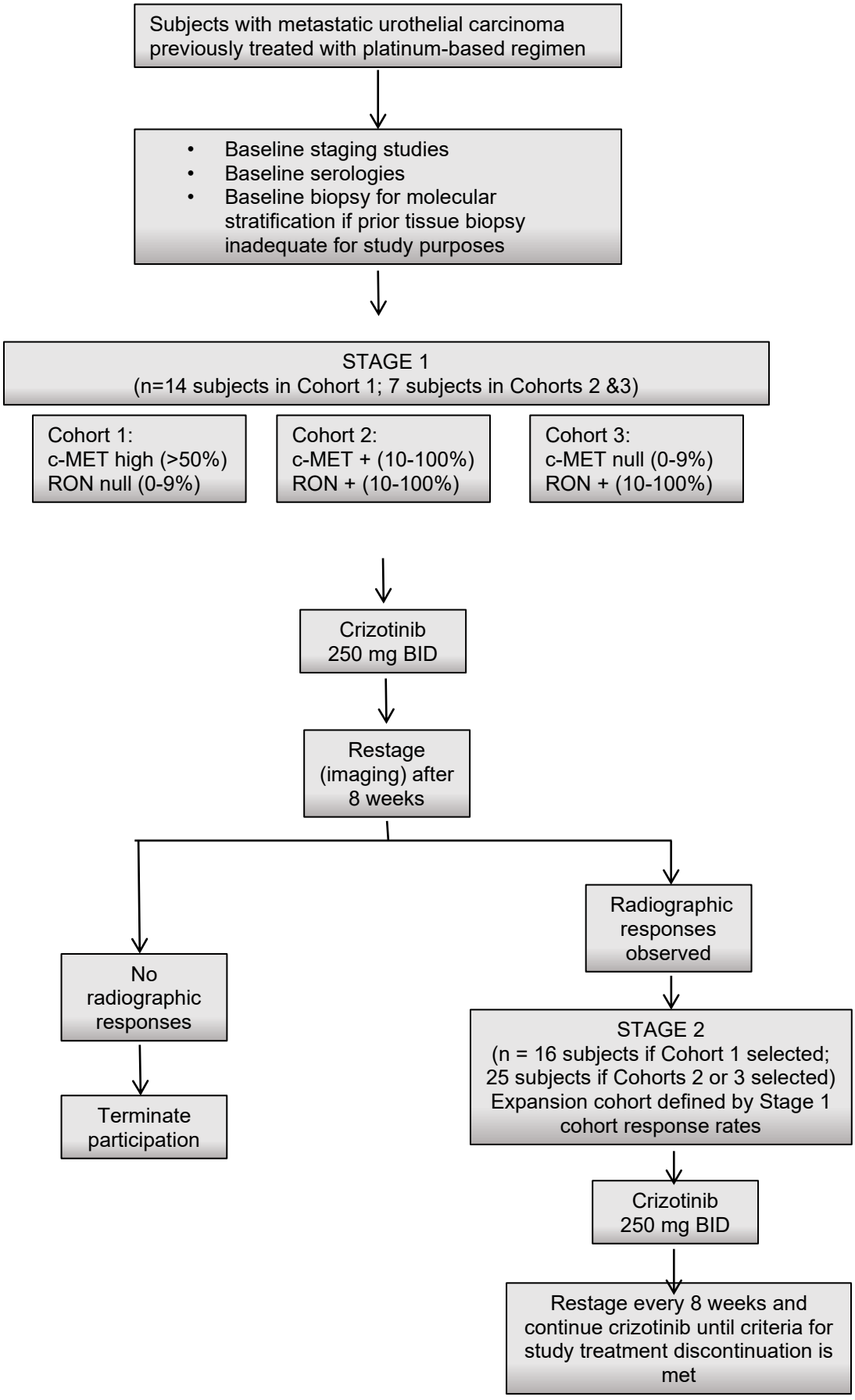
Phase 2 / Version 3 / April 21, 2018 **PROTOCOL SUMMARY**	
A. Study Title	A Phase II Study of Crizotinib in Patients with c-MET or RON-Positive Metastatic Urothelial Cancer
B. Indication	Metastatic urothelial carcinoma after failure of platinum-based chemotherapy
C. Clinical Phase	II
D. Summary of Rationale	Patients with refractory metastatic urothelial carcinoma have a dismal prognosis, and great medical need exists to identify effective therapeutic strategies for this population. After failure of first line platinum-based chemotherapy, limited therapeutic options currently exist, and cytotoxic monotherapies demonstrate an overall response rate of 10-20% with a time to progression of only 3 months. No molecularly targeted therapy has demonstrated meaningful activity in this setting. c-MET is a receptor tyrosine kinase implicated in tumorigenesis and metastasis that is expressed in almost 50% of patients with locally advanced urothelial cancer. Additionally, RON, a related receptor tyrosine kinase, is expressed in approximately 30% of bladder cancers. Crizotinib, a small molecule tyrosine kinase inhibitor, is currently FDA approved for patients with ALK-positive lung cancer, but is also capable of inhibiting c-MET and RON, suggesting that crizotinib may have anti-tumoral activity in patients with c-MET or RON-positive urothelial carcinoma.
E. Study Objectives	This study seeks to evaluate the potential efficacy of crizotinib in subjects with refractory, advanced c-MET or RON-positive urothelial carcinoma. The primary objective is to assess the objective response rate. Secondary objectives include assessment of progression free survival, overall survival and toxicity.
F. Sample	28 subjects will be enrolled in Stage 1 into three separate molecularly defined cohorts (14 in Cohort 1, 7 in each of Cohorts 2 and 3). If a cohort is selected for expansion, then additional subjects will be enrolled in Stage 2 in that cohort (16 in Cohort 1 or 25 in Cohorts 2 or 3).

G. Inclusion/ Exclusion	Inclusion: • Histologically confirmed metastatic urothelial carcinoma of the bladder or upper urinary tract • Prior treatment with a cisplatin or carboplatin based regimen • ECOG Performance Status 0-2 Exclusion: • Uncontrolled and/or current illness including active infection, congestive heart failure, etc. • Currently receiving any medications or substances which are strong inhibitors or inducers of CYP3A • Pregnant or breast feeding
H. Dosage/ Dosage Form, Route, And Dose Regimen	Subjects will take one 250 mg crizotinib capsules by mouth twice daily with or without food continuously until criteria for treatment discontinuation has been met.
I. Statistical Analysis	The overall response rate will be measured in subjects enrolled into three molecularly defined cohorts. If clinical activity is observed in at least one cohort, an expansion cohort may be enrolled to test the null hypothesis that the objective response rate is less than or equal to 5%. Based on an alpha = 0.05 significance level, this sample size will provide at least 90% power to reject the null hypothesis, assuming the overall response rate is 30%.

SCHEMA


Subjects with metastatic urothelial carcinoma previously treated with platinum-based regimen
• Baseline staging studies
• Baseline serologies
• Baseline biopsy for molecular stratification if prior tissue biopsy inadequate for study purposes
STAGE 1
(n=14 subjects in Cohort 1; 7 subjects in Cohorts 2 &3)
Cohort 1:
c-MET high (>50%)
RON null (0-9%)
Cohort 2:
c-MET + (10-100%)
RON + (10-100%)
Cohort 3:
c-MET null (0-9%)
RON + (10-100%)
Crizotinib
250 mg BID
Restage
(imaging) after
8 weeks
No
radiographic
responses
Terminate
participation
Radiographic
responses
observed
STAGE 2
(n = 16 subjects if Cohort 1 selected;
25 subjects if Cohorts 2 or 3 selected)
Expansion cohort defined by Stage 1
cohort response rates
Crizotinib
250 mg BID
Restage every 8 weeks and
continue crizotinib until criteria for
study treatment discontinuation is
met

LIST OF ABBREVIATIONS

AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BID	Twice a day
BPM	Beats per minute
BRR	Best response rate
BSA	Body surface area
BUN	Blood urea nitrogen
CI	Confidence interval
CPT	Cell preparation tube
CR	Complete response
cCR	Clinical complete response
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case report form
EML4	Echinoderm microtubule associated protein like 4
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
IDS	Investigational Drug Services
IHC	Immunohistochemistry
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
LCI	Levine Cancer Institute
LDH	Lactate dehydrogenase
MET	Mesenchymal epithelial transition factor
MSEC	Milliseconds
MTD	Maximum tolerated dose
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PET	Positron emission tomography
PR	Partial response
PI	Principal Investigator
PFS	Progression-free survival
RECIST	Response Evaluation Criteria in Solid Tumors
RON	Recepteur d'Origine Nantais
SAE	Serious adverse event
SAR	Suspected adverse reaction
SD	Stable disease
SI	Sponsor-investigator

SOP	Standard operating procedure
TTP	Time-to-progression
UAP	Unanticipated adverse problem

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1. OBJECTIVES

1.1. Primary Objective

To assess the objective response rate (ORR) of crizotinib in subjects with c-MET or RON-positive advanced urothelial carcinoma previously treated with a platinum-based regimen.

1.2. Secondary Objectives

To assess overall survival (OS), progression-free survival (PFS), and the safety and toxicity profile with this regimen.

1.3. Safety Objectives

The safety objectives are to evaluate treatment administration, adverse events assessed by NCI Common Terminology Criteria for Adverse Events version 4.0, and serious adverse events including deaths on study.

2. BACKGROUND AND RATIONALE

2.1. Bladder Cancer

Bladder cancer is the fourth most common malignancy in men.[1] In 2014, over seventy thousand new cases and over fifteen thousand deaths were anticipated in the United States in males and females.[1] Although patients derived modest benefit following the introduction of cisplatin-based chemotherapy in prior decades, no significant clinical advances have occurred in recent years.

Patients with advanced refractory urothelial cancer have a poor prognosis with a median survival of 14-15 months.[2] In patients who progress after first line platinum-based regimens, limited effective therapeutic options exist. Commonly used cytotoxic monotherapies demonstrate an overall response rate of 10-20% with a time to progression of 3 months in the second-line setting. No molecularly targeted agent has yet to demonstrate clinically meaningful activity, which highlights a large unmet medical need for this patient population.[3]

2.2. c-MET/RON

c-MET is a receptor tyrosine kinase for hepatocyte growth factor that can regulate epithelial cell proliferation and motility[4] and is implicated in tumorigenesis and metastasis.[5] Dysregulation of the c-MET pathway is commonly observed in many human tumors.[6] Recepteur d'Origine Nantais (RON) is a related receptor tyrosine kinase that can heterodimerize with and transactivate c-MET,[7] which may be necessary for c-MET driven oncogene addiction in malignancy.[8]

Preclinical evidence suggests that activation of the c-MET pathway can enhance bladder tumor cell invasion.[9] Expression of c-MET is common in urothelial carcinoma of the bladder and correlates with adverse clinicopathologic features and poor outcome.[10-12] In one series of 142 patients with non-metastatic bladder cancer, expression of c-MET was observed in 21% of patients with non-invasive disease, expression positively associated with stage, and was observed in 45% of patients with more advanced muscle-invasive disease.[11] Multivariate analysis revealed that high c-MET expression (more than 50% of tumor cells) predicted for increased likelihood of disease progression and death.

In an expanded cohort of 183 patients with bladder cancer from Cheng and colleagues, overall and high c-MET expression was observed in 45% and 33% of patients, respectively.[10] In this cohort, the investigators also measured expression of RON and observed overall and high RON expression in 33% and 23% of patients, respectively. Co-expression of RON and c-MET occurred in 19% of patients. In this series, multivariate analysis showed that overexpression of RON and coexpression of both receptors correlated with inferior survival.

2.3. Crizotinib

Preclinical evidence suggests that therapeutic targeting of the c-MET pathway may be efficacious in patients with urothelial cancers dependent on c-Met activation.[13] Crizotinib is a specific inhibitor of the c-MET, RON and ALK receptor tyrosine kinases that is currently approved for use in patients with ALK-positive non-small cell lung cancer.[14,15] Pharmacodynamic modeling suggests that the currently recommended dose (250 mg twice daily) can achieve clinically significant c-MET inhibition in human tumors.[16] The potential efficacy of crizotinib for targeting c-MET driven tumors is illustrated by the antitumoral activity in human cancer xenografts possessing c-MET activation.[15,17] Furthermore, in a small case series of patients with esophagogastric adenocarcinoma harboring c-MET amplification, two of four patients treated with crizotinib demonstrated tumor shrinkage, providing support to the rationale behind this therapeutic strategy.[18]

2.4. Rationale

Patients with metastatic urothelial carcinoma who have failed prior platinum-based therapy have a poor prognosis with limited therapeutic options. Overexpression of c-MET and RON has been observed in patients with non-metastatic urothelial carcinoma of the bladder and connotes a poor prognosis, though the therapeutic efficacy of targeting the c-MET pathway in patients with urothelial carcinoma remains unknown. Crizotinib, an inhibitor of c-MET and RON, is well tolerated in patients with advanced lung cancer harboring EML4-ALK fusions and may also be an effective therapeutic strategy for targeting c-MET dependent tumors. This study seeks to determine whether crizotinib has anti-tumoral activity in patients with c-MET or RON-positive urothelial carcinoma, as well as to determine whether c-MET or RON tumor expression and tumor derived mutational profiling can predict therapeutic response.

3. SUBJECT SELECTION

3.1. Accrual

Following informed consent and registration, subjects will undergo tissue pre-screen eligibility screening. Tumor specimens from potential subjects will then undergo c-MET and RON expression characterization as described in section 12.1. Prior to presenting treatment consent, the c-Met/RON expression results must be evaluated to confirm that the subject meets the criteria for one of the open cohorts. Eligible subjects will then be enrolled into available open molecularly defined cohorts as described in section 4.2.

If the Stage 1 response criteria are met within a cohort (2 responses in Cohort 1 or 1 response in either Cohorts 2 or 3), it will be considered for expansion with additional subjects enrolled. The cohort showing the highest response rate will be given highest consideration, as determined by the Sponsor-Investigator. Trial accrual is anticipated to occur with 28 subjects enrolled during the first stage (14 in Cohort 1, 7 in each of Cohorts 2 and 3) with the opportunity for additional subjects to be enrolled if a cohort is expanded (16 more in Cohort 1, 25 more in Cohorts 2 and 3).

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

3.2. Inclusion Criteria

Subjects must meet all of the following criteria:

1. Histologically confirmed stage IV urothelial carcinoma of the bladder, upper urinary tract or urethra.

2. Prior treatment for metastatic disease with at least one cisplatin or carboplatin-based multi-agent chemotherapeutic regimen. Prior immunotherapy with anti-PD-L1 or anti-PD1 agents is allowed.

    - Chemotherapy received peri-operatively for non-metastatic bladder cancer will be considered a prior regimen if less than 24 months have elapsed since treatment.

3. Measurable disease per RECIST 1.1. See Section 10 for the evaluation of measurable disease.

4. Tissue Pre-screen: Archived tissue must have been obtained within 60 months of subject signing tissue pre-screen consent. Biopsy accessible disease if adequate archival tissue does not exist for molecular characterization.

   Treatment: Available tumor specimen C-MET/RON expression results that meet the criteria for one of the three molecularly defined cohorts per Section 4.2

5. Age ≥ 18 years

6. ECOG performance status ≤ 2

7. Adequate liver function: AST and ALT ≤ 2x upper limit of normal, bilirubin ≤ 1.5x upper limit of normal

8. Adequate bone marrow function: Platelets ≥ 100,000 cells/mm^3, hemoglobin > 8.0 g/dL and ANC ≥ 1,500 cells/mm^3

9. Adequate renal function with a creatinine clearance (based on Cockgroft-Gault formula) ≥ 45 mL/min

10. Ability to understand and the willingness to sign a written informed consent document

11. Able to swallow oral medication

3.3. Exclusion Criteria

Subjects must not meet any of the following criteria.

1. Currently receiving any other investigational agents, a prior c-MET inhibitor, or crizotinib

2. Pregnant or breast feeding, because crizotinib can cause fetal harm

3. Uncontrolled and current illness including, but no limited to:

    - Ongoing or active infection
    - Symptomatic congestive heart failure
    - Unstable angina pectoris
    - Cardiac arrhythmia, or
    - Psychiatric illness/social situations that would limit compliance with study requirements

4. Presence of any of the following within the previous 3 months of treatment consent:

    - Myocardial infarction
    - Severe/unstable angina
    - Coronary/peripheral artery bypass graft
    - Congestive heart failure, or
    - Cerebrovascular accident including transient ischemia attack

5. History of active malignancy other than urothelial carcinoma within the prior 12 months of the date of treatment consent (except non-melanoma skin cancer or localized, treated prostate cancer)

6. Prolonged QT interval (QTc > 480 msec), symptomatic bradycardia, ongoing cardiac dysrhythmias of CTCAE version 4.0 grade 2 ≥ or uncontrolled atrial fibrillation of any grade

7. Pulmonary disorder requiring supplemental oxygen or history of pulmonary fibrosis. Sleep apnea considered to be a sleep disorder (and not a pulmonary disorder) by the investigator will be allowed.

8. Subjects receiving any medications or substances that are strong inhibitors or inducers of CYP3A are ineligible. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently updated list such as http://medicine.iupui.edu/clinpharm/ddis/table/aspx; medical reference texts such as the Physicians' Desk Reference may also provide this information. As part of the enrollment/informed consent procedures, the subject will be counseled on the risk of interactions with other agents, and what to do if new medications need to

be prescribed or if the subject is considering a new over-the-counter medicine or herbal product.

- Medical condition requiring the use of strong CPY3A inhibitors, including but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, suboxone, telithromycin, troleandomycin, and voriconazole.
- **Use of grapefruit or grapefruit juice, which are considered strong CYP3A inhibitors.**
- Medical condition requiring the use of strong CYP3A inducers, including but not limited to carbamazepine, efavirenz, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's Wort, and troglitazone.

9. Receiving any medications that are CYP3A substrates with a narrow therapeutic range (alfentanil, cyclosporine, dihydroergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus)

10. Subjects may be screened for study participation though may not begin study treatment:

- Within 4 weeks of major surgery
- Within 2 weeks of prior systemic therapy
- Within 2 weeks of prior non-palliative radiotherapy
- Within 48 hours of completion of palliative radiotherapy (≤ 10 fractions)
- Until recovery of adverse events due to prior therapies to ≤ 1 (except alopecia)

11. Presence of untreated brain metastases or ≤ 6 months from prior treatment (from the time of enrollment), active neurologic symptoms or the use of prohibited medications in subjects with a history of brain metastases

4. INVESTIGATIONAL PLAN

4.1. Milestone Date Definitions

Registration date: the date the subject signs the tissue pre-screen informed consent form.
Eligibility date: the date of the last documented criterion that confirmed subject eligibility.

Enrollment date: the date of initiation of crizotinib treatment.
Treatment discontinuation date: the date the Investigator decides to discontinue the subject from crizotinib treatment.

4.2. Overall Study Design

This is a single arm two-stage phase II study designed to evaluate the objective response rate in subjects with metastatic urothelial cancer demonstrating c-MET or RON overexpression who have received prior therapy with a cisplatin or carboplatin containing regimen.

Subjects will be recruited at Levine Cancer Institute (LCI) and other participating sites.

Immunohistochemistry will be utilized to define tumor sample c-MET and RON protein expression patterns for assignment into molecular cohorts as described in section 12.1.
In the first stage of this study, subjects will be enrolled in parallel to three molecularly defined cohorts as follows:

1. c-MET high (>50%), RON null (0-9%) (n = 14 subjects)
2. c-MET-positive (10-100%), RON-positive (10-100%) (n = 7 subjects)
3. c-MET null (0-9%), RON-positive (10-100%) (n = 7 subjects)

All enrolled subjects will continue with study treatment until criteria for treatment discontinuation has been met (as defined in Section 4.9.2).

If Stage 1 response criteria are met in a cohort, the cohort may be considered for expansion, and additional subjects (16 in Cohort 1 or 25 in Cohorts 2 or 3) may then be enrolled into that cohort in Stage 2. An expansion cohort will be defined by the Sponsor- Investigator following review of all available trial data which will be conducted after the first Stage 1 cohort has completed accrual and at least every six months thereafter until all Stage 1 cohorts have completed accrual.

If more than one cohort meets Stage 1 response criteria (2 responses out of 14 subjects for Cohort 1 or 1 response out of 7 subjects for each of Cohorts 2 and 3), then the cohort showing the highest response rate will be given highest consideration for expansion.

It is possible that the cohort with the highest response rate can be determined prior to completion of Stage 1 enrollment in all cohorts. If there is a significant lag in

enrollment in Stage 1 cohorts, an expansion decision may be made without regard to the lagging cohorts. Incompletely accrued Stage 1 cohorts may continue to enroll subjects after an expansion cohort has been identified. Additionally, individual cohorts may be closed at the discretion of the Sponsor-Investigator based on efficacy/safety/accrual.

Exploratory biomarker analysis including c-MET and RON protein expression will be correlated with clinicopathologic outcome. Additional specimens from selected subjects (e.g., those demonstrating clinical benefit) may also be assessed for other markers including c-MET gene amplification by fluorescence in situ hybridization or the presence of mutations in downstream genes found with high prevalence in urothelial carcinoma[19-21] to identify potential markers predictive of response or resistance to crizotinib.

Data from this study will be collected on electronic case report forms (eCRFs) and stored in the clinical trial management system (CTMS).

4.3. Registration and Enrollment

Potentially eligible and interested patients will be presented with the tissue pre-screening consent and asked for an archived tissue sample, or asked if a new tissue sample may be collected. The date the tissue prescreening consent is signed will be the registration date. A Study ID number will then be sequentially assigned by the Coordinating Center. The Study ID will be a four digit number, where 1001 will be the Study ID assigned to the first registered subject. The samples provided will be tested for molecular eligibility (i.e. molecular expression meets the criteria in an open cohort). The Coordinating Center must grant approval prior to presenting the subject with the treatment consent for molecularly eligible subjects that are still potentially eligible and interested in the treatment study.

4.4. Pre-treatment Screening

No protocol-related assessments may be performed prior to obtaining written informed consent. Men and women of child bearing potential on study will be counseled regarding risk of teratogenicity and the need to use contraception throughout the course of the study and for 90 days after completion of crizotinib administration.

Baseline assessments include:

- **Demographics and Medical History**
  - A complete medical history should be obtained, including documentation of any clinically significant pre-existing condition.

- **Physical Examination**

  Evaluation by body system, height, weight, and body surface area (BSA) should be documented. Vital signs will be recorded and should include temperature, pulse rate, blood pressure, respiratory rate and oxygen saturation. ECOG performance status should be documented at baseline.

- **Ophthalmologic Examination**
  - A baseline exam including visual acuity, fundoscopy and slit lamp exam should be performed by an ophthalmologist in subjects with history of photopsia or increase in vitreous floaters. If clinically indicated, additional eye examinations will be performed when visual disturbances have been observed and when there is an increase in grade for visual disturbances.

- **Pregnancy Test**
  - A serum or urine pregnancy test will be performed at screening and as clinically indicated for women of childbearing potential.

- **Concomitant Medications**
  - Any medications, other than crizotinib, taken up to 14 calendar days prior to signing of the treatment informed consent will be considered a concomitant medication. Dose, route, frequency, administration and start/stop dates will be documented. Concomitant medications include but are not limited to over the counter medications, supplements, and vitamins.

- **Symptoms and Toxicities**
  - Baseline adverse events will be documented at screening.

- **Clinical Laboratory Tests**
  - The blood-based clinical laboratory tests will be performed at screening and include a complete blood count with differential and platelets, a complete metabolic panel (including sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, albumin, total protein, total bilirubin, AST, ALT, alkaline phosphatase), magnesium, phosphorus, and LDH.

- **Electrocardiogram**
  - A baseline 12 lead electrocardiogram (EKG) will be required at screening for assessment of QT interval.

- **Radiology and Tumor Measurements**
  - A computed tomography (CT) scan with oral and intravenous contrast of the chest, abdomen and pelvis and radionuclide bone scan or positron emission tomography (PET)/CT scan defining the extent of existing disease must be performed and documented within 30 days prior to the first dose of study treatment. If a PET/CT scan is utilized to document extent of metastatic disease at baseline, measurable target lesions must be identified by the CT portion of the exam and cannot solely be determined by an abnormal fluorodeoxyglucose signal alone if lesion size cannot be easily measured by the corresponding CT images.

- **Tissue Biomarkers**
  - See the Manual of Procedures for tissue requirements and shipping instructions (Participating Sites)

  - Subjects must undergo core needle biopsy of a metastatic lesion to define c-MET/RON expression status if an adequate archival tumor specimen is not available. Adequate archival specimens include diagnostic slides from the urothelial primary or metastatic lesion and corresponding paraffin-embedded tumor block and must have been obtained within 60 months prior to the date of subject signing tissue pre-screen consent. Adequacy of archival specimen will be determined by the study pathologist.

  - If an archival specimen derived from a primary tumor is utilized for screening purposes and does not demonstrate c-MET or RON protein expression, subject may undergo a fresh biopsy of a metastatic lesion to assess for discordant expression patterns and will be eligible for study participation if c-MET or RON protein expression is observed on the subsequent fresh biopsy specimen.

  - For newly collected tissue specimens, core biopsy samples will be collected per standard operating procedures and immediately placed in 10% neutral-buffered formalin for a total fixation time between 6 and 48 hours.

  - Tissue is to be shipped to:

Atrium Health Biospecimen Repository
10545 Blair Rd., Suite 1001
Mint Hill, NC 28227

(704) 863-4001

- c-MET and RON protein expression will be assessed by immunohistochemistry as described in section 12.1, and subjects with expression patterns required for enrollment in open cohorts as defined in section 4.2 will be eligible to receive study treatment.

4.5. Treatment

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the subject's malignancy.

Subjects will receive treatment as described in Sections 5 and 6. Treatment assessments include:

- **Physical Examination**
  Evaluation by body system, weight, and body surface area (BSA) should be documented. Vital signs will be recorded and should include temperature, pulse rate, blood pressure, respiratory rate and oxygen saturation.

- **Symptoms and Toxicities**
  - All adverse events and serious adverse events will be documented regardless of attribution on an ongoing basis from study treatment initiation through 30 days after last dose of study treatment**.**

- **Concomitant Medications**
  - Any medications, other than crizotinib, taken up to 14 calendar days before completing the treatment informed consent through 30 days after last dose of study treatment will be considered a concomitant medication and dose, route, frequency, administration and start/stop dates will be documented. This includes but is not limited to, over the counter drugs, vitamins, and supplements.

- **Electrocardiogram**

- A 12 lead EKG will be obtained 28 days (+/- 7 days) after the start of therapy and then as indicated by the subject's clinical history and treating physician's discretion. Subjects at increased risk of QTc prolongation include those with bradyarrhythmia or congestive heart failure.

- **Clinical Laboratory Tests**
  - The blood-based clinical laboratory tests will include a complete blood count with differential and platelets, a complete metabolic panel (including sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, albumin, total protein, total bilirubin, AST, ALT, alkaline phosphatase), magnesium, phosphorus, and LDH obtained prior to the start of each cycle. Additionally, liver function tests (including total bilirubin, AST, ALT, alkaline phosphatase) will be obtained on day 15 (+/-7 days) of the first two cycles only.

- **Radiology and Tumor Measurements**
  - A CT scan with oral and intravenous contrast of the chest, abdomen and pelvis or PET/CT defining the extent of disease will be performed every 8 weeks (+/- 7 days) . The first follow-up imaging timepoint should be 8 weeks (+/- 7 days) from C1D1. Subsequent follow-up imaging should be performed every 8 weeks (+/- 7 days) based on the timepoint of the previous scan, not C1D1. For subjects being followed with CT scan of chest/abdomen pelvis, a radionuclide bone scan will also be obtained at the same frequency as the CT scan if skeletal metastases are present at baseline or if the subject develops new skeletal pain or abnormal alkaline phosphatase (> upper limit of normal) in the absence of hepatic metastasis. Identical methodology should be used for disease assessment at baseline and throughout the study.

4.6. End-of-Treatment

Subjects will continue study treatment until criteria for treatment discontinuation are met (as defined in Section 4.9.2). Every subject will undergo an end-of-treatment evaluation at the time it is determined that he or she is no longer eligible to receive study treatment. End of treatment evaluations will include a physical examination with vital signs and weight measurements, toxicity evaluation, concomitant medications evaluation, and laboratory evaluation per Section 5.0. The end of

treatment evaluation must be completed within 30 days after the last dose of study treatment.

4.7. Follow-up

Subjects will be tracked for at least 30 days following cessation of treatment to monitor for adverse events, serious adverse reactions, and any other unanticipated problems. If the end of treatment visit occurs prior to 30 days from last dose, subjects will be contacted by telephone on day 30 or next business day by telephone for monitoring. If subject cannot be contacted following three attempted telephone calls on subsequent days, subject will be contacted in writing. Following this period, subjects will be contacted every 6 months by telephone, in writing, or during clinic visits after treatment discontinuation for collection of follow-up data until death, lost to follow-up, or until the criteria for final analyses have been met (Section 11.4.1). Lost to follow-up is defined as three consecutive unsuccessful documented attempts at contacting the subject. Follow-up clinical information may also be obtained through chart reviews or other data sources (e.g. death registries).

All subjects, regardless of when they discontinue treatment, will be followed per standard of care procedures until all treatment-related toxicities have resolved, returned to baseline, stabilized, or are deemed irreversible.

4.8. Off-Study

Subjects will be considered off-study when death or lost to follow-up occurs. Subjects who withdraw consent voluntarily and subjects withdrawn by the Investigator are considered off-study per the documented date of withdrawal. Additionally, subjects will be considered off-study when it is determined that the follow-up period for the study is ended (per criteria in Section 11.4.1). Off-study subjects will not receive study treatment or participate in any study procedures, including data collection.

4.9. Changes in Subject Participation Status

4.9.1. Subject Replacements

Enrolled subjects who have discontinued treatment or who have withdrawn after receiving their first dose of study drug will not be replaced.

A subject who, for any reason (e.g. failure to satisfy the selection criteria or withdraws consent), terminates participation in the study before receiving first

dose of study drug is regarded as a “screen failure”. Screen failures may be replaced.

All screen failures will be tracked in the CTMS.

4.9.2. Treatment Discontinuation

Subjects are discontinued from treatment if there is evidence of progressive disease, unacceptable toxicity, or they withdraw consent for treatment only. Additionally, a subject may be discontinued from treatment if, in the Investigator's opinion, continuation of the treatment would be harmful to the subject.

These subjects are still considered to be on-study and may continue to participate in study procedures (e.g. labs, scans, follow-up).

Other reasons for treatment discontinuation include, but are not limited to:

- Pregnancy. Pregnancy will be reported as an SAE per Section 9.6. (Note: Subjects who have discontinued treatment with study drug because of pregnancy should not undergo CT scans [with contrast] or bone scans while pregnant.)
- Deterioration of ECOG performance status to 4
- Use of illicit drugs or other substances that may, in the opinion of the Investigator, have a reasonable chance of contributing to toxicity or otherwise skewing trial result
- Severe allergic reaction to crizotinib (Grade 3 or 4 hypersensitivity reaction)
- The development of a second cancer
- Any other (non-disease related) reason, at the Investigator’s discretion

4.9.3. Subject Withdrawal

Subjects are defined as withdrawn from the study if they revoke consent for both treatment and study procedures or the Investigator withdraws them from the study. Subjects **must be** withdrawn from the trial for the following reasons:

- Subject withdraws consent from study treatment and study procedures. A subject must be removed from the trial at his/her own request. At any time during the trial and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- Subject is lost to follow-up after three consecutive unsuccessful documented attempts at contacting the subject.

Subjects **may be** withdrawn from the study by the Investigator for the following reasons:

- The subject is non-compliant with study drug, study procedures, or both (as determined by the Investigator); including the use of anti-cancer therapy not prescribed by the study protocol.
- Development of an intercurrent illness or situation which would, in the judgment of the Investigator, significantly affect assessments of clinical status and trial endpoints.

Any subject who withdraws themselves or who is withdrawn from the study by the Investigator will remain under medical supervision until discharge or transfer is medically acceptable.

In all cases, the reason for withdrawal must be documented in the subject's medical records and/or research chart and recorded in the CTMS. Withdrawn subjects are considered to be off-study.

Details for the premature termination of the study as a whole are provided in Section 13.2.

5. STUDY CALENDAR

Required Procedures	Tissue Pre-Screen	Screening	Study Treatment[a]					Post-Treatment	
			Cycle 1		Cycle 2		Cycles ≥ 3	End of Treatment	Follow-up
		Within 30 days prior to treatment initiation unless otherwise specified	Day 1 (+/- 7 days)	Day 15 (+/- 7 days)	Day 1 (+/- 7 days)	Day 15 (+/- 7 days)	Day 1 (+/- 7 days) unless otherwise specified	Within 30 days after the last dose of study treatment unless otherwise specified	Every 6 months until death or lost to follow-up up to at least 2 years
Informed consent	X	X							
Demographics		X							
Medical and Treatment History		X							
Physical Exam[m]		X	X		X		X	X	
Pregnancy Test (serum or urine)		X[c]			If/when clinically indicated		If/when clinically indicated	If/when clinically indicated	
Ophthalmologic Exam		X[d]	If new or an increase in grade of visual disturbances						
Symptoms & Toxicities		X[e]	Documented on a continuous basis until 30 days after last dose of study treatment						
Concomitant Medications		X[f]	Documented on a continuous basis until 30 days after last dose of study treatment						
Laboratory Tests		X[l]	X[b,k]	X[g]	X[k]	X[g]	X[k]	X[k]	
12 lead EKG		X			X[l]		X[h]		
Radiology & Tumor Measurements[i]		X	Every 8 weeks (+/- 7 days) until documented progression or initiation of subsequent anti-cancer therapy						
Tissue Collection for Biomarker Analysis	X[j]								
Survival Status									X

a. study cycle length is 28 days.
b. required if study treatment is not started within 7 days of screening visit.
c. in women of child-bearing potential
d. baseline exam required only in subjects who report a history of photopsia or increase in visual floaters in 90 days prior to signing the treatment consent.
e. Baseline adverse events will be documented at screening
f. Concomitant medications taken up to 14 calendar days prior to the treatment informed consent should be documented at screening
g. total bilirubin, AST, ALT, alkaline phosphatase only
h. additional EKGs should be obtained at the discretion of Investigator.
i. CT of the chest, abdomen and pelvis and radionuclide bone scan or PET/CT scan at screening. See Section 4.4 for criteria for PET/CT. Identical methodology should be used for subsequent imaging. The first follow-up imaging timepoint should be 8 weeks (+/- 7 days) from C1D1. Subsequent follow-up imaging should be performed every 8 weeks (+/- 7 days) based on the timepoint of the previous scan. For subjects

being followed with CT scan of chest/abdomen pelvis, a bone scan is also required at the same frequency as the CT scan if skeletal metastases are identified at baseline or at the time of developing new skeletal pain or abnormal alkaline phosphatase in the absence of liver metastasis. For subjects who discontinue study treatment and have not had progression or initiated subsequent anti-cancer therapy, the frequency of imaging will be determined by the treating investigator.

j. After tissue pre-screen informed consent; fresh tissue to be obtained if adequate archival tissue is unavailable as described in Section 4.4
k. including CBC/differential, a complete metabolic panel (including sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, albumin, total protein, total bilirubin, AST, ALT, alkaline phosphatase), magnesium, LDH, and phosphorous
l. A 12 lead EKG will be obtained 28 days (+/- 7 days) after the start of study treatment
m. To include height and ECOG performance status at screening only. All time-points to include weight and vital signs including oxygen saturation.
n. Baseline adverse events will be documented at screening

6. TREATMENT PLAN

6.1. Crizotinib Dosage and Administration

Treatment will be administered orally on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Dose modifications are described in Section 7. No investigational or commercial agents or therapies other than crizotinib may be administered with the intent to treat the subject's malignancy. The study drug will be exclusively used for the investigation specified in this protocol and it will only be accessible to authorized staff.

Crizotinib will be started on the day of the enrollment visit (Cycle 1 Day 1). Crizotinib is administered orally at 250mg twice daily. Subjects will swallow one 250mg crizotinib capsule whole with or without food each morning and evening. Capsules should not be broken or crushed. If a dose is missed, subject will make up that dose unless the next dose is due within 6 hours. If vomiting occurs after taking a dose of study drug, an extra dose should not be taken. The subject should take the next dose at the regular time. Each study cycle length is 28 days.

6.1.1. Crizotinib Drug Supply

Crizotinib capsules for oral administration are formulated as a hard gelatin capsules in two dosages. 250mg capsules contain a pink opaque cap and body with “Pfizer” on the cap and “CRZ250” on the body. 200mg capsules contain a white opaque body and pink opaque cap with “Pfizer” on the cap and “CRZ 200” on the body. Crizotinib will be supplied by Pfizer. To request crizotinib from Pfizer, LCI Investigational Drug Services (IDS) Pharmacy will complete the Pfizer-provided Drug Supply Request Form. Participating Sites will request crizotinib supplies from the LCI IDS utilizing the study specific Drug Order

Form. Drug inventory levels should be able to provide subjects with crizotinib for up to four weeks while waiting for additional ordered supplies.

Crizotinib will be supplied in study drug bottles containing 60 capsules each(250mg or 200mg dosage). The study drug bottles will have a label affixed containing study identification, product identification and quantity of capsules.

Once the drug has been received, it must be kept in a secure, dry location. Study drug must be stored in its original study drug bottle at room temperature 20° to 25°C (68° to 77°F). Temperature excursions between 15° to 30°C (59° to 86°F) are permitted.

Study drug bottles dispensed to subjects will be labeled as an investigational treatment and subjects will be instructed to comply with the following directions:

- Store capsules in the original study drug bottle.
- Take capsule at the same time twice daily, unless otherwise instructed, with or without food.
- Swallow capsule whole.
- If a dose is missed, it should be taken as soon as possible. Unless it is close to the next dose (within 6 hours), in which case the normal dose should be taken at the usual time.
- If vomiting occurs after taking a dose, an additional dose should not be taken. The next dose should be taken when due.
- Avoid grapefruit and the use of grapefruit juice while taking study treatment.
- Subjects of childbearing potential should use adequate contraceptive methods (per Section 7.1.1) while taking study treatment and for at least 90 days after completing therapy.

6.1.2. Concomitant Therapy Medications

6.1.2.1. Medications

Anticancer therapy with agents other than crizotinib is not permitted. Medication that is considered necessary for the subject's welfare, and which is not expected to interfere with the study treatment, may be given at the discretion of the Investigator. Crizotinib inhibits CYP3A in vivo. Specific caution should be taken when considering administration of a concomitant medication that is metabolized by the cytochrome enzyme CYP3A. Such concomitant medication should be avoided if possible.

Concomitant use of crizotinib with strong CYP3A inhibitors, inducers or CYP3A substrates with a narrow therapeutic range as listed in section 3.3 while on study treatment is prohibited.

Grapefruit or grapefruit juice should be avoided while on study per exclusion criteria.

Bisphosphonate therapy for metastatic skeletal involvement is permitted.

6.1.2.2. Radiotherapy

The development of a new symptomatic disease site requiring palliative radiotherapy constitutes subjective disease progression as defined in section 10.1.4 and requires subject discontinuation from study treatment. Palliative radiotherapy may begin at least one day after crizotinib treatment is stopped.

6.1.2.3. Surgery

The impact of crizotinib on wound healing is not known. If surgical intervention is necessary during study participation, crizotinib should be stopped 48 hours before surgery and resumed no sooner than 48 hours after surgery.

6.2. Treatment Compliance

Study drug will be dispensed to subjects with instructions to bring all study drug containers to each study visit (do not discard). At the end of each cycle, the study drug pill bottles will be returned to the research staff and counted. The number of capsules taken by the subject per cycle will be derived from these capsule counts rather than reported by the subjects on a pill diary.

Subject compliance with the treatment and protocol includes willingness to comply with all aspects of the protocol. Subjects will be asked to return used study drug bottles. Compliance with study treatment will be assessed at the end of each cycle.

At the discretion of the Sponsor-Investigator or the subject's Physician Investigator, a subject may be discontinued from the protocol for non-compliance with study visits or study drug.

6.3. Drug Accountability

All study drugs will be stored at the investigational site in accordance with Good Clinical Practice (GCP) and Good Manufacturing Practices (GMP) requirements and will be inaccessible to unauthorized personnel.

An adequate record of receipt, distribution, and destruction of all study drugs must be kept in the form of a Drug Accountability Form. The Investigator, or responsible party designated by the Investigator, will maintain a careful record of the inventory using the Drug Accountability Form.

6.4. Destruction

At the end of the study, unused supplies of crizotinib will be destroyed and documented according to institutional pharmacy policies. Destruction records will be reviewed and confirmed by the LCI IDS Pharmacy staff who will then complete the Study Closure Form provided by Pfizer certifying that all remaining drug was destroyed.

7. TREATMENT-RELATED ADVERSE EVENTS

7.1. Adverse Events Related to Crizotinib

Based on prior clinical studies with crizotinib, the Investigator should anticipate that any of the following AEs could occur with the use of this medication. The occurrence of AEs and SAEs should prompt immediate notification of the appropriate agencies as outlined in Section 9.

7.1.1. Reproductive Risks

Crizotinib can cause harm to the developing human fetus. For this reason, women of childbearing potential and men must agree to use adequate contraception (e.g., prior surgical sterilization, hormonal or barrier method of birth control; abstinence) prior to study entry, the duration of study participation and for at least 90 days after completion of study treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician and the investigator immediately

7.2. Dose Modifications for Adverse Events

The starting dose of crizotinib is 250mg twice daily (dose level 0). Doses will be delayed or reduced for clinically significant hematologic and non-hematologic toxicities that are related to protoco7l therapy according to the guidelines shown in the tables that follow. Dose modifications will follow pre-defined dose levels. Dose adjustments for hematologic toxicity are based on the blood counts obtained in

preparation for the day of treatment. In the event of a treatment delay at the scheduled Day 1 of a cycle, Day 1 of the cycle will be delayed until crizotinib is re-started. This may cause the cycle to extend to longer than 28 days.

Dose Level	***Crizotinib* Dose**
0	*250 mg, twice daily*
-1	*200 mg, twice daily*
-2	*250 mg, once daily*

If a subject experiences more than one toxicity, dose reduction should be according to the toxicity with the highest grade. In the case of two or more toxicities of the same grade, the Investigator may dose reduce according to that deemed most causally related to study treatments. If treatment is held for more than 4 weeks due to toxicity or if dose reductions beyond dose level -2 are necessary, then treatment will be permanently discontinued.

Table 1: Dose Adjustments for Treatment-Related Toxicities

Dose Adjustments for Treatment-Related Toxicities[a]				
Toxicity	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Non-hematologic General (except as noted below).	Continue at the same dose level.	Continue at the same dose level.	Withhold dose until toxicity is grade ≤1, or has returned to baseline, then resume treatment at the same dose level or reduce the dose by 1 level at the discretion of the investigator[b].	Withhold dose until toxicity is grade ≤1, or has returned to baseline, then reduce the dose by 1 level and resume treatment, or discontinue at the discretion of the investigator[b].

[a] Utilizing NCI Common Terminology Criteria for Adverse Events version 4.0
[b] Patients who develop Grade 4 hyperuricemia or Grade 3 hypophosphatemia without clinical symptoms may continue study treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy, to require dose modification. Administration of study treatment with food may reduce likelihood of nausea.

Table 2: Dose Adjustments for Hematologic Toxicities[a]

CTCAE[b] Grade	**Crizotinib Dosing**
≤ Grade 2	No change in dose
Grade 3	Hold until ≤ Grade 2. Resume at same dose level.
Grade 4	Hold until ≤ Grade 2. Resume at next lower dose level.

[a] Excluding lymphopenia unless associated with clinical event such as related infection.
[b] NCI Common Terminology Criteria for Adverse Events version 4.0

Table 3: Dose adjustments for abnormal liver function related to study drug[a]

CTCAE Grade	**Crizotinib Dosing**
Grade 3 or 4 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation with Grade ≤ 1 total bilirubin	Hold until ≤ Grade 1 or baseline, then resume at next lower dose level.
Grade 2, 3 or 4 alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation with concurrent Grade 2, 3 or 4 total bilirubin elevation in the absence of cholestasis or hemolysis	Permanently discontinue.

[a]Abnormal elevations in AST or ALT or both, concurrent with abnormal elevations in total bilirubin (as defined in Section 9.5), with no other known cause of liver injury must be reported as a SAE to Pfizer per Section 9.8.

Table 4: Dose adjustments for pneumonitis

CTCAE Grade	**Crizotinib Dosing**
Any grade pneumonitis	Permanently discontinue.

Table 5: Dose adjustments for QTc prolongation

Grade 3 QTc prolongation	Hold until recovery to baseline or QTc < 481 msec, then resume at next lower dose level.
Grade 4 QTc prolongation	Permanently discontinue.

Table 6: Dose adjustments for bradycardia

Grade 2, 3 bradycardia	Hold until recovery to asymptomatic bradycardia or heart rate ≥ 60 bpm, evaluate concomitant medications. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume crizotinib at previous dose after recovery (asymptomatic bradycardia or heart rate ≥ 60 bpm). If no contributing concomitant medication is identified, or if contributing concomitant medication is not dose adjusted or discontinued, resume at next lower dose level after recovery (asymptomatic bradycardia or heart rate ≥ 60 bpm).
Grade 4 bradycardia	If contributing concomitant medication is identified and dose adjusted or discontinued, resume crizotinib at 250 mg once daily after recovery (asymptomatic bradycardia or heart rate ≥ 60 bpm), with monitoring of pulse rate at least once per week for a minimum of three weeks Permanently discontinue crizotinib if no contributing concomitant medication is identified.

Table 7: Dose adjustments for visual disturbance

Toxicity[a]	Grade 1	Grade 2	Grade 3	Grade 4
Visual Disturbance	Continue at the same dose level. Repeat ophthalmologic examination.[b]	Continue at the same dose level. Repeat ophthalmologic examination.[b]	Hold until recovery. Repeat ophthalmologic examination.[b] Resume treatment by reducing by one dose level.	Permanently discontinue treatment. Repeat ophthalmologic examination.[b]

[a] NCI Common Terminology Criteria for Adverse Events version 4.0
[b] Ophthalmologic examination includes visual acuity, fundoscopy, and slit lamp and should be performed by an ophthalmologist.

8. DATA AND SAFETY MONITORING PLAN

8.1. Safety Monitoring

This protocol will be monitored according to the processes in effect for all Levine Cancer Institute investigator- initiated studies and the protocol-specific monitoring plan, and will abide by standard operating procedures set forth by both the Atrium Health Office of Clinical and Translational Research and the Levine Cancer Institute. It is the responsibility of the Sponsor-Investigator to monitor the safety data for this study. The Sponsor-Investigator, Statistician, and other Coordinating Center team members as needed will meet regularly to monitor subject consents, enrollment and retention, safety data for all subjects [including adverse events (AEs) for all grades and attributions, serious adverse events (SAEs)], study drug administration, and validity/integrity of the data. Documentation of these meetings will be kept with study records. SAEs will be reported to the IRB per their requirements. Major protocol deviations that result in a threat to subject safety or the integrity of the study will be reported to the IRB per their requirements. The Sponsor-Investigator will submit data

to the LCI Data and Safety Monitoring Committee according to the overarching LCI Data and Safety Monitoring Plan.

8.2. Data Quality Assurance

This study will be organized, performed, and reported in compliance with the study protocol, institutional standard operating procedures (SOPs) Atrium Health and other applicable regulations and guidelines (e.g. GCP).

Data will be collected on electronic Case Report Forms (eCRFs).

Subjects will be monitored by Levine Cancer Institute Research Monitors routinely for data quality. This monitoring will be done by comparing source documentation to the eCRFs.

The study database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be generated and addressed by the appropriate research personnel. Only authorized personnel will make corrections to the study database and all corrections will be documented in an electronic audit trail.

Any variation between source documentation and the data set will be discussed with the appropriate research personnel.

8.3. Communication Between Investigational Sites

Investigational sites will be required to report SAEs, problems with study drug administration, or any other problem that could affect the validity/integrity of the study data to the Sponsor-Investigator. All investigational sites will record AEs using the eCRFs and SAEs using the SAE reporting function in the CTMS to the Sponsor. SAEs will be reported within 24 hours of the Investigator learning of the event. Any problem impacting subject safety or data integrity should be communicated to the Sponsor-Investigator by email or phone as soon as possible but within 2 business days of the Investigator learning of the event.

9. SAFETY DATA COLLECTION, RECORDING AND REPORTING

All subjects who receive at least one dose of study treatment will be evaluable for the safety analysis. All observations pertinent to the safety of the study treatment will be recorded and included in the final report.

Safety variables include the following: treatment administration, AEs, and SAEs (whether related to crizotinib or not), safety and tolerability, relationship to treatment and intensity will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All adverse events (Grades 1 – 5) will be determined by the Investigator and documented in subject study charts.

9.1. Unanticipated Problem (UAP) Definition

An UAP is any incidence, experience or outcome that is unexpected, given the information provided in research-related documentation (e.g. Investigator's brochure, protocol, informed consent) and the study population characteristics that is related or possibly related to participation in the research study and places the participant at an increased risk.

9.2. Adverse Event (AE) Definition

An adverse event or adverse experience is any untoward medical occurrence in a study subject who is administered a study drug that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of the study drug, whether or not considered related to the study drug. Pre-existing conditions that increase in frequency or severity or change in nature during or as a consequence of use of a drug in human clinical trials are also considered adverse events. Adverse events may also include complications that occur as a result of protocol mandated procedures (e.g., invasive procedures such as biopsies).

Any continuing medical condition or clinically significant laboratory abnormality with an onset date before the first date of study drug administration should be considered pre-existing and should be documented in the subject's medical records and/or in the research chart.

An AE does not include:

- relapse or progression of the underlying malignant disease; however, the associated signs, symptoms, or diagnoses should be recorded as adverse events (e.g., "jaundice" due to new or increasing liver metastases, or "tumor pain" or "bone pain" due to progressive disease);

- medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion). The condition that leads to the procedure is the adverse event;
- situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions);
- overdose of either study drug or concomitant medication without any signs or symptoms unless the subject is hospitalized for observation; and
- pregnancy (pregnancy during treatment should be reported as an SAE).

Laboratory abnormalities are usually not recorded as adverse events; however, signs and/or symptoms that are associated with laboratory findings requiring study withdrawal, dose modification, or medical intervention (e.g., anemia requiring transfusions or hyperglycemia requiring treatment) or other abnormal assessments (e.g., ECG, radiographs, vital signs) must be recorded as adverse events if they meet the definition of an adverse event. In addition, laboratory abnormalities marked as **clinically significant** by the Investigator should also be recorded as adverse events on the eCRF. The Investigator will record the most severe grade of the **clinically significant** laboratory abnormality and will evaluate its relationship to the study drug and clinical condition if/when a **clinically significant** laboratory abnormality occurs.

All adverse events (including event name, grade, start/stop date and attribution) will be documented in the medical record and/or research chart.

The Investigator is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

9.2.1. Adverse Event Attribution

Descriptions and grading scales listed in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all AE reporting. Each AE will be assigned an attribution to one of the following categories:

Definite – The AE is clearly related to the study treatment.

Probable – The AE is likely related to the study treatment.

Possible – The AE is possibly related to the study treatment.

Unlikely – The AE is doubtfully related to the study treatment.

Unrelated – The AE is clearly NOT related to the study treatment.

For the purposes of statistical analyses, the relationship to study drug will be further dichotomized into the following categories:

"Not Related": This includes events that are considered *unlikely* or *unrelated* to study drug. In the Investigator's opinion, the AE has an etiology other than the study drug (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

"Related": This includes events that are considered *possibly*, *probably*, or *definitely* related to study drug. A temporal relationship exists between the event onset and administration of the study drug. It cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies. In the case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge. Ineffective study drug treatment should not be considered as causally related in the context of AE reporting.

9.3. Suspected Adverse Reaction (SAR) Definition

A SAR is an adverse event in which there is reasonable possibility that the study drug caused the adverse event as defined by 21 CFR 312.32. The Investigator is responsible for judging whether it is a reasonable possibility that the study drug caused the adverse event.

9.4. "Unexpected" Definition

An AE or SAR is to be considered unexpected if the event is not listed in the current version of the Investigator Brochure (IB), package insert or is not listed in the severity or specificity observed. Investigators should refer to the Safety Information section of the current IB and/or package insert for crizotinib, including the DCSI (development core safety information), for the expected side effects of crizotinib. As with any agent, there is always the potential for unexpected AEs, including hypersensitivity reactions.

9.5. Serious Adverse Event (SAE) Definition

Adverse events may also be considered serious adverse events. An SAE is any adverse event, without regard to causality, that is life-threatening (i.e., causes an immediate risk of death) or that results in any of the following outcomes:

- Death;

- In-patient hospitalization or prolongation of existing hospitalization;
- Persistent or significant disability or incapacity (i.e., substantial disruption of the ability to conduct normal life functions);
- Secondary malignancies (defined as *new* cancers, not transformations or progression of original disease),
- Grade ≥ 2 Potential Sight Threatening (PST) (with the exception of Visual field defect, for which grade ≥ 3 is the standard)/Severe Visual Loss (SVL). Please refer to the list of terms that are considered indicative of a PST or SVL event later in this section*
- Exposure to crizotinib during pregnancy or lactation;
- Congenital anomaly or birth defect in the offspring of a subject who received study drug;
- Occupational exposure to crizotinib;
- Lack of effect of crizotinib if associated with an SAE
- Any other medical event that, in the medical judgment of the Sponsor-Investigator, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above is also considered an SAE. The following criteria are considered medically important events for this protocol and should be reported as SAEs:
    - Hy's Law Cases:
        - Subjects with AST/ALT and TBili baseline values **within the normal range** who subsequently present with AST OR ALT values >3 x ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value < 2 x ULN or not available
        - For subjects with AST or ALT OR TBili baseline values **above the ULN,** the following threshold values are used in the definition mentioned above, as needed, depending on which value(s) are above the ULN at baseline:
            - Preexisting AST or ALT baseline values above the normal range: AST or ALT values > 2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).
            - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN or if the value reaches >3 × ULN (whichever is smaller).

***Terms included as PST or SVL events:**

Amaurosis, Amaurosis fugax, Blindness, Blindness cortical, Blindness day, Blindness night, Blindness transient, Blindness unilateral, Hemianopia, Hemianopia heteronymous, Hemianopia homonymous, Optic atrophy, Optic ischaemic neuropathy, Optic nerve disorder, Optic neuropathy, Quadranopia, Retinopathy, Sudden visual (or vision) loss, Toxic optic neuropathy, Tunnel vision, Visual cortex atrophy, Visual field defect, Visual pathway disorder, Retinal oedema, Retinal detachment, Maculopathy, Iritis, Uveitis, Visual field test abnormal.

The occurrence of Grade ≥2 of any of these events should be treated as a SAE, except for Visual field defect, for which only Grade ≥3 should be treated as a SAE. Grade 2 events are considered to be PST and Grade ≥3 events are considered to be SVL.

Planned hospitalizations:
Elective surgeries that have been planned prior to subject enrollment in the study or for conditions existing prior to study enrollment do not need to be captured as SAEs, unless complications occur or the conditions are worse than the subject's baseline. If there are complications, they should be clearly documented.

A planned medical or surgical procedure is not, in itself, an SAE.

9.6. Safety Reporting to the Sponsor

SAEs will reported to the Sponsor-Investigator within 24 hours of investigator awareness (immediately if fatal or life-threatening) via the CTMS.

SAEs will be reported from the time of enrollment through 30 days after the date of the last study drug administration.

SAEs will be followed until clinical recovery is complete and laboratory tests have returned to baseline, until progression has been stabilized, or until there has been acceptable resolution of the event. This may at times cause the follow-up period for SAEs to be greater than 30 days. The above referenced 30-day time period applies even if the subject is taken off study treatment and initiated on new treatment during this time period. Similarly, the Sponsor-Investigator is responsible for following the subject during the required follow-up period even if the subject lives elsewhere or has been released from his or her care and is being treated by another provider.

SAEs determined to be related to study treatment or procedures are reportable from informed consent throughout the duration of the subject's participation in the study.

All SAEs (including event name, grade, start/stop date and attribution) will be documented in the medical record and/or research chart and recorded on the eCRF for this protocol. SAE attributions follow the same scale as described in Section 9.2.1.

The Investigator is responsible for verifying and providing source documentation for all SAEs and assigning the attribution for each event for all subjects enrolled on the trial.

9.7. Safety Reporting to the IRB

All events occurring during the conduct of a protocol and meeting the definition of an UAP or SAE will be reported to the IRB per their reporting requirements.

Protocol deviations will be reported to the IRB per their reporting requirements.

9.8. Safety Reporting to Pfizer

SAEs will be reported to Pfizer within 24 hours of the Sponsor-Investigator learning of the event (immediately if fatal or life-threatening). SAEs are reportable to Pfizer from first dose of study drug through 28 days after last dose of study drug. SAEs determined to be related to study drug and reportable to Pfizer from first dose of study drug throughout the duration of the subject's participation in the study.

<u>Exceptions for SAE reporting to Pfizer:</u>

- Any SAE identified in the protocol as anticipated to occur in the study population at some frequency independent of drug exposure, unless the Sponsor-Investigator assesses such an event as related to study drug
- Any SAE judged by the Sponsor-Investigator to represent progression of the malignancy under study, unless it results in death within the SAE reporting period

SAE reports should be completed using the Pfizer-provided Investigator-Initiated Research Serious Adverse Event Form.

All reports shall be sent via facsimile to:
Pfizer U.S. Clinical Trial Department
Fax: 1-866-997-8322

10. MEASUREMENT OF EFFECT

10.1. Anti-tumor Effect – Solid Tumor

Response and progression will be evaluated in this study using the revised response evaluation criteria in solid tumors (RECIST) guideline version 1.1.

10.1.1. Definition

Evaluable for overall response. Only those subjects who have measurable disease present at baseline and have received at least one dose of study therapy will be considered evaluable for overall response. These subjects will have their response classified according to the definitions stated in Section 10.1.4.

10.1.2. Disease Parameters

Target lesions: When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as *target lesions* and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. *Lymph nodes* merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the *short* axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane). The smaller of these measures is the short axis. All other pathological nodes (those with short axis ≥ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed. A *sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the *baseline sum diameters*. If lymph nodes are to be included in the sum, then as noted above, only the *short* axis is added into the sum. The baseline sum diameters will be used as reference to further

characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including pathological lymph nodes should be identified as *non-target lesions* and should also be followed as 'present', 'absent', or in rare cases 'unequivocal progression'.

10.1.3. Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and within 30 days prior to first dose of study therapy.

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

10.1.4. Response Criteria

Response will be evaluated using RECIST 1.1 Criteria.

Complete Response:

- Target lesion: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Non-target lesion: Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

Partial Response:

- Target lesion: At least a 30% decrease in the sum of diameters of target, taking as reference the baseline sum diameters.
- Non-target lesion: Not applicable

Stable Disease:

- Target lesion: Neither sufficient shrinkage to qualify for a partial response, nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.

- Non-target lesion: Not applicable.

Progressive Disease:

- Target lesion: At least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (*Note:* the appearance of one or more new lesions is also considered progression).
- Non-target lesion: *Unequivocal progression* (as described in RECIST version 1.1) of existing non-target lesions. (*Note:* the appearance of one or more new lesions is also considered progression).

Non-Complete Response / Non-Progressive Disease:

- Target lesion: Not applicable
- Non-target lesion: Persistence of one or more non-target lesion(s)

Table 8: Summary of RECIST:

Target Lesions	Non-target Lesions	New Lesions	Overall Response	Best Response for this Category also requires
CR	CR	No	CR	Documented at least once ≥ 4 weeks from baseline
CR	Non-CR/Non-PD	No	PR	Documented at least once ≥ 4 weeks from baseline
CR	Not evaluated	No	PR	
PR	Non-PD or not all evaluated	No	PR	
SD	Non-PD or not all evaluated	No	SD	Documented at least once ≥ 4 weeks from baseline
Not all evaluated	Non-PD	No	NE	N/A
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression

CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease, and NE = inevaluable.

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. This means that subjects with CR may not have a total sum of the diameters of 'zero'.

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is *not* a descriptor of an objective response: it is a reason for stopping study therapy. It is included as part of the criteria for determination of Progression Free Survival. The objective response status of such subjects is to be determined by evaluation of target and non-target disease.

The development of pain or alternate symptoms requiring palliative radiotherapy constitutes subjective clinical disease progression, and study treatment should be stopped.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

11. STATISTICAL CONSIDERATIONS

11.1. Sample Size

Subjects will be enrolled in parallel to the three molecularly defined cohorts as described in Section 4.2. Due to the observed prevalence of the molecular expression patterns, the Cohort 1 Stage 1 sample size is designed to be larger than that of Cohorts 2 and 3.

For Cohort 1, a 2-stage design was selected, where the Stage 1 sample size will be 14 subjects. Objective response (OR) will be evaluated on the Stage 1 subjects and, if two or more responders (CR or PR) are observed in Stage 1, the cohort will be expanded. If Cohort 1 is expanded, an additional 16 subjects will be enrolled in the second stage, for a total of 30 Cohort 1 subjects. This design will be used to test the hypothesis that the ORR for a cohort of subjects is less than or equal to 5%. If objective responses occur in at least 5 of 30 subjects, the null hypothesis will be

rejected and the use of crizotinib for treatment of patients with previously treated metastatic urothelial carcinoma may be considered for further evaluation. Based on an alpha = 0.05 significance level, this sample size will provide at least 90% power to reject the null hypothesis, assuming the overall response rate (ORR) is 30%.

A 2-stage design was selected so that the Stage 1 sample size was minimized for Cohorts 2 and 3 (due to the low prevalence of the c-MET and RON protein expression patterns in those cohorts) while the alpha and power constraints as described below were met. This will be accomplished with a Stage 1 sample size of 7 subjects in each of the 2 cohorts. Objective response (OR) will be evaluated on the Stage 1 subjects. If one or more responders (CR or PR) are observed in Stage 1, the cohort may be considered for expansion. If either molecular cohort 2 or 3 is expanded, an additional 25 subjects will be enrolled in the second stage (total of 32 subjects in that cohort). This design will be used to test the hypothesis that the ORR for a cohort of subjects is less than or equal to 5%. If objective responses occur in at least 4 of 32 subjects, the null hypothesis will be rejected and the use of crizotinib for treatment of patients with previously treated metastatic urothelial carcinoma may be considered for further evaluation. Based on an alpha = 0.05 significance level, this sample size will provide at least 90% power to reject the null hypothesis, assuming the ORR is 30%.

More detail regarding selection of the molecularly defined cohort for Stage 2 expansion is provided in Section 4.2.

11.2. Endpoint Definitions

11.2.1. Objective Response

Objective response will be determined for each subject as a binary variable indicating whether or not the subject achieved a best overall response of CR or PR as determined by RECIST 1.1. For the purposes of response determination, a confirmatory scan for CR and PR is required.

11.2.2. Progression-Free Survival

PFS is defined as the duration of time from enrollment to the study to first occurrence of either progressive disease or death. Disease progression can be objectively determined as per Section 10.1.4 (RECIST 1.1 criteria) or progression can be clinically determined by the investigator. Evidence for clinical progression must be documented in the medical records. For objective disease progression, the date of PD is the date of the radiologic assessment that identified RECIST-defined progressive disease. For clinical disease progression, the date of PD is the date

that the clinician makes the determination of disease progression. If the subject died without documented disease progression, the date of progression will be the date of death. For surviving subjects who do not have documented disease progression, PFS will be censored at the date of last radiologic assessment. For subjects who receive subsequent anti-cancer therapy prior to documented disease progression, PFS will be censored at the date of last radiologic assessment prior to the commencement of subsequent therapy. Subjects who have an initial PFS event immediately following 2 or more consecutive missed assessments will be censored at the date of the last assessment prior to those missed assessments. For participants with only one missed assessment, the documented progressive disease status and assessment date will be used.

11.2.3. Overall Survival

Overall survival is defined as the duration from enrollment date to the date of death from any cause. Subjects who are alive or lost to follow-up at the time of the analysis will be censored at the last known date they were alive.

11.2.4. Safety Endpoints

Safety endpoints will include treatment administration (dose intensity, planned dose intensity, and relative dose intensity), AEs, SAEs, and deaths while on study therapy.

11.3. Analysis Populations

Efficacy and safety analyses will be conducted on the population of subjects who begin crizotinib treatment. The date of initiation of crizotinib treatment will be the enrollment date. Analysis of objective response rate will be conducted on those subjects in the efficacy population with measurable disease present at baseline.

11.4. Analysis Methods

11.4.1. Timing of Analysis

For each cohort, the Stage 1 analysis will occur after the best overall response has been determined for all Stage 1 subjects. The primary analysis of an expanded cohort will be conducted after the best overall response has been determined for all subjects in that cohort. Secondary analyses of all cohorts will be conducted after the overall PFS censoring rate reaches 20% or when all surviving subjects have at least 1 year of follow-up, whichever occurs first. A final analysis will be conducted after the overall

survival censoring rate reaches 20% or after all surviving subjects have at least 2 years of follow up.

11.4.2. Subject Disposition

An accounting of all consenting subjects will be provided at the end of the study. This will include a breakdown of subjects who consented, were treated, discontinued treatment, died, and were lost to follow-up or withdrew consent.

11.4.3. Baseline Subject and Disease Characteristics

A summary of subject demographics and disease-related characteristics will be completed and subject medical history will be assessed.

11.4.4. Efficacy Analyses

11.4.4.1. Primary Analysis

The frequency and proportion of responders will be calculated for the cohort that was expanded to Stage 2. A corresponding 95% confidence interval will be estimated using the Clopper-Pearson method. A one-sided test for binomial proportions using the rejection regions described in Section 11.1 will be carried out, testing the null hypothesis that the ORR is less than 5%. Based on the 2-stage design and corresponding sample size calculations described in Section 11.1, if there are at least 5 responders in Cohort 1 or 4 responders in Cohort 2 or 3, the null hypothesis can be rejected.

Based on pooling all three molecular cohorts of subjects, logistic regression techniques will be used to correlate response rate to c-MET and RON levels. This will include multiple regression models incorporating key baseline subject and disease characteristics.

11.4.4.2. Secondary Analyses

Overall and progression free survival will be analyzed using Kaplan Meier techniques. Medians, 25^{th}, and 75^{th} percentiles will be estimated. Selected landmarks for OS (1, 3, 6, and 9 month survival rates) and PFS (1, 3, and 6 month PFS rates) will form the Kaplan Meier curve. Based on pooling all three molecular cohorts of subjects, Cox proportional hazards models will be used to correlate OS and PFS to c-MET and RON

levels. This will include multiple regression models incorporating key baseline patient and disease characteristics.

11.4.5. Safety Analyses

The number of cycles administered, dose intensity, and relative dose intensity will be summarized quantitatively.
Incident rates for treatment emergent adverse events, SAEs, and deaths while on study therapy will be summarized. Treatment emergent adverse events are defined as follows:

- An adverse event that occurs after treatment start that was not present at the time of treatment start; OR
- An adverse event that increases in severity after treatment start if the event was present at the time of treatment start.

11.4.6. Exploratory Analyses

Cox proportional hazards models and logistic regression will be used to assess the correlation between additional baseline biomarkers with clinical outcomes.

11.5. Interim Analyses

For each molecular cohort an evaluation of ORR will be made after Stage 1 as described in Section 4.2.

12. BIOMARKER ANALYSIS

12.1. Immunohistochemistry

Tumor specimens as defined in section 4.4 from all subjects will be assessed for c-MET and RON protein expression by immunohistochemistry in a semi-quantitative fashion for the purpose of determining subject eligibility for enrollment into open study cohorts. Protein expression will be graded based on the percentage of positive staining tumor cells. Specimens with 0-9% of tumor cells staining positive will be considered negative for protein expression for the purposes of this study. c-MET and RON protein expression will also be correlated with primary and secondary endpoints.

12.2. Genomic Analysis

Additional specimens from selected subjects may also be assessed for other markers including c-MET gene amplification by fluorescence in situ hybridization or undergo tumor genomic sequencing for the purpose of therapeutic biomarker discovery.

13. STUDY COMPLETION

13.1. Completion

The study will be considered complete when one or more of the following conditions is met:

- All subjects are dead and/or withdrawn from the study.
- All subjects have discontinued from the study.
- The IRB, LCI DSMC, Sponsor-Investigator or Pfizer discontinues the study because of safety considerations.
- The Sponsor-Investigator defines an administrative or clinical cut-off date.

13.2. Termination

The study will be terminated when one or more of the following conditions occur:

If risk-benefit ratio becomes unacceptable owing to, for example:

- Safety findings from this study (e.g. SAEs)
- Results of any interim analysis
- Results of parallel clinical studies
- Results of parallel animal studies (e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g. recruitment rate; screen failure rate; withdrawal rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

The Sponsor-Investigator has the right to close the trial at any site and at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties.
- All affected institutions must be informed as applicable according to local law.
- In case of a partial study closure, ongoing subjects, including those in follow-up, must be taken care of in an ethical manner.

Details for individual subject's withdrawal can be found in Section 4.9.3.

14. RETENTION OF RECORDS

Essential documentation (e.g. adverse events, records of study drug receipt and dispensation), including all IRB correspondence, will be retained for at least 2 years after the investigation is completed. Documentation will be readily available upon request.

15. ETHICAL AND LEGAL ISSUES

15.1. Ethical and Legal Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Investigator abides by Good Clinical Practice (GCP) guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate agencies (e.g. IRB) will be obtained for all participating centers before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of IRB approval must be obtained and forwarded to Pfizer.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct. The Investigators may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by the Sponsor-Investigator without discussion and agreement by Pfizer. However, the Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior approval from applicable agencies. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the appropriate agencies. Any deviations from the protocol must be explained and documented by the Investigator.

The Sponsor-Investigator is responsible for the conduct of the clinical trial at the sites in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Sponsor-Investigator is responsible for overseeing the treatment of all study subjects. The Sponsor-Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all applicable regulations and guidelines regarding clinical trials both during and after study completion.

The Sponsor-Investigator will be responsible for assuring that all the required data will be collected and properly documented.

15.2. Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

15.3. Publication

The Sponsor-Investigator must send a draft manuscript of the publication or abstract to Pfizer prior to submission of the final version for publication or congress presentation. All relevant aspects regarding data reporting and publication will be part of the contract between Pfizer and the Sponsor-Investigator.

The Sponsor-Investigator will ensure that the information regarding the study be publicly available on the internet at www.clinicaltrials.gov.

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