A Phase 2 Study of Savolitinib in Subjects with MET Amplified Metastatic Colorectal Cancer

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TITLE: A Phase 2 Study of Savolitinib in Subjects with MET Amplified Metastatic Colorectal Cancer

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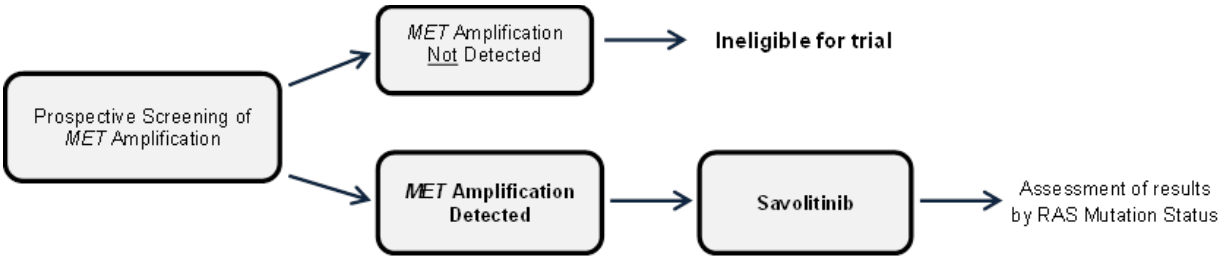


Patient Selection

Patients with metastatic CRC who have received prior anti-EGFR monoclonal antibody therapy (cetuximab or panitumumab) will be prospectively screened for *MET* amplification using a cell free DNA assay (Guardant 360^{TM}). Patients with *MET* amplification will be enrolled and treated with savolitinib.

NOTE: There are two consent forms for this study. Patients will sign the Screening Consent Form prior to the Guardant 360. If *MET* amplification is detected in the Guardant 360, the patient will sign the Main Consent Form prior to screening for the study treatment portion of the study.

Treatment Plan

Study Drug Regimen: After satisfying eligibility and screening criteria, subjects will be treated with savolitinib on 28-day cycles. Treatment will continue until unacceptable drug-related toxicity or disease progression. Savolitinib dosing may be modified, suspended, or discontinued due to unacceptable treatment-related side effects.

Follow-Up: While on study treatment, subjects will be followed for progression every 2 cycles until documented progression, start of a new anti-cancer therapy, death, loss to follow-up, or study completion. Subjects who discontinue study treatment for any reason (e.g., toxicity) other than disease progression will be followed with tumor evaluations every 12 weeks until documented disease progression or start of a new anti-cancer therapy. Study completion is 2 years after the last subject starts study drug regimen.

Study Assessments

All subjects will complete an extensive medical history, physical examination and clinical assessment prior to starting study treatment to ensure subject eligibility requirement, during study treatment to monitor the efficacy and toxicity and safety, as well as during follow up period after discontinuation of the study treatment.

Toxicity and Safety Assessments: Toxicity will be assessed at every visit using NCI-CTCAE version 5.0. Safety assessments will be performed weekly during the first cycle, then every two weeks for 3 cycles, then monthly thereafter. Safety assessments will include vital signs, ECOG performance status, medical history, physical examination, review of concomitant medications, complete blood count (CBC), and chemistries with liver function tests. Symptom management and supportive care will be provided as clinically indicated to ensure optimal patient care. After discontinuation of study treatment, subjects will have safety assessments 30 days after the last dose of study drug.

Efficacy: Restaging scans and tumor markers will be repeated every two cycles while on protocol therapy. Tumor response will be assessed using Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1).

Correlatives Studies

Blood-based studies. Peripheral blood samples will be obtained at specified time points from all treated subjects. Blood- based correlative studies include the following:

- *Cell free tumor DNA (cfDNA)*. Plasma obtained at baseline, Cycle 1 Day 15, each restaging, and end of study treatment will be analyzed for mutations of interest.

- *Circulating protein studies*. Plasma obtained at baseline, Cycle 1 Day 15, each restaging, and end of study treatment will be analyzed for multiple soluble protein analytes.

- *Pharmacogenomics*. Whole blood obtained at baseline for pharmacogenomics.

Tumor tissue studies. Archival tumor tissue will be collected from all evaluable subjects. Tissue-based correlative studies include the following:

- *Tumor protein expression.* All tumors (archival) will be tested for c-MET expression by IHC and *MET* amplification by FISH.

- *Tumor mutation analysis.* Comprehensive mutational analysis will be performed on archived formalin fixed paraffin embedded (FFPE) tumor samples. This analysis will include Next Generation Sequencing and FISH for *MET* gene amplification.

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To estimate the objective response rate (ORR) of savolitinib in patients with *MET* amplified metastatic CRC.

1.2 Secondary Objectives

1.2.1 To describe the clinical activity (duration of response, progression free survival [PFS]) of savolitinib in patients with *MET* amplified metastatic CRC.

1.2.2 To describe the toxicities of savolitinib in patients with *MET* amplified metastatic CRC.

1.2.3 To explore the effect of *RAS* mutation status on response to savolitinib.

1.2.4 To explore any correlation between tissue and blood based biomarkers and clinical outcomes.

2. BACKGROUND

2.1 Colorectal Cancer

Colorectal cancer (CRC) is the second leading cause of cancer death in the United States [1]. Approximately half of all patients with metastatic CRC have *KRAS* or *NRAS* (*RAS*) wild-type tumors [2], and these patients are eligible to receive the epidermal growth factor receptor (EGFR) monoclonal antibodies panitumumab or cetuximab. To further improve the benefit of anti-EGFR therapies, efforts are needed to better understand and treat the molecular drivers of acquired resistance. This study will prospectively identify and treat patients whose tumors harbor *MET* gene amplification – an important driver of acquired EGFR resistance.

2.2 Savolitinib

AZD6094 (also known as HMPL-504, volitinib [Chinese accepted name] and savolitinib [international non-proprietary name]) is a potent and selective small molecule MET kinase inhibitor with significant antitumour activity. Savolitinib is active against *MET* amplified gastrointestinal malignancies, and is well tolerated [3]. The maximum tolerated dose (MTD) of the once-daily dosing is 800 mg. The most common adverse events are constipation, diarrhea, fatigue, nausea, vomiting, dizziness and peripheral edema, but these adverse events are usually mild to moderate in severity (grades 1 or 2). To maximize efficacy and tolerability, current monotherapy and combination clinical trials are using a dose of 600mg for weight ≥ 55 kg and 300 mg if weight < 55kg [4-6] (www.clinicaltrials.gov).

Non-clinical Information
The nonclinical safety of AZD6094 has been evaluated in general toxicology studies in rats and dogs. Maximum tolerated doses have been explored and target organs/tissues for toxicity

identified. In repeat-dose oral studies, a key target for toxicity was the lymphoreticular system. Decreased cellularity was observed in various tissues, including lymph nodes, thymus, spleen and Peyer's patches. There were also various changes in the GI tract in both species, including stomach erosions in rats and oral ulceration in dogs, and effects on the kidney and urinary tract in rats.

After dosing for 4 weeks, in addition to GI tract and lymphoreticular effects, there were findings in the heart, liver, thyroid, adrenals, eyes, prostate and female reproductive tract. All toxicities had recovered 28 days after the cessation of dosing with the exception of eye changes in dogs, and stomach epithelial hyperplasia, hepatocyte hypertrophy and thyroid follicular cell hypertrophy in rats, where low-grade effects were noted.

After dosing for 13 weeks, in addition to GI and lymphoreticular effects, there were findings in the liver and adrenals. In rats only, there were findings in the thyroid gland, kidney, urinary bladder, urinary tract and heart. In dogs, there was evidence of testicular toxicity.
In rats, there was evidence of reproductive toxicity, including adverse effects on embryofoetal survival and development.

In safety pharmacology studies, there were no noteworthy effects on cardiovascular, neurobehavioral or respiratory parameters. Some transient increases in heart rate were noted following repeated dosing in dogs.

AZD6094 was not genotoxic in vitro or in vivo.

In vitro data suggest a potential for phototoxicity. A tissue distribution study in the rat showed distribution of AZD6094 was limited, though there was evidence of distribution to the skin.

<u>Efficacy</u>
Efficacy data are based on data from completed studies at a data cut-off date of 27 February 2017.

- In Study D5081C00001, there were 48 patients in the All Subjects population, and of these, 3 patients experienced a partial response. Hence the best overall response rate (ORR) (either complete response or partial response) for all patients overall was 6.3% (95% confidence interval [CI] 1.3%, 17.2%). All 3 responders were PRCC patients with Stage IV disease.

- In Study D5082C00002, the Phase II study of PRCC, 8 of 109 patients dosed with AZD6094 have experienced partial responses. In the safety analysis population, 8 of 44 (18.2%) c-MET positive patients achieved a partial response. All of the responders had a local pathology report showing PRCC, although central laboratory review was hampered by small amounts of tumour tissue on occasion. Thirty-eight (34.9%) patients in the safety analysis maintained stable disease ≥5 weeks.

In summary, AZD6094 has shown promising efficacy in patients with tumour MET alterations.

Pharmacokinetics and Drug metabolism in Humans

The PK in humans has been studied, following dosing of AZD6094 in the fed state, in the dose escalation phase of Study D5081C00001 and Study D5081C00002. Both QD and BID dosing have been investigated across a dose range of 100 mg to 1200 mg (total dose). In addition, preliminary unvalidated PK data from D5082C00002 (600 mg QD; patients in the fed state) is available.

In general, AZD6094 is rapidly absorbed with a relatively short tmax. Maximum plasma concentration and AUC appear to show dose proportionality across the dose ranges investigated. The apparent t½ is short and as a result there is no accumulation of AZD6094 after QD or BID dosing. Interpatient variability is moderate-to-high with a CV of over 30%. Two metabolites (M2 and M3), thought to be major metabolites in humans based on nonclinical and in vitro work, have also been characterised. Both metabolites are rapidly formed and have short half-lives similar to that of the parent. Both metabolites appear to have a constant parent:metabolite ratio independent of dose.

The food effect study showed a small but statistically significant difference between the PK after dosing in the fed compared to the fasted state. Due to the higher AE incidence following dosing in the fasted state, it is recommended that all patients should take AZD6094 in the fed state.

Safety

As of the data cut-off date (27 February 2017), 4 clinical studies had completed and 4 were ongoing; all completed and ongoing studies at the time of the data cut-off are open label studies. Safety data were available for 245 patients who received monotherapy AZD6094 (in Studies D5081C00001, D5081C00002, D5160C00006C or D5082C00002). In addition, data are presented from 124 patients who received combination therapy in Studies D5081C00003, D5080C00001, D5160C00006 and D5160C0006B, and 25 healthy volunteers who received a single dose of AZD6094 in the completed food-effect study (Study D5081C00004). The food-effect study is not included in the pooled data and is summarised in Investigator's Brochure.

The majority of patients receiving monotherapy AZD6094 had at least 1 AE (237/245 patients [96.7%]), and most patients (211/245 [86.1%]) had an AE that was considered by the Investigator to be causally related to AZD6094 treatment. A total of 126/245 patients (51.4%) had an AE of CTCAE Grade ≥3. A total of 30.6% patients (75/245) had SAEs and 13.9% patients (34/245) had a causally related SAE. There were 6 patients who died, but there are 7 AEs leading to death, as 1 patient had 2 AEs with a fatal outcome. Forty-five patients (18.4%) had an AE that resulted in discontinuation from treatment.

The majority of patients receiving AZD6094 in combination had at least 1 AE (118/124 patients, 95.2%). A total of 100/124 patients (80.6%) had an AE that was considered by the Investigator to be related to treatment. Forty-two patients (33.9%) had SAEs and 17 patients (13.7%) had a treatment related SAE. Nine patients (7.3%) had an AE resulting in death, and 1 patient (0.8%) had a fatal AE that was considered to be related to AZD6094 treatment by the

Investigator. Twenty-one patients (16.9%) had an AE that resulted in discontinuation from treatment.

2.3 Rationale

The receptor tyrosine kinase c-MET (mesenchymal-epithelial transition factor) is associated with tumor cell invasiveness, metastasis, proliferation, and treatment resistance. In patients with treatment-naive CRC, *MET* amplification is rare, occurring in less than 3% of tumors [7-9]. On the other hand, several studies indicate that *MET* amplification increases under the selective pressure of anti-EGFR therapy [10-14]. As a result, tumor profiling studies performed on primary tumors underestimate the prevalence of *MET* amplification in the treatment refractory setting, where *MET* amplification may not only be more common, but also more biologically and clinically relevant.

Functional crosstalk between c-MET and EGFR provides compensatory signal transduction, leading downstream MAPK and PI3K pathway activation in the presence of upstream EGFR blockade [15]. *MET* amplification emerged in post-treatment tumor biopsies in 3 out of 7 patients with metastatic CRC who developed acquired resistance to anti-EGFR antibody. Furthermore, *MET*-amplified CRC tumors did not respond to cetuximab treatment in mouse xenograft model, suggesting MET amplification is associated with resistance to anti-EGFR therapy in patients with metastatic CRC [14].

Access to treatment-refractory tumor tissue is a significant barrier to the identification of acquired *MET* amplification. Technology now exists to identify patients with *MET* amplified tumors from a routine blood draw. In several studies assessing simultaneously obtained "liquid" and tissue biopsies, concordance between mutation profiles approached 90% [16-19]. For patients with metastatic CRC, a peripheral blood draw for acquired mutations may be particularly valuable. In a case series of 56 patients with *KRAS* wild-type/ *MET* non-amplified tumors treated with anti-EGFR therapy, 14% of patients had acquired *MET* amplification in peripheral blood upon progression [13]. Fifty percent (50%) of these patients with acquired *MET* amplification also had acquired *KRAS* or *NRAS* (*RAS*) co-mutations. These results have been reproduced in an ongoing clinical trial of cabozantinib plus panitumumab (NCT02008383). Among the first 64 patients with EGFR-refractory metastatic CRC receiving blood-based genomic profiling, 11 patients (17%) had *MET* amplified tumors [20]. Concurrent *BRAF* and/or *RAS* somatic mutations were detected in 5 out of these 11 patients. These results illustrate the genomic complexity of acquired resistance.

MET inhibitors have significant single-agent activity against *MET* amplified advanced solid tumors. In a case series of 6 patients with *MET* amplified, treatment refractory non-small cell lung cancer (NSCLC), the c-MET inhibitor crizotinib had an ORR of 67% [21]. This included 3 patients with a partial response, and 1 patient with a complete response. The median duration of response was 1.4 years. In addition, several selective MET inhibitors have monotherapy response rates exceeding 50%, including ABT-700 [21], SAR125844 [23], and AMG337 [24]. In patient-derived tumor xenograft models, savolitinib has demonstrated anti-tumor efficacy in *MET* amplified gastric cancer [25] and papillary renal cell carcinoma [26]. More recently, in a phase 2 trial of savolitinib in patients with advanced papillary renal cell carcinoma (pRCC), MET

activation was strongly associated with response [5]. In a subgroup analysis, eight patients (18%) with MET-driven pRCC had partial response to savolitinib treatment, whereas none of the patients with MET-independent pRCC had a response. The median PFS for patients with MET-driven pRCC was 6.2 months, significantly higher than that for patients with MET-independent pRCC (1.4 months).

The activity of MET inhibitors in anti-EGFR antibody refractory metastatic CRC has been demonstrated in preclinical and clinical studies. In mice engrafted with a CRC tumor that was anti-EGFR antibody refractory, tumor growth was inhibited by treatment with a MET tyrosine kinase inhibitor [14]. Similarly, tumor regression was seen with MET inhibitor in a CRC xenograft mouse model genetically engineered to overexpress human HGF [27]. Although the clinical activity of *MET* inhibitors in patients with *MET* amplified CRC is not well established, a recent case report suggests clinical activity [28]. In this report, a patient with *RAS* wild-type metastatic CRC who experienced disease progression on chemotherapy and panitumumab was enrolled in a clinical trial evaluating the combination of the c-MET inhibitor cabozantinib plus panitumumab. The patient experienced a significant response . Although tissue was negative for *MET* amplification, cfDNA revealed *MET* amplification. This case suggests that *MET* amplification in cfDNA may predict sensitivity to MET inhibitors in patients with *MET* amplified metastatic CRC.

This trial will evaluate the clinical activity and tolerability of savolitinib, an oral, potent and selective c-MET inhibitor, in patients with *MET* amplified metastatic CRC. Additionally, this study will include tissue and blood-based correlative studies to better understand biomarkers of sensitivity and resistance.

2.4 Correlative Studies Background

2.4.1 **Cell free DNA (cfDNA)**. Plasma obtained at baseline, each restaging, and end of study treatment will be analyzed for the presence of mutations and amplifications of genes of interest. Mutations of interest include *KRAS* and *NRAS* exons 2, 3, and 4, *BRAF*, *PIK3CA*, *EGFR*, *AKT*, *PTEN*, and *MET*. Amplifications of interest include *MET*, *EGFR*, and *ERBB2*. The allele frequency and copy number of these mutations and amplifications will be followed until progression (or end of study treatment). These analyses will help to characterize genomic contributions to treatment outcome and analyze genomic changes over time on treatment.

2.4.2 **Circulating protein studies**. Plasma obtained at baseline, each restaging, and end of study treatment will be analyzed for multiple soluble protein analytes, including (but not limited to) HGF, c-MET, EGF, HBEGF, TGF-α, EGFR, VEGFA-D, HER2, HER3, GAS6, and AXL. Additional biomarkers may also be explored using multiplex array technology. The results will help to characterize the relationship between soluble protein analyte expression and response to treatment. This analysis will also explore the association between soluble protein c-MET expression and gene amplification in tumor tissue.

2.4.3 **c-MET expression and *MET* amplification in tumor tissue**. Archival tumor tissue will be analyzed by IHC and FISH to assess c-MET protein expression and *MET* gene amplification in tumor tissue. The results will help to explore the association between c-MET protein expression and amplification, the association between soluble c-MET expression in whole blood and c-MET protein expression in tumor tissue, as well as the association between *MET* gene amplification in cfDNA and amplification in tumor tissue.

2.4.4 **Comprehensive mutational analysis in tumor tissue.** Archival tumor tissue will be analyzed by Next Generation Sequencing (NGS) to characterize genomic alterations, including *MET* gene amplification, in tumor tissue. These results will help to explore the contribution of these alterations to treatment outcome and prognosis.

3. PATIENT SELECTION

3.1 Inclusion Criteria

3.1.1 Histologically or cytologically confirmed adenocarcinoma of the colon or rectum that is metastatic and/or unresectable.

3.1.2 Documented wild-type in *KRAS* and *NRAS* (codons 12, 13, 59, 61, 117, and 146) and in BRAF codon 600, based on tumor tissue taken from primary or metastatic site prior to anti-EGFR antibody treatment.

3.1.3 At least one site of disease that is measurable by RECIST criteria as defined in Section 11.1.2.

3.1.4 *MET* amplification detected by the Guardant360 cfDNA screening assay (*MET* copy number ≥ 2.2).

3.1.5 Clinical or radiographic progression on treatments containing a fluoropyrimidine (e.g., 5- fluorouracil or capecitabine), oxaliplatin, irinotecan, an anti-VEGF monoclonal antibody (bevacizumab, ziv-aflibercept) or anti-VEGFR monoclonal antibody (ramucirumab), and an anti-PD1 monoclonal antibody (nivolumab or pembrolizumab) for patients with MSI-high/MMR deficient tumors, or the treatments were not tolerated or contraindicated.

3.1.6 Clinical or radiographic progression on prior anti-EGFR antibody therapy (either panitumumab or cetuximab).

3.1.7 Age ≥18 years.

3.1.8 ECOG performance status 0-1 (Karnofsky ≥80%, see Appendix A).

3.1.9 Adequate hematological function defined as:
- Absolute neutrophil count (ANC) ≥1,500/mcL
- Hemoglobin (Hgb) ≥9 g/dL (no transfusion in the past 2 weeks)
- Platelets ≥100,000/mcL (no transfusion in the past 10 days)

3.1.10 Adequate liver function defined as:
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x the institutional upper limit of normal (ULN) with total bilirubin (TBL) ≤1 x ULN
OR
- Total bilirubin (TBL) >ULN ≤1.5 × ULN with ALT and AST ≤ 1x ULN

3.1.11 Adequate renal function defined as:
- GFR ≥60 mL/min/1.73m2 unless data exists supporting safe use at lower kidney function values, no lower than 30 mL/min/1.73m2

3.1.12 Adequate coagulation parameters, defined as:
- International Normalization Ratio (INR) <1.5 x ULN and activated partial thromboplastin time (aPTT) <1.5 x ULN unless patients are receiving therapeutic anticoagulation which affects these parameters

3.1.13 Females of childbearing potential should be willing to use adequate contraceptive measures (see Section 5.2.2), should not be breast feeding, and must have a negative pregnancy test if of childbearing potential or must have evidence of non-childbearing potential by fulfilling one of the following criteria at screening:
- post-menopausal is defined as aged more than 50 years and amenorrheic for at least 12 months following cessation of all exogenous hormonal treatments; women under the age of 50 years would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range for the institution; or women with documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.

3.1.14 Male patients with female partner of childbearing potential should be willing to use barrier contraception during the study and for 6 months following discontinuation of study drug.

3.1.15 Ability to swallow and retain oral medications.

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

3.2 Exclusion Criteria

3.2.1 Cytotoxic chemotherapy (including investigational cytotoxic chemotherapy) or biologic agents (eg. Cytokines or antibodies) within 3 weeks of first dose of study treatment.

3.2.2 Not recovered to baseline or CTCAE ≤ Grade 1 from adverse events due to all prior anti-cancer therapies except alopecia, oxaliplatin-related neuropathy, and other non-clinically significant adverse events.

3.2.3 Any other investigational agents within 21 days before the first dose of study treatment.

3.2.4 Wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) administered ≤28 days or limited field radiation for palliation ≤7 days prior to starting study drug or has not recovered from side effects of such therapy.

3.2.5 Known brain metastases. (Radiated or resected lesions are permitted, provided the lesions are fully treated and inactive, patient is asymptomatic, and no steroids have been administered for at least 30 days).

3.2.6 History of allergic reactions attributed to compounds of similar chemical or biologic composition to savolitinib.

3.2.7 Prior treatment with a small molecule inhibitor of c-MET or monoclonal antibody against c-MET or HGF.

3.2.8 Any of the following concurrent medication use:

a. Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (dhea), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug (three weeks for St. John's wort).
b. Patients receiving or requiring strong inducers or strong inhibitors of CYP3A4, strong inhibitors of CYP1A2, or CYP3A4 substrates which have a narrow therapeutic range within 2 weeks of the first dose of study treatment (3 weeks for st john's wort) will be excluded.
c. Concomitant use of drugs that are known to be strong inhibitors of CYP3A4 or CYP1A2 is not permitted during the trial or must be stopped at least 2 weeks prior to receiving the first dose of savolitinib.

3.2.9 Any of the following cardiac disease currently or within the last 6 months:

a. Unstable angina pectoris
b. Congestive heart failure (New York Heart Association (NYHA) ≥ Grade II; See Appendix D for details of NYHA grading system)
c. Acute myocardial infarction
d. Stroke or transient ischemic attack

3.2.10 Known hypersensitivity to the active or inactive excipients of AZD6094.

3.2.11 Uncontrolled hypertension (BP ≥150/95 mmHg despite medical therapy)

3.2.12 Active gastrointestinal disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of oral therapy (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea Grade ≥2, and malabsorption syndrome).

3.2.13 Mean resting correct QT interval (QTcF) >470 msec for women and >450 msec for men on screening obtained from 3 electrocardiograms (ECGs).

3.2.14 Any factors that may increase the risk of QTc prolongation such as chronic hypokalaemia not correctable with supplements, congenital or familial long QT syndrome; or family history of unexplained sudden death under 40 years of age in first-degree relatives or any concomitant medications known to prolong QT interval and cause Torsade de Pointes (TdP).

3.2.15 Any clinically important abnormalities in rhythm, conduction or morphology of resting electrocardiograms (ECGs), e.g. complete left bundle branch block, third degree heart block, second degree heart block, PR interval >250 msec.

3.2.16 Major surgical procedures ≤28 days of beginning study drug or minor surgical procedures ≤7 days. No waiting is required following port-a-cath placement.

3.2.17 Serious underlying medical condition at the time of treatment that would impair the ability of the patient to receive protocol treatment.

3.2.18 Active hepatitis B (positive HBV surface antigen (HBsAg) result) or hepatitis C (HCV) infection. Patients with positive HCV antibody are eligible only if the polymerase chain reaction is negative for HCV RNA. Patients with a past or resolved HBV infection are eligible if:

- negative for HBsAg and positive for hepatitis B core antibody [anti-HBc]
  OR
- positive for HBsAg, but for > 6 months have had normal transaminases and HBV DNA levels between 0 – 2000 IU/ml (inactive carrier state) and willing to start and maintain antiviral treatment for at least the duration of the study
  OR
- HBV DNA levels >2000 IU/ml but on prophylactic antiviral treatment for the past 3 months and will maintain the antiviral treatment during the study

3.2.19 Known serious active infection requiring antibiotic, antiviral or antifungal therapy. HIV-positive patients are eligible only if meeting ALL criteria below:

- No history of AIDS-defining conditions
- Has been on the current HARRT regimen for the past 3 months and will remain on the same regimen during the study
- Current HARRT regimen has a low potential for drug-drug interaction with the study drug
- HIV viral load consistently below detectable limit for the past 3 months

– CD4 count consistently >200 cells/mm3 for the past 3 months

3.2.20 Presence of other active cancers, or history of treatment for invasive cancer, within the last 5 years. Patients with Stage I cancer who have received definitive local treatment at least 3 years previously, and are considered unlikely (less than 5% probability) to recur are eligible. All patients with previously treated in situ carcinoma (i.e., non-invasive) are eligible, as are patients with history of non-melanoma skin cancer.

3.2.21 Psychiatric illness/social situations that would limit compliance with study requirements. Patients with impaired decision-making capacity who have a close caregiver or legal guardian are also eligible with the consent of the caregiver/guardian.

3.2.22 Judgment by the investigator that the patients should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.

3.3 Inclusion of Women and Minorities

Men and women of all races and ethnic groups are eligible for this study.

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research.

Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require IND sponsors to select qualified investigators. NCI policy requires all persons participating in any NCI-sponsored clinical trial to register and renew their registration annually. To register, all individuals must obtain a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN or RAVE or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	**IVR**	**NPIVR**	**AP**	**A**
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov

4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the **10181** protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP-IAM username and password.
- Click on the Protocols tab in the upper left of your screen.
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, then select **LAO-NC010**, and protocol #**10181**.
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

4.2.2 Requirements For 10181 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- Site Initiation Meeting (SIM) by the Study Chair/Lead Principal Investigator (Prior to the start of subject enrollment, participating sites must contact Duke Cancer Institute LAO by emailing ETCTN-LAO-NC010@dm.duke.edu to schedule a SIM. In cooperation with the participating site, Duke Cancer Institute LAO will arrange a web conference meeting. Once the SIM is completed, Duke Cancer Institute LAO will notify the CTSU of participating site's training fulfillment.)

- ETCTN Specimen Tracking Training
  - At least one individual at each participating site will need to complete the Theradex-led training.
  - Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal.
  - The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU.
  - This training will need to be completed before first/further patient enrollment at a given site
  - Peter Clark is the main point of contact at Theradex for the training (802-456-8735, PClark@theradex.com). Nafeesa Sarakhawas is the backup contact (609.480.2693, NSarakhawas@theradex.com).

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission

When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

4.2.4 Checking **Site** Registration Status

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

NOTE: There are two consent forms for this study. Patients will sign the Screening Consent Form prior to the Guardant360 test. If *MET* amplification is detected from the Guardant360 test, the patient will sign the Main Consent Form prior to screening for the study treatment portion of the study.

4.3.1 OPEN / IWRS

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster data interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in OPEN / IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

4.3.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
- To enroll patients or request slot reservations: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- To approve slot reservations or access cohort management: Be identified to Theradex as the "Client Admin" for the study.
- Have regulatory approval for the conduct of the study at their site.

Prior to accessing OPEN/IWRS, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- If applicable, all patients have signed an appropriate consent form and HIPAA authorization form.

4.3.3 Special Instructions for Patient Enrollment

The following information will be requested:

- Protocol Number
- Investigator Identification
    - Institution and affiliate name

  - Investigator's name
- Eligibility Verification: Patients must meet all the eligibility requirements listed in Section *3.1*.
- Additional Requirements:
  - Patients must provide a signed and dated, written informed consent form.

Upon enrolling a patient, IWRS will communicate with OPEN, assigning two separate and unique identification numbers to the patient, a Universal patient ID (UPID) and a Treatment patient ID. The UPID is associated with the patient and used each and every time the patient engages with the ETCTN Biobanking and Molecular Characterization portion of this protocol. The UPID contains no information or link to the treatment protocol. IWRS will maintain an association between the UPID for ETCTN biobanking and molecular characterization and any treatment protocols the patient participates in, thereby allowing analysis of the molecular characterization results with the clinical data.

Immediately following enrollment, the institutional anatomical pathology report for the diagnosis under which the patient is being enrolled must be uploaded into Rave. The report must include the surgical pathology ID (SPID) and the IWRS-assigned UPID for this trial. **Important: Remove any personally identifying information, including, but not limited to, the patient's name, initials, and patient ID# for this treatment trial, from the institutional pathology report prior to submission.**

4.3.4 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

5. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Savolitinib	N/A	600 mg once daily for weight	Orally	Days 1-28	28 days (4 weeks)

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
		≥ 50 kg and 400 mg once daily if weight < 50kg once daily			

Savolitinib must be taken with food. Tablet must be swallowed whole with water. Savolitinib dosing may be modified, suspended or discontinued due to unacceptable treatment-related side effects. The patient will be requested to maintain a medication diary of each dose of medication to assess compliance with treatment. Appendix B (Patient Drug Diary Card) should be provided to patients at each cycle. The medication diary will be returned to clinic staff at the end of each course.

5.2 General Concomitant Medication and Supportive Care Guidelines

Studies indicate that savolitinib has little induction potential for major CYP isoforms. Because there is a potential for interaction of savolitinib with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. Regulator guidelines suggested that the exposure to medications whose disposition is dependent on CYPs 2C8, 3A4/5, P-gp may be increased when co-administered with savolitinib. The likelihood of a clinically meaningful drug-drug interaction with savolitinib substrates whose disposition is depended on drug transporters BCRP, OATPIB1, MATE1 and MATE2-K cannot be discounted. The potential of savolitinib to inhibit the metabolism of substrates of UGT1A1 cannot be ruled out but is considered unlikely. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix C (Patient Drug Information Handout and Wallet Card) should be provided to patients if available.

5.2.1 Concomitant Medications

Statins
Discontinuation of statins is advised unless considered essential, in which case, the patients should be prescribed the lowest dose available and monitored for the effects of increased statin exposure.

Acetaminophen (paracetamol)
The administration of acetaminophen (paracetamol) to a patient is restricted to 3 grams per day or the maximum dose approved locally (if less than 3 gm/day) during the study.

Metformin
Metformin should be used with caution and patients monitored for the effect of increased metformin exposure.

Antivirals
Adefovir, lamivudine and tenofovir should be used with caution and patients monitored for the effects of increased exposure.

Other Medication Restrictions
Discontinuation of strong inducers of CYP3A4 and CYP3A4 substrates which have a narrow therapeutic range or CYP3A4 sensitive is advised unless considered essential by the investigator, in which case patients must be monitored closely for potentially reduced efficacy or increased toxicity due to drug-drug interactions.

Those drugs defined as strong CYP2C8 substrates (almost exclusively metabolised by CYP2C8, such as repaglinide and rosiglitazone) should be used with caution.

Drugs that are known to be affected by P-gp such as digoxin, quinidine, loperamide, ritonavir and saquinavir should be used with caution.

Drugs that prolong QT interval
The concomitant administration of drugs known to prolong QT interval is restricted unless considered essential due to patient management, in which case, patients should be closely monitored with frequent ECGs. Additional guidance on drugs known to prolong QT interval is provided in the protocol appendix "GUIDANCE REGARDING POTENTIAL INTERACTIONS WITH CONCOMITANT MEDICATIONS KNOWN TO PROLONG QT INTERVAL."

5.2.2 Pregnancy and Contraception

Females of childbearing potential must agree to use two medically acceptable contraceptive methods from the time of screening until 4 weeks after last dose of study drug. One contraceptive method must be a barrier method. Medically acceptable contraceptives include: (1) surgical sterilization (such as a tubal ligation or hysterectomy), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Female condoms and male condoms should never be used at the same time. Contraceptive measures such as Plan BTM, sold for emergency use after unprotected sex, are not acceptable methods for routine use.

Male patients sexually active with a female partner of childbearing potential must agree to use two medically acceptable forms of birth control, one of which is a barrier method, at the same time in order to be in this study and until 6 months after the last dose of study drug. Medically acceptable contraceptives include: (1) surgical sterilization (such as a vasectomy), or (2) a condom used with a spermicide. Acceptable contraceptive methods for women include: (1) surgical sterilization (such as a tubal ligation or hysterectomy), (2) approved hormonal

contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Female condoms and male condoms should never be used at the same time. Contraceptive measures such as Plan B ™, sold for emergency use after unprotected sex, are not acceptable methods for routine use.

Male patients should refrain from donating sperm from the start of dosing until 6 months after discontinuing study treatment.

5.2.3 Food Restrictions

Patients should abstain from eating large amounts of grapefruit and seville oranges (and other products containing these fruits eg, grapefruit juice or marmalade) during the study (e.g., no more than a small glass of grapefruit juice (120 ml) or half a grapefruit or 1-2 teaspoons (15g) of seville orange marmalade daily).

5.2.4 UV Exposure

During savolitinib therapy and for 4 weeks after the last dose patients should be advised to avoid prolonged exposure to the sun, wear protective clothing, a hat and seek shade from the sun as far as possible; in addition SPF30+ sunscreen should be used. Exposure to other sources of UV light including sun beds and tanning booths, etc. should be avoided.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Radiographic disease progression as defined by RECIST criteria.
- Clinical disease progression indicated by worsening signs and symptoms related to disease with or without radiographic disease progression.
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Patient non-compliance
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

- The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.

- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

5.4 Duration of Follow Up

Patients who discontinue study treatment for any reason (e.g. toxicity) other than disease progression will be followed until disease progression, or start of a new anti-cancer therapy, or until death, loss to follow-up, or study completion, whichever occurs first. Study completion is 2 years after the last subject starts study treatment.

6. DOSING DELAYS/DOSE MODIFICATIONS

Substantial acute toxicities should be managed as medically indicated and with temporary suspension of study drug, as appropriate.

Dose reductions or holds are allowed as clinically indicated by the treating physician and in line with Table 1. For each patient, a maximum of 2 dose reductions will be allowed unless the patient has started at 400 mg savolitinib due to weight < 50 kg, where only one dose reduction is allowed. No dose re-escalations are allowed. Guidance on dose level reduction is presented in the table below.

Table 1 Savolitinib dose level modification

Dose Level	**Savolitinib Daily Dose**	
Starting	*600 mg QD (weight ≥ 50 kg)*	*400 mg QD (weight < 50kg)*
-1	*400 mg QD*	*200 mg QD*
-2	*200 mg QD*	

Below are dose modification guidance for hepatic and non-hepatic drug-related toxicities. Please use as appropriate. If a patient experiences several adverse events and there are conflicting recommendations, the investigator should use the recommended dose adjustment that reduces the dose to the lowest level.

6.1 Hepatic Toxicities

Promptly evaluate patients with elevated LFTs during study treatment for alternative etiologies and potential Hy's law criteria, and discontinue potential contributing concomitant medications or alternative causal agents, as well as anti-coagulants, if appropriate.

If a patient discontinues due to LFT abnormality, LFT monitoring should continue until resolved to grade 1 or baseline or an apparent plateau has been reached.

Paracetamol/acetaminophen dose should not exceed 3 g per day or the maximum dose approved locally (if this was less than 3 g/day) during the study.

Investigators should review the patient's current concomitant medications and evaluate the need for the patient to continue on hepatic metabolism modifying agents, such as statins.

Follow the general guidance below for dose interruptions/reductions:

Dose modifications for hepatic study drug-related toxicities
· **Discontinue drug if** - ALT or AST >8xULN, or - ALT or AST >5xULN for >2 weeks, or - ALT or AST >3xULN and (TB >2xULN or INR >1.5 if not on anticoagulants that elevate the INR) - AST or ALT >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia >5% · **Withhold dosing if ALT or AST >5-8xULN without TB elevation above baseline or ULN, repeat LFT testing twice a week for 1 week;** - If improved to Grade 1 or baseline in 1 week, resume at reduced dose with LFT testing twice a week for 6 weeks; - If not, discontinue · **Withhold dosing if ALT or AST >3xULN and concurrent TB 1.5~2xULN, repeat LFT testing twice a week for 1 week,** - If both ALT/AST and TB improved to Grade 1 or baseline in 1 week, resume at reduced dose with LFT testing twice a week for 6 weeks - If not, discontinue · **Continue dosing if ALT or AST >3-5xULN without TB elevation above baseline or ULN, repeat LFT testing every week** - If ALT or AST trending upward, withhold dosing and repeat LFT twice a week for 1 week; - If improve to Grade 1 or baseline in 1 week, resume at same dose with LFT testing every week for 6 weeks - If improve to Grade 1 or baseline in 2 weeks, resume at reduced dose with LFT testing every week for 6 weeks - If not, discontinue · **Discontinue for recurrent ALT or AST >5xULN** · **Discontinue for recurrent ALT or AST >3-5xULN and TB >1.5~2xULN** · **Withhold dosing for recurrent ALT or AST >3-5xULN without TB elevation above baseline or ULN, repeat LFT testing twice a week for 1 week** - if improve to grade 1 or baseline in 1 week, resume at reduced dose with LFT testing every week for 6 weeks; if not, discontinue

6.2 Non-hepatic Toxicities

Dose modification guidelines for non-hepatic study drug-related toxicities are shown below. Appropriate and optimal treatment of the toxicity is assumed prior to considering dose modifications. Prior to discontinuation of study drug due to toxicities please consult with the study physician.

Dose modifications for non-hepatic study drug-related toxicities	
NCI CTCAE v5.0 Toxicity Grade	**Action**
Grade 0, 1, or 2	Hold dosing or reduce dose following algorithm below for persistent and/or intolerable grade 2 toxicities.
Grade 3 [a] · Grade 3 toxicity for ≤7 days and resolves to ≤Grade 1 or baseline · Grade 3 toxicity for >7 days	Hold dosing and follow algorithm below · Resume dosing at one reduced dose level (maximum of 2 dose reductions unless the patient has started at 400 mg savolitinib due to weight < 50 kg, where only one dose reduction is allowed) · Discontinue study drug
Grade 4 · Expected to be manageable/reversible with dose reduction · Not expected to be manageable/reversible with dose reduction	· Hold dose and consult with study medical monitor · Discontinue study drug
Recurrence of Grade 3 · Grade 3 toxicity for ≤7 days and resolves to ≤Grade 1 or baseline · Grade 3 toxicity for >7 days	· Resume dosing at one reduced dose level (maximum of 2 dose reductions maximum of 2 dose reductions unless the patient has started at 400 mg savolitinib due to weight < 50 kg, where only one dose reduction is allowed) · Discontinue study drug
Recurrence of Grade 4	Discontinue study drug

No more than 2 dose reductions will be allowed for any patient. Patients requiring additional dose modifications due to toxicity will discontinue study treatment.

[a] *Despite appropriate supportive care*

CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute

Dermatologic

A case of Stevens-Johnson syndrome (SJS) has been reported in temporal association with savolitinib. Patients who show symptoms or signs suggesting emerging Stevens-Johnson syndrome (SJS) while on study treatment (e.g., progressive skin rash often with blisters or mucosal lesions), must discontinue savolitinib immediately and receive appropriate treatment. If emerging SJS is suspected, re-challenge with savolitinib must be avoided.

Hypersensitivity
Hypersensitivity, which may manifest as drug eruption, hypotension or myalgia has been reported after savolitinib dosing. Patients who show symptoms of suspected savolitinib related hypersensitivity must follow the dose modifications for non-hepatic study drug-related toxicities. Dosing with savolitinib can resume only after consultation with the study physician.

Pyrexia
If fever occurs savolitinib must be interrupted until etiology is established after thorough investigation. In cases where fever is considered causally related to savolitinib, then savolitinib must be discontinued.

Nausea/Vomiting
If vomiting occurs after taking savolitinib, the patient should be instructed not to retake the dose. Patients should take the next scheduled dose of savolitinib. Patient reports of nausea and vomiting are expected to be evaluated and treated by investigators according to local practice (eg, use of antiemetic therapy, intravenous fluid replacement).

Peripheral edema/Edema
Treatment interruption may be considered. Diuretic therapy should be considered at the discretion of the Investigator. Renal function should be carefully monitored.

Fatigue
Follow the general guidance in table titled, *Dose modifications for non-hepatic study drug-related toxicities*, in Section 6.2 the protocol for dose interruptions/reductions/discontinuations in response to this AE.

QTc prolongation
If there is a marked prolongation of the QT/QTcF interval, QT/QTcF >500 msec or of >60 msec over baseline, during treatment with savolitinib, the patient must hold dosing and must be evaluated by a cardiologist to validate ECG finding and determine further management as clinically indicated.

Dose modifications for savolitinib-related QTc prolongation	
NCI CTCAE Toxicity Grade	**Action**
Grade 0, 1, or 2	None
Grade 3	Hold dosing and follow algorithm below

Dose modifications for savolitinib-related QTc prolongation	
NCI CTCAE Toxicity Grade	**Action**
○ Patients with QTcF prolongation to >500 msec on at least two separate ECGs	○ Consult with cardiologist to validate ECG finding. Ensure cardiac surveillance and take actions in accordance with clinical standards. Regular ECGs performed until resolution to QTcF <481 msec. Restart drug at one reduced dose level
○ If the toxicity does not resolve to QTcF < 481msec within 21 days	○ Discontinue study drug and consult with a cardiologist to validate ECG finding and management as clinically indicated
Grade 4	
○ QTcF >= 501 or >60 msec change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	○ Discontinue study drug and consult with a cardiologist for further management as clinically indicated

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Sections 7.2 and 7.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 381 patients.* Below is the CAEPR for Savolitinib (AZD6094).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, April 2, 2020[1]

Adverse Events with Possible Relationship to Savolitinib (AZD6094) (CTCAE 5.0 Term) [n= 381]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Edema limbs			***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (hepatotoxicity)[2]		
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	Blood bilirubin increased		
	Creatinine increased		
		Electrocardiogram QT corrected interval prolonged	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Hypoalbuminemia		***Hypoalbuminemia (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Stevens-Johnson syndrome	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Hepatoxicity may manifest as increased liver enzymes (e.g., Alanine aminotransferase increased, Aspartate aminotransferase increased, Alkaline phosphatase increased, Blood bilirubin increased), hepatic function abnormal, and drug-induced liver injury (DILI).

Adverse events reported on savolitinib (AZD6094) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that savolitinib (AZD6094) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Disseminated intravascular coagulation; Febrile neutropenia
CARDIAC DISORDERS - Heart failure
ENDOCRINE DISORDERS - Adrenal insufficiency
EYE DISORDERS - Blurred vision; Eye disorders - Other (diplopia)
GASTROINTESTINAL DISORDERS - Abdominal pain; Ascites; Dyspepsia; Gastritis; Gastrointestinal disorders - Other (abdominal incarcerated hernia); Gastrointestinal disorders - Other (GI [anastomotic] perforation); Ileus; Mucositis oral; Small intestinal obstruction; Upper gastrointestinal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Edema face; Generalized edema; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatic pain; Hepatobiliary disorders - Other (hepatic encephalopathy); Hepatobiliary disorders - Other (hepatomegaly); Hepatobiliary disorders - Other (cholestasis); Hepatobiliary disorders - Other (hepatic lesion)
INFECTIONS AND INFESTATIONS - Abdominal infection; Conjunctivitis; Fungemia; Lung infection; Sepsis; Upper respiratory infection; Urinary tract infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Injury, poisoning and procedural complications - Other (craniocerebral injury)
INVESTIGATIONS - GGT increased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hypoglycemia; Hypokalemia; Hyponatremia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Flank pain; Myalgia
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (malignant neoplasm progression)
NERVOUS SYSTEM DISORDERS - Dizziness; Dysgeusia; Headache; Spinal cord compression
PSYCHIATRIC DISORDERS - Confusion
RENAL AND URINARY DISORDERS - Acute kidney injury; Chronic kidney disease; Renal and urinary disorders - Other (urine albumin/creatinine ratio increased)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Genital edema
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Dyspnea; Hypoxia; Pleural effusion; Pneumonitis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Photosensitivity; Pruritus; Rash maculo-papular
VASCULAR DISORDERS - Hematoma; Hypertension; Hypotension; Thromboembolic event

Note: Savolitinib (AZD6094) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

- **Attribution** of the AE:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be 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.

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease Progression" in the system organ class (SOC) "General disorders and administration site conditions."** . Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration

of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions.**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

7.5 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

7.6 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.7 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1.

8.1 Savolitinib (NSC #785348)

Chemical Name: 1-[(S)-1-(imidazo[1,2-a]pyridin-6-yl)ethyl]-6-(1-methyl-1H-pyrazol-4-yl)-1H-[1,2,3]-triazolo[4,5-b]pyrazine

Other Names: volitinib, HMPL-504

Classification: oral c-Met kinase inhibitor

CAS Registry Number: 1313725-88-0

Molecular Formula: $C_{17}H_{15}N_9$ **M.W.:** 345.36

Approximate Solubility: Savolitinib (AZD6094) has solubility of 64.07 to 21.56 mg/mL at pH 1.2, 1.3 mg/mL to 0.92 mg/mL at pH 4.5 and 0.06 to 0.04 mg/mL at pH 6.8. Additional solubility in bio-relevant media was measured at 0.11 mg/mL in fasted-state simulated intestinal fluid and 0.94 to 0.65 mg/mL in fed-state simulated intestinal fluid.

Mode of Action: Savolitinib ((AZD6094) is an oral, potent and selective c-Met kinase inhibitor. The MET (mesenchymal epithelial transition) pathway is one of the most dysregulated pathways associated with a wide range of human malignancies. The MET receptor is normally phosphorylated by hepatocyte growth factor (HGF) which leads to downstream signaling of two major pathways, RAS/RAF/MEK/ERK and AKT/PI3K/mTOR. Both downstream pathways contribute to cell proliferation and survival and when dysregulated, support tumor expansion and progression.

Description: Savolitinib ((AZD6094) is off-white to yellow crystalline powder

How Supplied: Astra Zeneca supplies and CTEP, NCI, DCTD distributes savolitinib ((AZD6094) as coated tablets. Bottles are secured with a child-resistant closure; induction-sealed membranes provide tamper evidence. Savolitinib (AZD6094) tablets are supplied in 24-count HDPE bottles containing desiccant in the following strengths and descriptions:

- 200 mg yellow, plain, oval (7.25 x 14.5 mm)

Savolitinib (AZD6094) tablets consist of drug substance, microcrystalline cellulose, mannitol, hydroxypropyl cellulose, and magnesium stearate. The film coating consists of hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol 400, black iron oxide, yellow iron oxide and red iron oxide.

Storage: Store the savolitinib (AZD6094) tablets at controlled room temperature (20°C-25°C). Short excursions at clinical study sites are permitted as follows: *Brief excursions are permitted between 15°C and 30°C.*

If a storage temperature excursion is identified, promptly return savolitinib (AZD6094) to controlled room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Stability studies are ongoing. The manufacturer does not have stability information to support repackaging tablets. Dispense in the original container.

Route and Method of Administration: Oral. Take savolitinib ((AZD6094)) tablets with food. Swallow whole with water.

Potential Drug Interactions: According to *in vitro* studies, savolitinib (AZD6094) is primarily metabolized by CYP 3A4/5 and 1A2 and some NADPH-independent non-CYP enzymes. Avoid administration of strong CYP 3A4/5 and 1A2 inducers and inhibitors within 2 weeks of starting and during savolitinib (AZD6094) study treatment. Savolitinib (AZD6094) is not a P-glycoprotein (P-gp) substrate.

In vitro, savolitinib (AZD6094) and its metabolites weakly and reversibly inhibited CYP450 1A2, 2C8, 2C9, 2D6 and 3A4/5 isoforms and UGT1A1 . A drug interaction with substrates of CYP2C8/9 and/or CYP3A4/5 or UGT1A1 may occur when savolitinib (AZD6094) is dosed at the maximum tolerated dose. Use caution in patients who are taking concomitant medications whose clearance is exclusively dependent on CYP2C8, CYP2C9, CYP3A4/5 or UGT1A1 because exposure of the concomitant medication may be increased. Since there is limited clinical experience with this agent, patients on concomitant drugs with narrow therapeutic ranges, such as warfarin, should be monitored closely.

Studies indicate that savolitinib (AZD6094) has little induction potential for major CYP isoforms.

In vitro studies demonstrate that savolitinib (AZD6094) and its major metabolite inhibit a number of drug transporters to varying degrees. The manufacturer cautions that when administered at clinically relevant doses, savolitinib (AZD6094) has the potential to inhibit P-gp, BCRP (breast cancer resistance protein), OATP1B1, MATE1 and MATE2K. Therefore, co-administration of substrates that are dependent on these drug transporter systems should be used with caution. The potential for drug-drug interaction is considered unlikely when co-administering substrates of OATP1B3, OAT1, OAT3 or OCT2.

Patient Care Implications: Advise women study participants of child-bearing potential to use effective contraception from the time of screening until 4 weeks after discontinuing study treatment. Refer to the protocol for specific guidance.

Advise male study participants to use a condom with female partners of child-bearing potential during the study and for 4 weeks after discontinuing study treatment. If the female partner of a male study participant is not using effective contraception, men must use a

condom during the study and for 6 months after discontinuing study treatment. Also advise men to avoid fathering a child and refraining from sperm donation from study start to 6 months after discontinuing study treatment. Refer to the protocol for specific guidance.

Advise patients to avoid prolonged sun exposure and use protective clothing, hats and SPF 30+ sunscreen during study treatment and for 4 weeks after the last dose. Consult the protocol document for any dose modification necessary if sunburn occurs.

8.1.1 Agent Ordering and Agent Accountability

8.1.1.1 NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

In general, sites may order initial agent supplies when a subject is being screened for enrollment onto the study."

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

8.1.1.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

8.1.2 Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password, and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

8.1.3 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP/
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Summary Table for Specimen Collection

Time Point	Specimen and Quantity	Send Specimens to:
Screening		
	• 20 mL blood in cfDNA Streck tubes	Guardant Health
Baseline (prior to start of study drug)		
	• 6 mL blood in pink or lavender top ETDA tube • 30 mL blood in lavender top EDTA tubes processed for plasma • Archival tissue[1] (primary and/or metastatic) Submit 1 FFPE block, or – From the same block (cut sequentially), section forty (40) 5-micron sections: ▪ 1 H&E stained slide ▪ Thirty-eight (38) on positively charged SuperFrost or any positively charged slides ▪ Two (2) on Dako Flex or any silanized slides	ETCTN Biorepository
Cycle 1 Day 15		

Time Point	Specimen and Quantity	Send Specimens to:
	• 30 mL blood in lavender top EDTA tubes processed for plasma	ETCTN Biorepository
Each Restaging - prior to the start of study drug on Day 1 of Cycle 3 and every 2 cycles thereafter (Cycle 5, 7, 9, etc)		
	• 30 mL blood in lavender top EDTA tubes processed for plasma	ETCTN Biorepository
At Study Drug Discontinuation		
	• 30 mL blood in lavender top EDTA tubes processed for plasma	ETCTN Biorepository

[1]For archival tissue, a copy of the corresponding anatomic pathology report must be sent with the tissue and uploaded to Rave.

9.2 Specimen Procurement Kits and Scheduling

9.2.1 Specimen Shipping Kits for cfDNA Streck Blood

Guardant360 kit is provided for whole blood collection in cfDNA Streck tubes at the Screening time point. The kit contains tubes, a requisition form, blood draw and shipping instructions, shipping box with materials and a FedEx shipping label.

An initial supply of Guardant360 kits will be shipped to the participating site after the Study Initiation Meeting (SIM) is scheduled with the Study Chair/Lead Principal Investigator. (Participating sites must contact Duke Cancer Institute LAO by emailing ETCTN-LAO-NC010@dm.duke.edu to schedule a SIM.) Kits can be re-ordered by emailing a request to clientservices@guardanthealth.com. In the email request, please include the study number 10181 and the participating site's CTEP ID. Kits are shipped overnight within 2 business days from the date the email request is received.

9.2.2 Specimen Shipping Kits for Frozen Specimens

Kits for the shipment of specimens to the ETCTN Biorepository can be ordered online via the Kit Management system:
(https://ricapps.nationwidechildrens.org/KitManagement).

Users at the clinical sites will need to set up an account in the Kit Management system and select a specific clinical trial protocol to request a kit. Please note that protocol may include more than one type of kit. Each user may order two kit types per protocol per day (daily max = 6 kits). Kits are shipped ground, so please allow 5-7 days for receipt. A complete list of kit contents for each kit type is located on the Kit Management system website.

Note: Kits or supplies are only provided for specimens shipped to the Biorepository. Institutional supplies must be used for all other specimen collection and processing.

9.2.3 Blood Collection and Processing Supplies

Blood collection and processing supplies for the plasma samples are provided by each participating site (i.e. not supplied by study).

9.2.4 Scheduling of Specimen Collections

Frozen plasma can be collected on any day, but must be stored frozen and shipped overnight to the ETCTN Biorepository on Monday through Thursday. In the event that frozen specimens cannot be shipped immediately, they must be maintained in a -80°C freezer.

Frozen whole blood specimens can be collected on any day, but must be stored frozen and shipped overnight to the ETCTN Biorepository on Monday through Thursday. In the event that frozen specimens cannot be shipped immediately, they must be maintained in a -80°C freezer.

Fresh blood specimens may be collected and shipped ambient overnight to Guardant Health on Monday through Friday. Guardant Health can receive shipments on Saturday.

9.3 Specimen Collection

9.3.1 Archival Formalin-Fixed Paraffin-Embedded (FFPE) Tumor Specimen

If previously-collected FFPE tissue will be submitted, then the following criteria must be met:

- Tissue must have been collected within 6 months prior to registration
- Formalin-fixed paraffin-embedded tumor tissue block(s) must be submitted. The optimal block is at least 70% tumor. Specimen size requirement is as follows:
  - Surface area: 25 mm^2 is optimal. Minimum is 5 mm^2.
  - Volume: 1 mm^3 optimal. Minimum volume is 0.2 mm^3, however the success of DNA extraction decreases at suboptimal tissue volume.

Submission of a block is preferred. If an existing block cannot be submitted, then the following are requested, for each available archival (primary and/or metastatic) paraffin tumor block:

1. Face the block (i.e. cut 1-2 microns of the top section) and discard the cut tissue.
2. Cut one (1) H&E stained slide
3. Cut two (2) 5-micron sections and place on Dako Flex or any silanized slides.
4. Cut thirty-eight (38) 5-micron sections and place on positively charged SuperFrost or any positively charged slides.

Note: **all slides must be sequentially numbered** and prepared from the same block.

In the event there is limited archival tissue to send all the requested slides, please use the following instructions, which is based on the priority of tissue analysis.

- If available archived tissue yields less than 40 slides, the following is requested:
    1. Cut one (1) H&E stained slide
    2. Cut two (2) 5-micron sections and place on Dako Flex or any silanized slides.
    3. Cut the remaining into 5-micron sections and place on positively charged SuperFrost or any positively charged slides.

See Section 9.4.2 for labeling instructions.

9.3.2 Collection of Blood in cfDNA Streck Tube

1. At Screening, label two 10ml Streck tubes (cell-free DNA BCT) per instructions provided in the Guardant360 kit (see Appendix E).
2. Fill the tubes completely.
3. Mix tubes by gentle inversion 8-10 times.
4. Do not refrigerate or freeze blood samples.
5. Store blood samples at room temperature and ship within 24 hours of collection.
6. Complete the requisition form provided in the kit. Keep a copy of the completed requisition form for study records. Ensure all fields of the requisition form are complete and clearly written as processing of samples may be delayed if information is missing or illegible on requisition.

9.3.3 Collection of Blood in EDTA Tubes for Plasma Processing

1. Label EDTA tubes (BD Vacutainer, Catalog no. 366643 or K_2EDTA equivalent) according to the instructions in Section 9.4.1.
2. Collect 30 mL blood in EDTA tube(s) and gently invert tube to mix.
3. Process plasma by centrifuging for 15 minutes at 2,500 x g at 4°C.
4. Using a sterile transfer pipette, remove plasma into two separate clean 15 mL polypropylene tubes.
5. Repeat centrifugation for 15 minutes at 2,500 x g at 4°C.
6. Using a clean sterile transfer pipette, remove plasma, taking care to avoid contact with the buffy coat (white, yellowish or grayish layer between the plasma and red blood cells) by keeping the pipet above the buffy coat layer and leaving a small amount (about 0.5 cm) of plasma in the tube.
7. Aliquot plasma into 10 labeled cryovials in approximately equal volumes.
8. Tightly secure the cap of the vials before storage.
9. Store plasma cryovials upright in a specimen box or rack in an -70°C to -90°C or colder freezer prior to shipping to the Biorepository. Do not allow specimens to thaw after freezing.

NOTE: EDTA tubes for plasma must be processed and frozen within 2 hours of

collection time.

9.3.4 Collection of Whole Blood in EDTA Tubes

1. Label EDTA tube (BD Vacutainer, Catalog no. 367899 or K_2EDTA equivalent) according to the instructions in Section 9.4.1.
2. Collect 6 mL blood in EDTA tube(s) and gently invert tube to mix.
3. Store tube upright in a specimen box or rack in an -70°C to -90°C or colder freezer prior to shipping to the Biorepository. Do not allow specimens to thaw after freezing.

9.4 Specimen Tracking System Instructions

All biospecimens collected for this trial must be submitted using the ETCTN Rave Specimen Tracking System (STS) unless otherwise noted. The system is accessed through special Rave user roles: "CRA Specimen Tracking" for data entry at the treating institutions and "Biorepository" for users receiving the specimens for processing and storage at reference labs and the Biorepository. Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website under the Rave/DQP tab.

Important: Failure to complete required fields in STS may result in a delay in sample processing. Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS.

Additionally, please note that the STS software creates pop-up windows when reports are generated, so you will need to enable pop-ups within your web browser while using the software.

For questions regarding the Specimen Tracking System, please contact the Theradex Help Desk at CTMSSupport@theradex.com.

A shipping manifest **must** be included with all sample submissions.

9.4.1 Specimen Labeling

9.4.1.1 Blood Specimen Labels

Include the following on blood specimens (including whole blood and frozen, processed blood products – like plasma):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point

- Specimen type (e.g. blood, serum)
- Collection date

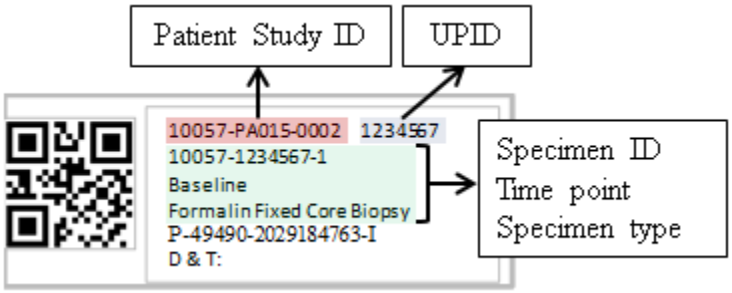
9.4.1.2 Tissue Specimen Labels

Include the following on all tissue specimens or containers (e.g. formalin jar).

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, FFPE Block)
- Tissue type (P for primary, M for metastatic or N for normal)
- Collection date
- Surgical pathology ID (SPID) number
- Block number from the corresponding pathology report (archival only)
- Sequentially number slides (archival only) to indicate the cut order

9.4.1.3 Example of Specimen Label

The following image is an example of a tissue specimen label printed on a standard Avery label that is 1" high and 2.625" wide.



The QR code in the above example is for the Specimen ID shown on the second line.
NOTE: The QR code label is currently under development at Theradex as of 31-Aug-2018; therefore, labels generated by the STS for this study may not include a QR code.

The second line item from the end includes four data points joined together:

1. Tissue only: Primary (P), Metastatic (M), Normal (N) tissue indicated at the beginning of the specimen ID; this field is blank if not relevant (e.g., for blood)
2. Block ID or blank if not relevant
3. SPID (Surgical Pathology ID) or blank if none
4. The last alpha-numeric code is protocol specific and is only included if the protocol requires an additional special code classification

The last line on the example label is for the handwritten date and optional time.

9.4.2 Overview of Process at Treating Site

9.4.2.1 OPEN Registration

All registrations will be performed using the Oncology Patient Enrollment Network (OPEN) system. OPEN communicates automatically with the Interactive Web Response System (IWRS) which handles identifier assignments, any study randomization and any prescribed slot assignments. If specimen analysis is required to determine eligibility, the protocol will be setup with multi-step registration.

Registration with eligibility specimen analysis:

1. Site enters first step data into OPEN.
2. IWRS receives data from OPEN, generates the Patient Study ID and the Universal Patient ID, both of which are sent back to OPEN.
3. IWRS sends first step registration data, including the IDs and a TAC of "NOT REG" directly to Rave.
4. The specimen tracking system in Rave is utilized for the specimen that contributes to eligibility determination.
5. Site enters second and any subsequent step data into OPEN including results of specimen analysis.
6. IWRS receives all data from OPEN, then sends it onto Rave with either the treatment TAC or a TAC of "SCRN FAIL".
7. In addition to the specimen tracking forms completed to determine eligibility, data entry for screen failure patients should include Histology and Disease, all forms in the Baseline folder, any lab forms connected to eligibility determination, and Off Treatment/Off Study.

Any data entry errors made during enrollment should be corrected in Rave.

9.4.2.2 Rave Specimen Tracking Process Steps

Step 1: Complete the **Histology and Disease** form (but do not upload reports until a specimen label can be applied to them) and the Baseline forms regarding **Prior Therapies**. Enter the initial clinical specimen data:

- **Specimen Tracking Enrollment** CRF**:** Enter Time Point, Specimen Category, Specimen Type, Block number, Tissue type, Surgical Path ID, number of labels needed (include extra labels to apply to reports to be uploaded). CRF generates unique Specimen ID.

Step 2: Print labels using report in EDC and collect specimen.

- Label specimen containers and write collection date and for blood samples include collection time on each label.
- After collection, store labeled specimens as described in Section 9.3.
- Apply an extra specimen label to ***each*** report before scanning. Return to the **Histology and Disease** form to upload any initial Pathology, Radiology,

Molecular Reports (up to 4), Surgical reports and Pathology Verification form (when applicable). Return to **Specimen Tracking Enrollment** CRF to upload any molecular report (one per specimen) and/or specimen specific pathology or related report (one per specimen). Uploaded reports should have PHI data like name, mailing address, medical record number or SSN redacted. Do not redact SPID, block number or relevant dates.

Step 3: Complete specimen data entry.

- **Specimen Transmittal** Form**:** Enter Collection date and time and other required specimen details.

Step 4: When ready to ship, enter shipment information.

- **Shipping Status** CRF**:** Enter tracking number, your contact information, recipient, number of containers and ship date once for the 1st specimen in a shipment.
- **Copy Shipping** CRF**:** Select additional specimens to add to an existing shipment referenced by the tracking number.

Step 5: Print shipping list report and prepare to ship.

- Print two copies of the shipping list, one to provide in the box, the other for your own records.
- Print pathology or other required reports to include in the box. Be sure the printed copy includes the specimen label.

Step 6: Send email notification.

- For only one of the specimens in the shipment, click "Send Email Alert" checkbox on the **Shipping Status** CRF to email recipient.

Step 7: Ship the specimen(s).

9.5 Shipping Specimens from Clinical Site to the ETCTN Biorepository

For all archival tissue, the corresponding anatomical clinical pathology report is required both in the package and uploaded in the ETCTN specimen tracking system. If this is not available at the time of shipment, then it must be uploaded to the ETCTN specimen tracking system, or the specimen will not be processed. The pathology report must state the disease diagnosis made by the reviewing pathologist.

9.5.1 Specimen Shipping Instructions

Archival tissue and frozen specimens may be shipped to the ETCTN Biorepository on Monday through Thursday. Archival tissue is shipped at room temperature.

Fresh blood may be shipped to Guardant on Monday through Friday. Please select "Saturday Delivery" when shipping fresh blood on a Friday.

9.5.1.1 Shipping Frozen Specimens to the ETCTN Biorepository

1. Before packaging specimens, verify that each specimen is labeled according to the instructions above and that lids of all primary receptacles containing liquid are tightly sealed.
2. Place the specimens in zip-lock bags. Use a separate zip-lock bag for each specimen type and time point.
3. Place the zip-lock bags in a biohazard envelope containing absorbent material. Expel as much air as possible and seal securely.
4. Put the secondary envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
5. Place frozen specimens in an insulated box with dry ice. Layer the bottom of the compartment with dry ice until it is approximately one-third full. Place the frozen specimens on top of the dry ice. Cover the specimens with the dry ice until the compartment is almost completely full. When packaging specimens, ensure that you leave enough room completely cover the specimens in dry ice.
6. Do not tape the insulated container shut.
7. Insert a copy of the required forms into a plastic bag and place in the shipping box.
8. Close the shipping box and tape it shut with durable sealing tape. Do not completely seal the container.
9. Complete a FedEx air bill and attach to top of shipping container.
10. Complete a dry ice label.
11. Attach the dry ice label and an Exempt Human Specimen sticker to the side of the shipping container.

Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

9.5.2 ETCTN Biorepository Shipping Address

Ship to the address below. Ship formalin-fixed and fresh blood specimens the same day of specimen collection. Do not ship specimens the day before a holiday.

ETCTN Biorepository
The Research Institute at Nationwide Children's Hospital
700 Children's Drive, WA1340
Columbus, Ohio 43205
PH: (614) 722-2865
FAX: (614) 722-2897
Email: BPCBank@nationwidechildrens.org

FedEx Priority Overnight service is very strongly preferred.

NOTE: The ETCTN Biorepository FedEx Account will not be provided to submitting institutions.

9.5.3 Contact Information for Assistance

For all queries, please use the contact information below:

ETCTN Biorepository
Toll-free Phone: (800) 347-2486
E-mail: BPCBank@nationwidechildrens.org

9.6 Shipping of Specimens to Other Laboratories

9.6.1 Shipping Blood in cfDNA Streck tubes to Guardant at Screening

No patient identifiers are to be included on the tubes and requisition form sent to Guardant Health.

Ensure all fields of the requisition form are complete and clearly written as processing of samples may be delayed if information is missing or illegible on requisition.

Within 24 hours of blood collection, Streck blood tubes and completed requisition form must be shipped to Guardant Health at room temperature by overnight courier service delivery Monday through Friday (no holidays) to the following address:

Guardant Health
2686 Middlefield Road, Ste E
Redwood City, CA 97063

Once blood sample kit is received by Guardant Health, results are expected within 14 business days.

For each patient who has a Guardant360 test completed for this study, the Lead Principal Investigator will provide the patient's treating physician with the Guardant360 test results via email.

9.7 Integral/Integrated Laboratory Studies

Biomarker Name AND Lab PI and Site	Assay	Use (Integral, Integrated, or Exploratory) AND Purpose	Tissue/Body Fluid Tested and Timing of Sample Collection	Mandatory (M) / Optional (O) Collection	Protocol Section
ctDNA analysis of *MET* gene amplification Guardant Health	Guardant360	Integral Detect MET gene amplification in ctDNA	Blood in cfDNA Streck Screening	M	9.7.1
>70-gene panel including KRAS, NRAS, EGFR, MET, etc. (cell free tumor DNA) Guardant Health	Guardant360	Integrated Characterize genetic alterations to treatment outcome	Blood in cfDNA Streck Screening	M	9.7.2

Biomarker Name AND Lab PI and Site	Assay	Use (Integral, Integrated, or Exploratory) AND Purpose	Tissue/Body Fluid Tested and Timing of Sample Collection	Mandatory (M) / Optional (O) Collection	Protocol Section
ctDNA analysis of MET amplification Williams, Mickey / Molecular Characterization Laboratory (MoCha) at NCI Frederick	Next Generation Sequencing	Exploratory Detect MET gene amplification in ctDNA	Blood Baseline, C1D15, each restaging, and at study drug discontinuation	M	9.8.1
Panel including KRAS, NRAS, EGFR, MET, etc. (ctDNA) Williams, Mickey / Molecular Characterization Laboratory (MoCha) at NCI Frederick	Next Generation Sequencing	Exploratory Characterize genetic contributions to treatment outcome and analyze genetic changes over time on treatment	Blood Baseline, C1D15, each restaging, and at study drug discontinuation	M	9.8.1
Soluble protein analytes including c-MET, HGF, EGF, AXL, etc. Nixon, Andrew / Duke University Medical Center	Multiplex ELISA	Exploratory Characterize the relationship between soluble protein analyte expression and response to treatment	Blood Baseline, C1D15, each restaging, and at study drug discontinuation	M	9.8.2
Pharmacogenomics Nixon, Andrew / Duke University Medical Center	Sequencing	Exploratory Assess variants in genes anticipated to be involved in the pharmacokinetics or pharmacodynamics of savolitinib	Blood Baseline	M	9.8.5
Whole exome sequencing Williams, Mickey / Molecular Characterization Laboratory (MoCha) at NCI Frederick	WES	Exploratory Characterize genetic contributions to treatment outcome	Tumor Archival	O	9.8.4
c-MET expression and amplification Nixon, Andrew / Duke University Medical Center	IHC and FISH	Exploratory Characterize c-MET expression and amplification in tumor tissue	Tumor Archival	O	9.8.3
MET gene amplification Nixon, Andrew / Duke University Medical Center	Next Generation Sequencing	Exploratory Characterize genomic alterations including MET gene amplification in tumor tissue	Tumor Archival	O	9.8.3

9.7.1 ***MET* gene amplification in blood (Integral)**

The hypothesis of this study is that *MET* amplification detected in the blood of patients with metastatic CRC will predict response to anti-MET therapy (savolitinib). Because *MET* amplification is typically acquired after exposure to anti-EGFR therapy, primary tissue is unlikely to identify patients with *MET* amplification. Blood-based profiling is a safe and non-invasive methodology to detect acquired *MET* amplification.

Guardant Health (Redwood City, CA) will perform the assay. The analyte is circulating tumor-derived cell-free DNA (cfDNA). The technical platform is Guardant360, a 73-gene hybridization capture, Illumina NGS-based panel offered by Guardant Health in their CLIA-certified (#05D2070300), CAP-accredited laboratory (Lanman et al., 2015). All assay components and reagents will be sourced through Guardant Health, and all testing performed to CLIA/CAP standards.

The specimens will be collected in Streck cfDNA BCT, from which plasma will be isolated and stored at -80°C until use. Samples will be processed according to Guardant Health's CLIA workflow.

Specimens will be collected from patients who are most likely to have *MET* amplification detected in blood. To maximize the probability of detecting *MET* amplification, this study will screen patients with *KRAS* and *NRAS* wild-type metastatic CRC who have received prior anti-EGFR therapy.

Guardant360's clinical utility is demonstrated by its ability to: 1) accurately predict clinical response to approved targeted therapy; 2) expand access to targeted therapy to patients for whom tissue is unavailable or insufficient; 3) decrease the time to treatment, and 4) decrease harm to patients caused by invasive biopsy.

Four outcome studies of advanced NSCLC cohorts show, in aggregate, that *EGFR*-directed targeted therapy response rates for Guardant360-selected patients are 85% (C-P Exact 55-98%) in the first-line (e.g. erlotinib) and 91% (C-P Exact 57-99%) in the second and greater (e.g. osimertinib), which are equivalent to those cited in these drugs' FDA approvals.

Table 1. Clinical studies of NSCLC patient drug response rate to Guardant360-directed therapy and corresponding FDA approvals.

Study	Key Findings	Indication
Lee *et al.* 2016 (NEXT-NSCLC) In review	• n=72 tissue QNS NSCLC • n=17 with therapeutic target identified • n=15 (all *EGFR* and *ALK*) treated with 13 PR (87% RR by RECIST	NSCLC
Villaflor et al. 2016 *Oncotarget*	• n=68 advanced NSCLC with 54% tissue QNS rate • n=10 *EGFR* mutations treated, 8 PR (80% RR by clinical CT assessment) • PFS=11.5 months (equivalent to reported literature survival)	NSCLC
Thompson et al. 2016 *Clinical Cancer Research*	• n=102 NSCLC with 51% tissue QNS rate (interim analysis) • On-label therapy options in 31%, off-label in 55% • n=3 available for outcome, all 3 with objective response (*EGFR* and *ALK*)	NSCLC

Rozenblum et al. 2016 *J Thor Oncol* (In Press)	• n=19 tissue QNS ctDNA genotyping rescues • n=6 (32%) with therapeutic target identified • n=5 treated with 3 PR (*EGFR*, *MET*), 2 SD (*RET*, *ERBB2*) by RECIST	NSCLC

Genomic Target	G360 Response Rate	Published Response Rate
EGFR ex19 deletion, L858R	11/13, 85% [55-98%]	65% [54-75%] (erlotinib)*
EGFR T790M	10/11, 91% [57-99%]	59% [54-64%] (osimertinib)#

Clopper-Pearson Exact 95% confidence intervals reported in brackets.
* http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021743s018lbl.pdf
# http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/208065s000lbl.pdf

Data collected will include qualitative (presence/absence) and quantitative mutation (variant allele fraction) and amplification (CNV) detection.

Amplification: Gene amplification results in increased copies of the gene present in the cfDNA. As the absolute number of copies in circulation is dependent on both tumor fraction and the magnitude of the tumor amplification, amplifications are reported on a semi-quantitative scale: Positive (+) amplification magnitude is in the lower 50th percentile of samples with amplifications; Strongly Positive (++) amplification magnitude is in the 50th to 90th percentile; Very Strongly Positive (+++) amplification magnitude is in the top 10th percentile. Copy number data will be available for all profiled blood samples.

For this study, any patient with *MET* amplification detected in blood (MET copy number ≥ 2.2) will be eligible for treatment with savolitinib.

Keep a copy of the completed requisition form for study records.

9.7.1.1 Specimen Receipt and Processing at Guardant

Plasma processed from blood collected in cfDNA Streck tubes will be used for this assay.

9.7.1.2 Site(s) Performing Correlative Study

Guardant Health (Redwood City, CA) is conducting the assay.

9.7.2 **> 70 gene circulating tumor DNA (ctDNA) panel (Integrated)**

See Section 9.7.1 for information regarding the 73-gene panel Guardant360 assay.
Mutations of interest include but are not limited to, mutations in *KRAS*, *NRAS* and *EGFR*. Amplifications of interest include, but are not limited to, *EGFR* and *ERBBR2*. The allele frequency and copy number of these mutations and amplifications will be measured to evaluate the effect of their presence on response to treatment.

9.7.2.1 Specimen Receipt and Processing at Guardant

Plasma processed from blood collected in cfDNA Streck tubes will be used for this assay.

9.7.2.2 Site(s) Performing Correlative Study

Guardant Health (Redwood City, CA) is conducting the assay.

9.8 Exploratory/Ancillary Correlative Studies

9.8.1 **Circulating tumor DNA (ctDNA) panel**

The ctDNA assay platform that will be used in this protocol is still being evaluated by the Molecular Characterization (MoCha) Laboratory. Exploratory mutations of interest include, but are not limited to *BRCA2, BRAF, PIK3CA, AKT, PTEN*, and *MAP2K1*. Amplifications of interest include, but not limited to, *MYC* and *FGFR1*. The allele frequency and copy number of these mutations and amplifications will be followed until progression (or end of study treatment).

9.8.1.1 Specimen Receipt and Processing at the ETCTN Biorepository

Frozen plasma processed from K_2EDTA tubes will be used for this assay. Upon receipt, frozen plasma aliquots will be accessioned, barcoded and banked in a -80°C freezer until distribution for testing.

9.8.1.2 Site(s) Performing Correlative Study

The analysis will be performed at the Molecular Characterization Laboratory (MoCha) at NCI Frederick.

9.8.2 **Circulating protein studies**

Plasma samples will be analyzed by multiplex ELISA assays for plasma-based biomarkers utilizing the Aushon Cirascan Imaging System. The Aushon Cirascan Imaging System is used specifically for the imaging and analysis of chemiluminescent protein arrays in a 96-well plate. The protein arrays are created by spotting up to 16 different capture antibodies per well in each well of the 96-well plate. The advantage of this system is that multiple target proteins of interest can be analyzed at the same time reducing the amount of sample required for analysis. In brief, a small volume of sample and/or standard is added to each well of the 96-well plate resulting in the capture of the target proteins by the arrayed antibodies. Biotinylated antibodies are then added that specifically bind the captured target proteins. Streptavidin conjugated to HRP (horseradish peroxidase) is then added followed by a chemiluminescent substrate. Imaging of the plate is performed using Aushon Cirascan Imaging System. Protein concentrations in the samples are quantified by comparing the intensity of the spots in the unknown wells to standard curves.

Multiple soluble protein analytes, including (but not limited to) HGF, c-MET, EGF, HBEGF, TGF-α, EGFR, VEGFA-D, HER2, HER3, GAS6, and AXL will be analyzed. Additional biomarkers may also be explored using multiplex array technology. The results will help to characterize the relationship between soluble protein analyte expression and response to treatment. This analysis will also explore the association between soluble protein c-MET expression and gene amplification in tumor tissue.

9.8.2.1 Specimen Receipt and Processing at the ETCTN Biorepository

Plasma processed from K_2EDTA) tubes will be used for this assay. Upon receipt, plasma will be accessioned, barcoded and banked in a -80°C freezer until distribution for testing.

9.8.2.2 Site(s) Performing Correlative Study

The analysis will be performed at the Duke Phase I Biomarker Laboratory.

9.8.3 **c-MET protein expression and *MET* gene amplification in tissue**

Archival tumor tissue will be analyzed by IHC and FISH to assess c-MET protein expression and *MET* gene amplification in tumor tissue. The results will help to explore the association between c-MET protein expression and amplification, the association between soluble c-MET expression in whole blood and c-MET protein expression in tumor tissue, as well as the association between *MET* gene amplification in cfDNA and amplification in tumor tissue.

We estimate that 90% of patients enrolled in the study should have archival tumor tissue available. Results from 12 tumors of 12 patients are sufficient to provide useful information on correlation of c-MET protein expression and *MET* gene amplification in tissue and blood.

Archival tumor tissue will be analyzed by Next Generation Sequencing (NGS) to characterize genomic alterations, including MET gene amplification, in tumor tissue. These results will help to explore the contribution of these alterations to treatment outcome and prognosis.

9.8.3.1 Specimen Receipt and Processing at the ETCTN Biorepository

Archival formalin-fixed, paraffin-embedded (FFPE) tissue will be used for this assay.

9.8.3.2 Site(s) Performing Correlative Study

The analysis will be performed at the Duke Phase I Biomarker Laboratory.

9.8.4 **Whole exome sequencing**

Whole exome sequencing may be performed in archived tumor tissue to characterize the genomic alterations in anti-EGFR antibody refractory patient population and compare the genomic landscape of the tumor tissue to that of the ctDNA from the same patient. This analysis

will provide novel and clinically relevant insight into tumor heterogeneity and therapeutic resistance.

It is optional for the patient to be notified of information (if actionable) that results from the whole exome sequencing analysis of their archived tissue.

9.8.4.1 Specimen Receipt and Processing at the ETCTN Biorepository

Archival formalin-fixed, paraffin-embedded (FFPE) tissue will be used for this assay. For all tumor specimens, the first section will be stained with H&E for pathology quality control review to assess tumor content; unstained slides will be macrodissected, if needed, and scraped for DNA and RNA co-extraction. DNA will be banked in a stock vial and RNA will be divided into 5 aliquots; all nucleic acids will be stored in a -80°C freezer until distribution for testing.

9.8.4.2 Site(s) Performing Correlative Study

The analysis will be performed at the Molecular Characterization Laboratory (MoCha) at NCI Frederick.

9.8.5 **Pharmacogenomics**

A one-time, blood sample collected at Baseline will be used for assessment of variants in genes anticipated to be involved in the pharmacokinetics or pharmacodynamics of savolitinib.

9.8.5.1 Specimen Receipt and Processing at the ETCTN Biorepository

DNA will be extracted from whole blood collected in EDTA tubes at Baseline. DNA will be stored in a -80°C freezer until distribution for testing.

9.8.5.2 Site Performing Correlative Studies

The analysis will be performed at the Duke Phase I Biomarker Laboratory.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 weeks prior to start of protocol therapy for the exception of scans. Scans must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-Study	Cycle 1		Cycle 2 and all subsequent cycles	Cycle 3 and every 2 cycles thereafter (Cycle 5, 7, 9, etc.)	End of Treatment	Observation	
		Prior to dosing on Day 1 (Baseline)	Prior to dosing on Day 15 (±3 days)	Prior to dosing on Day 1 (±3 days)	Prior to dosing on Day 1 (±3 days)	At disease progression/ drug discontinuation	30-days after last dose (±3 days)	Every 12 weeks (as clinically indicated)
Informed Consent	X							
Demographics	X							
Medical History	X							
Concurrent Medications	X	X----------					----------X	
Physical Exam	X	X	X	X		X	X	
Vital Signs	X	X	X	X		X	X	
Height	X							
Weight	X	X	X	X		X	X	
Performance Status	X	X	X	X		X	X	
B-HCG [a] (women of childbearing potential only)	X				X	X		
CBC w/diff, plts	X	X	X	X		X	X	
Serum Chemistry [b]	X	X	X	X		X	X	
Serum lactate dehydrogenase (LDH)	X	X	X	X		X	X	
Serum amylase	X	X	X	X		X	X	
Urine dipstick [i]	X	X	X	X		X	X	
EKG [c]	X	X	X	X		X		
Adverse Event Evaluation		X----------					----------X	
Savolitinib [A]		X----------			----------X			
Tumor Assessments [d]	X				X			X [e]
CEA (blood tumor marker)	X			X				X [e]
Whole blood in cfDNA Streck tubes (*MET* Amplification [f])	X							
EDTA blood for Cell free tumor DNA [g] and Circulating protein (plasma)		X	X		X	X		
6 mL EDTA whole blood		X						
Archival Tumor Tissue [h] (FFPE)	X							

A: Savolitinib: Dose as assigned and administration is once daily. Refer to Sections 5 and 6 for dose delay and modification schema. See Appendix B for patient drug diary card.

a. A pregnancy test on urine or blood sample will be performed for pre-menopausal women of childbearing potential, at baseline (must be ≤7 days prior to Cycle 1 Day 1), at every restaging (ie. every 2 cycles starting with Cycle 3), and at treatment discontinuation. Tests will be performed by the institutional laboratory. If results are positive the patient is ineligible/must be discontinued from the study. In the event of a suspected pregnancy during the study, the test should be repeated and if positive, the patient will be discontinued from study treatment immediately.

	Pre-Study	Cycle 1		Cycle 2 and all subsequent cycles	Cycle 3 and every 2 cycles thereafter (Cycle 5, 7, 9, etc.)	End of Treatment	Observation	
		Prior to dosing on Day 1 (Baseline)	Prior to dosing on Day 15 (±3 days)	Prior to dosing on Day 1 (±3 days)	Prior to dosing on Day 1 (±3 days)	At disease progression/ drug discontinuation	30-days after last dose (±3 days)	Every 12 weeks (as clinically indicated)

b. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
c. QTc evaluation will be done on triplicate 12 lead ECGs during the screening period, and every week in the first cycle and every cycle thereafter, and at the end of treatment as indicated in the study plan. A 28-day follow-up assessment will be required if an on-treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality.
d. CT or MRI of the chest, abdomen, and pelvis to assess sites of measurable disease as per RECIST 1.1. Unless clinically indicated, the same method for tumor assessment should be employed at every restaging. At baseline must be ≤28 days prior to Cycle 1 Day 1; every restaging (may occur ≤14 days prior to Day 1 of the new cycle); and as clinically indicated.
e. Subjects discontinued from study treatment with no documented disease progression and no subsequent anti-cancer treatment should be followed every 12 weeks or as clinically indicated with tumor assessments and CEA until disease progression or receipt of subsequent anti-cancer treatment is documented. No additional tumor assessment and CEA required for subjects discontinued from study treatment due to disease progression. Note: If subject is not able to return to the consenting institution, subject health records such as medical oncology physician notes, laboratory results, and/or radiology reports with tumor assessments from another institution is permissible for tumor assessment of disease progression or documentation of subsequent anti-cancer treatment.
f. Blood collected in cfDNA Streck tubes at pre-study (ie. screening) to determine presence of MET amplification. Once blood tubes are received by lab, there is approximately a 14-day turnaround time for results. Refer to Section 9 for details of collection and shipping instructions.
g. Blood collected in EDTA lavender top tubes at baseline (prior to first dose), Cycle 1 Day 15, every restaging, and at study drug discontinuation. Refer to Section 9 for details of collection, processing, and storage/shipping instructions.
h. If available, formalin-fixed paraffin embedded tissue collected from pre-study biopsy and/or surgical procedure. Refer to Section 9 for collection, processing, and storage/shipping instructions.
i. If 3+ or greater proteinuria is identified by dipstick assessment, a 24-hour urine collection for formal quantification of the level of protein excretion should be performed.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with savolitinib.

Evaluable for PFS. Patients who have received any protocol therapy regardless of duration.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one dose of treatment, and have had their disease re-evaluated will be considered evaluable for response. These patients will have

their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one dose of treatment, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area are considered measurable only if there is evidence of progression of those tumor lesions since the radiation and prior to the start of study treatment.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

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

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the

basis of their size (lesions with the longest diameter), 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. 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 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 any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 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 never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions
Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray
Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI
This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT

At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy

The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression

criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology
These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET
While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

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

Progressive Disease (PD): At least a 20% increase in the sum of the 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 (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

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

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation is required for this protocol.
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation is required for this protocol.
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients 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 the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.6 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of clinical or radiographic progression or death, whichever occurs first.

11.1.7 Response Review

Response will be reviewed at each participating institution using the RECIST guidelines provided in Section 11.

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

For this Phase 2 study, the Protocol Principal Investigator will have, at a minimum, quarterly conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and pharmacovigilance.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

12.2 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (check at https://ctepcore.nci.nih.gov/iam/.) and the appropriate Rave role (Rave CRA, Read-Only, CRA (Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold RAVE CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the RAVE Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in RAVE.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the PI, and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials) the recommended phase 2 dose (RP2D) and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

12.3 CTEP Multicenter Guidelines

N/A

12.4 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

12.5 Genomic Data Sharing Plan

N/A

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is an open-label phase II study to determine the clinical activity of savolitinib in patients with *MET* amplified metastatic CRC. Only patients with metastatic CRC who have received prior anti-EGFR monoclonal antibody therapy (cetuximab or panitumumab) are eligible. Patients will be considered evaluable for response as defined in Section 11.1.1.

The primary endpoint is objective overall response (ORR) defined as a complete response (CR) or partial response (PR) by RECIST 1.1 criteria at any time during treatment. The ORR will be estimated when response data are available for 15 evaluable patients.

The null hypothesis that the ORR is 0.10 (p=0.10) versus the alternative that the ORR is 0.25 (p=0.25) will be tested using the exact test of a binomial proportion. With 15 patients studied the power and significance level to test this difference are 0.764 and 0.184 (1-sided), respectively, at critical value 3.0. The null hypothesis will be rejected if 3 or more of 15 responses are observed. In this case, savolitinib will merit further investigation as a treatment for *MET* amplified metastatic CRC.

Enrollment to the study will end when 15 evaluable patients are accrued or 150 patients are prospectively screened, whichever time point is reached first.

If 14 evaluable patients are studied the power and significance level to test this hypothesis are 0.72 and 0.16 (1-sided), respectively, at critical value 3.0. The null hypothesis will be rejected if 3 or more of 14 responses are observed.

Alternative Analysis for the Number of Evaluable Patients, N≤14

If fewer than 14 evaluable patients are studied the power and significance level to test this hypothesis is less than 0.70 for 1-sided $\alpha \leq 0.2$. Therefore, if fewer than 14 evaluable patients are enrolled the exact 80% lower confidence bound (LCB) for ORR will be estimated. If the exact 80% LCB for ORR is ≥ 0.1, savolitinib will merit further investigation as a treatment for *MET* amplified metastatic CRC. The exact 80% LCB for ORR ≥ 0.1 is 3 patients respond for 13, 12, 11, 10, or 9 evaluable patients, or 2 patients respond for 8, 7, 6 or 5 evaluable patients. If fewer than 5 evaluable patients are enrolled the study design will be re-evaluated.

13.2 Sample Size/Accrual Rate

A maximum of 150 patients will be prospectively screened for *MET* amplification using a cf DNA assay (Guardant360^{TM}). In our experience (see Section 2.3), approximately 15% of patients with anti-EGFR refractory metastatic CRC have detectable *MET* amplification in cfDNA. Approximately 10% of all screened patients will meet study eligibility. Based on these assumptions, 15 patients will be enrolled and treated with savolitinib. Assuming 12 patients are screened per month, screening is expected to be completed in approximately 12.5 months.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	1	1	0	0	**2**
Asian	0	0	0	0	**0**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
Black or African American	2	3	1	1	**7**
White	1	2	1	1	**5**
More Than One Race	0	0	0	1	**1**
Total	**4**	**6**	**2**	**3**	**15**

PHS 398 / PHS 2590 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001/0002

13.3 Stratification Factors

No stratification factors are specified for this trial.

13.4 Analysis of Secondary Endpoints

Secondary endpoints include duration of response (11.1.5) and PFS (11.1.6). If the numbers of events permit these endpoints will be estimated using the Kaplan-Meier method.

Adverse events will be described by grade, frequency, and attribution according to CTCAE 5.0.

As secondary analyses: 1) ORR will be estimated within each *RAS* subgroup (mutant; wildtype). Based on the normal approximation, with 7 patients studied in each subgroup, ORR can be estimated to within at most +/- 0.24 with 80% confidence. Exact confidence limits will be wider with maximum length of 0.552. 2) PFS will be measured in patients who have received any protocol therapy.

In addition, potential associations between tissue and blood based biomarkers and clinical outcomes will be explored.

Due to the small sample size all secondary analyses will be considered descriptive.

13.5 Reporting and Exclusions

13.5.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with Savolitinib.

13.5.2 Evaluation of Response

All patients considered evaluable for response as defined in Section 11.1.1 must be assessed for response to treatment. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All patients considered evaluable for response as defined in Section 11.1.1 should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B PATIENT DRUG DIARY CARD

Savolitinib (AZD6094) – Patient Drug Diary Card

Subject ID Number: _____ Cycle #: _____ (___/___/_____ to ___/___/_____)

- You will be taking ____ 200 mg tablets per day.
- If you miss (accidentally skip or forget to take) a dose, do not make it up and continue with your next scheduled dose.
- If you vomit after taking a dose, do not make it up and continue with your next scheduled dose.
- Take savolitinib (AZD6094) with food and swallow tablets whole with water.
- Try to take savolitinib (AZD6094) at the same time each day.
- Avoid ingesting grapefruit juice, grapefruit and Seville oranges while talking savolitinib (AZD6094).
- Return unused drug and/or empty bottles at the next study visit.

Day	Date (mm/dd/yyyy)	# Tablets	Time (00:00 am/pm)	Day	Date (mm/dd/yyyy)	# Tablets	Time (00:00 am/pm)
1				15			
2				16			
3				17			
4				18			
5				19			
6				20			
7				21			
8				22			
9				23			
10				24			
11				25			
12				26			
13				27			
14				28			

To Be Completed By Study Staff Only:

Date Returned (mm/dd/yyyy)		# Tablets Returned	
Study Staff Initials		Discrepancy (circle)	Yes or No
If discrepancy, explain:			

APPENDIX C PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, **savolitinib (AZD6094).** This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

savolitinib (AZD6094) interacts with certain specific enzymes in the liver and certain transport proteins that help move drugs in and out of cells.

- The enzymes in question are CYP 3A4, 3A5, 1A2, 2C8, 2C9, and 2D6. savolitinib (AZD6094) is primarily metabolized by CYP 3A4/5 and 1A2 and some NADPH-independent non-CYP enzymes and may be affected by other drugs that strongly inhibit or induce CYP3A4/5 and CYP1A2. Savolitinib (AZD6094) inhibits CYP 3A4, 3A5, 1A2, 2C8, 2C9, 2D6 and UGT1A1 and may affect other drugs that are substrates of these enzymes.
- Savolitinib (AZD6094) inhibits P-gp, BCRP, OATP1B1, MATE1 and MATE2K transporters and this may affect transport of other drugs that is dependent on any of these transport proteins.
- Since there is limited clinical experience with this agent, patients on concomitant drugs with narrow therapeutic ranges, such as warfarin, should be monitored closely.

September 2017

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Savolitinib (AZD6094) may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Savolitinib (AZD6094) must be used very carefully with other medicines that need certain liver enzymes and transport proteins to be effective or to be cleared from your system. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of CYP 3A4, 3A5 and 1A2." Savolitinib (AZD6094) inhibits enzymes CYP 3A4, 3A5, 1A2, 2C8, 2C9, 2D6 and transport proteins P-glycoprotein (P-gp), BCRP (breast cancer resistance protein), OATP1B1, MATE1 and MATE2K. These characteristics may change how other medicine works in your body.

- The heart's electrical activity may be affected by savolitinib (AZD6094). The study doctor may be concerned about QTc prolongation and any other medicine that is associated with greater risk for having QTc prolongation.
- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Avoid ingesting grapefruit juice, grapefruit and Seville oranges while taking savolitinib (AZD6094).
- You may need to be monitored more frequently if you are taking any drugs that have narrow therapeutic ranges.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at _____.

September 2017

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **savolitinib (AZD6094).** This clinical trial is sponsored by the NCI. savolitinib (AZD6094) may interact with drugs that are processed by your liver, or use certain transport proteins in your body. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Avoid ingesting grapefruit, grapefruit juice and Seville oranges.
- You may need to be monitored more frequently if you are taking any drugs that have narrow therapeutic ranges, such as warfarin.

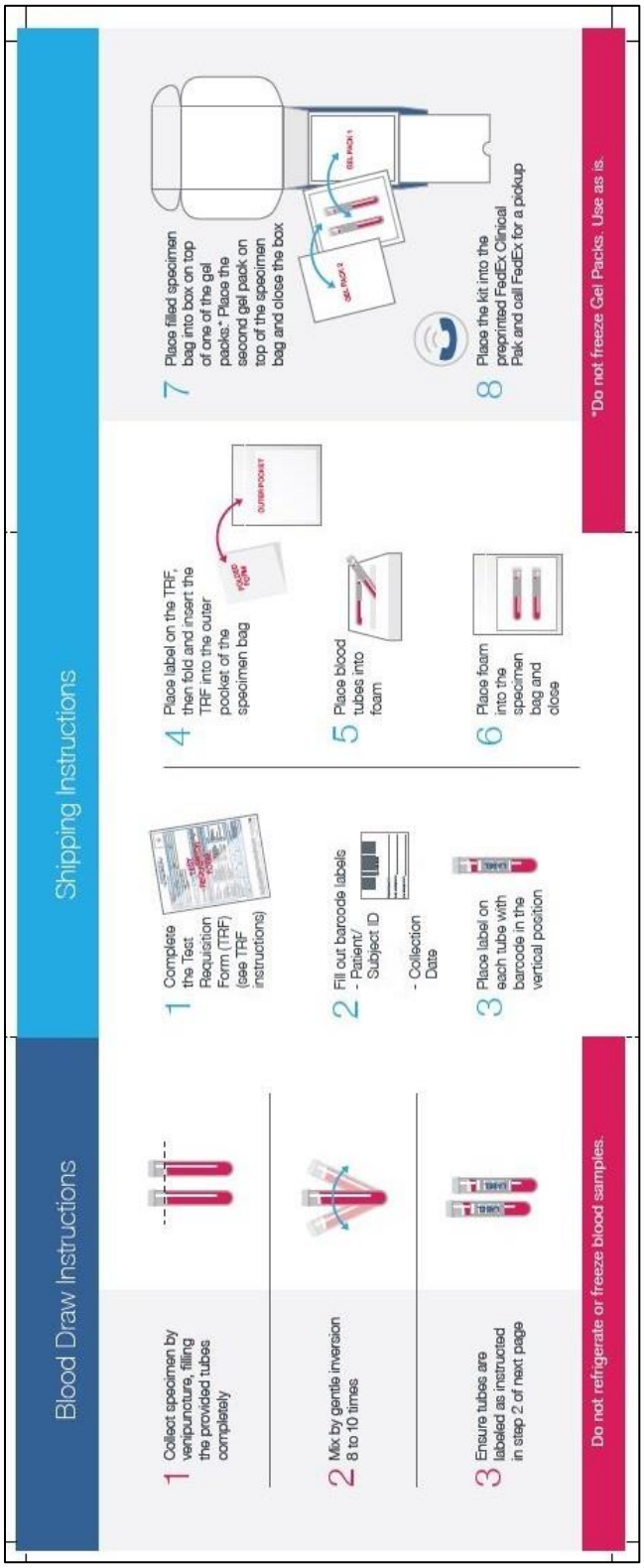
- savolitinib (AZD6094) interacts with CYP 1A2, 3A4/5, 2C8, 2C9, 2D6 and transport proteins, P-gp, BCRP, OATP1B1, MATE1 and MATE2K, and must be used very carefully with other medicines that interact with these enzymes and proteins.
- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of CYP 3A4/5, 1A2." savolitinib (AZD6094) inhibits CYP 3A4/5, 1A2, 2C8, 2C9, 2D6 and transporters, P-gp, BCRP, OATP1B1, MATE1 and MATE2K. It may change how other medicine works in your body.
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____

  and can be contacted at _____.

APPENDIX D NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

APPENDIX E GUARDANT360 BLOOD COLLECTION AND SHIPPING INSTRUCTIONS



APPENDIX F GUIDANCE REGARDING POTENTIAL INTERACTIONS WITH CONCOMITANT MEDICATIONS KNOWN TO PROLONG QT INTERVAL

Drugs that prolong QT interval

The drugs listed in this section are taken from information provided by the Arizona Center for Education and Research on Therapeutics website: https://www.crediblemeds.org. The website categorizes drugs based on the risk of inducing Torsades de Pointes (TdP). During screening the drugs that patients are currently prescribed should be checked opposite the ArizonaCert website above.

Drugs with a known risk of Torsades de Pointes

The following drugs prolong the QT interval and are clearly associated with a known risk of TdP, even when taken as recommended. These drugs must have been discontinued prior to the start of administration of study treatment in accordance with guidance provided in the table below and should not be co-administered with savolitinib and for a period of one week after discontinuing study treatment. The list of drugs may not be exhaustive and is subject to change as new information becomes available. As such investigators are recommended to search the website to provide the most up to date information.

Drugs with a known risk of TdP

Drug name	Withdrawal period prior to study treatment start
Anagrelide, ciprofloxacin, clarithromycin, cocaine, droperidol, erythromycin, levofloxacin, ondansetron, papaverine hydrochloride, procainamide, sulpiride, sultopride, terfenadine, terlipressin	2 days
Cilostazol, Cisapride, disopyramide, dofetilide, domperidone, flecainide, gatifloxacin, grepafloxacin, ibutilide, moxifloxacin, oxaliplatin, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sparfloxacin, thioridazine	7 days
Azithromycin bepridil, citalopram, chlorpromazine, dronedarone, escitalopram, fluconazole, halofantrine, haloperidol, levomepromazine, levosulpiride, mesoridazine	14 days
Donepezil, terodiline	3 weeks
Levomethadyl, methadone, pimozide	4 weeks
Arsenic trioxide*, Ibogaine	6 weeks
Pentamidine	8 weeks
Astemizole, Probucol, vandetanib	4 months
Amiodarone, chloroquine	1 year

* Estimated value as pharmacokinetics of arsenic trioxide has not been studied