NCI Protocol #: PBTC-049
Version Date: August 06, 2025

SUMMARY OF CHANGES – PROTOCOL DOCUMENT

For Protocol Amendment v11 to:

NCI Protocol #: PBTC-049
Local Protocol #: PBTC-049

NCI Version Date: August 06, 2025
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1.0 Investigator-Initiated changes (for protocol version date 08/06/2025):

#	Section	Change
1.	**General**	• Updated the protocol version date and version number, throughout. • Made minor administrative updates, including corrections of typos and formatting changes, throughout. • Relaced the word "gender" with "sex" throughout for consistency with the NCI and PBTC template.
2.	**Section 4.1** **Section 7.1** **Section 7.2** **Section 7.3.1** **Section 7.5** **Section 8.2.6** **Section 12.2** **Section 12.2.1** **Section 12.4**	Updated website links for CTEP clinical trials resources per NCI memo dated 07/09/2025.
3.	**Study Team Page** **Face Page** **Institution List Page**	• Study team page updated to include new biostatistician and correlative investigators listed in Section 9.1.4.4. • Administrative changes and updates made to individuals listed on the institution list page.

#	Section	Change
4.	Section 4.0 Section 7.0 Section 8.0 Section 12.0	Updated language for alignment with the NCI and PBTC protocol.
5.	Section 2.7	Added the following rationale for this amendment: "The protocol was amended to reflect a change in correlative study investigators for the c-MET expression and c-MET amplification correlatives in Section 9.1.4. Two new investigators from the same institution, Cincinnati Children's Hospital Medical Center, have been appointed to streamline study execution and ensure continuity of the correlative analyses."
6.	Section 4.0 Section 7.0 Section 8.0 Section 12.0	Updated language for alignment with the NCI and PBTC protocol.
7.	Section 9.1.4.4	• Updated section to include names and contact information of new correlative study investigators for c-MET expression and c-MET amplification. • Clarified the process for how correlative study samples will be received, distributed, and reviewed at Cincinnati Children's Hospital Medical Center.

NCI Protocol #: PBTC-049

Local Protocol #: PBTC-049

ClinicalTrials.gov Identifier: NCT03598244

TITLE: A Phase I Study of Savolitinib in Recurrent, Progressive, or Refractory Medulloblastoma, High-Grade Glioma, Diffuse Intrinsic Pontine Glioma, and CNS Tumors Harboring MET Aberrations

Coordinating Center: Operations, Biostatistics and Data Management Core (OBDMC) for the Pediatric Brain Tumor Consortium (PBTC), St. Jude Children's Research Hospital

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CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.		
For clinical questions (i.e., patient eligibility or treatment-related) Contact the Study PI and copy the Protocol Coordinator.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or email: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		

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Abstract and Schema

This is a multicenter Phase I trial for children with recurrent, progressive, or refractory primary central nervous system tumors.

Mesenchymal epithelial transition (MET) receptor, also known as c-MET, is an oncogene encoding for a trans-membrane tyrosine kinase receptor activated by the hepatocyte growth factor (HGF). MET has a normal function in organ development during embryogenesis and in tissue homeostasis during adult life.

Abnormal MET activation in cancer correlates with poor prognosis, where aberrantly active MET triggers tumor growth, formation of new blood vessels (angiogenesis) that supply the tumor with nutrients, and cancer spread to other organs (metastasis). Deregulation of HGF/MET signaling pathway is frequently observed in many cancer types of the kidney, liver, stomach, lung, breast, and brain, conferring invasive growth and tendency to progression. Thus, HGF and MET are therapeutic targets and anti HGF/MET agents may represent a potential antitumor strategy.

Savolitinib is a potent and selective small molecule inhibitor of c-MET kinase. It is found to inhibit c-MET kinase at the cellular and enzymatic levels with an IC_{50} between 3–5 nM. In preclinical studies, it demonstrated strong *in vitro* and *in vivo* activity against c-MET kinases and its downstream signaling targets and significantly decrease tumor cell growth.

This is a dose escalation study of savolitinib administered orally once a day to patients with recurrent, progressive, or refractory central nervous system tumors. There are three stages in this study: a dose escalation cohort, PK expansion cohort, and an efficacy expansion cohort. The dose escalation cohort is designed to determine the maximum tolerated dose (MTD)/recommended Phase II dose (RP2D), to evaluate the pharmacokinetics, safety, and preliminary anti-tumor activity of savolitinib. Once the MTD/RP2D is determined, the enrollment for an efficacy expansion cohort will open for patients whose tumors harbor genetic MET activation as determined by testing performed in a CLIA-certified laboratory.

Savolitinib will be given once a day orally for 28 days. Twenty-eight (28) consecutive days will constitute one course. The starting dose will be 150 mg/m^2 (Dose Level 1). As of protocol Version 4.0, Dose Level 2 was re-instated and Dose Level 3 was added based on guidance from the drug company that the adult RP2D has been revised to 600 mg/day as the maximum dose. Dosing should be adjusted based on BSA calculated at the beginning of each course for Courses 1–39. Therapy may continue up to 39 courses (approximately 3 years) in the absence of disease progression or unacceptable toxicity.

As of protocol version 7.0 (version date October 6, 2022), the RP2D has been declared as Dose Level 3 (350 mg/m^2). In addition, patients may receive extended therapy with savolitinib beyond 39 courses if there is evidence of clinical benefit, in the absence of disease progression or unacceptable toxicity. Provided that these extended therapy patients continue to meet study criteria, study treatment may continue until all other subjects meet off-treatment criteria.

Dose Escalation Schedule		
Dose Level	**Dose of savolitinib (mg/m^2 once a day)**	**BSA Requirements**
0	75 mg/m^2	$\geq 1.00\ m^2$
1*	150 mg/m^2	$\geq 0.55\ m^2$
2	240 mg/m^2	$\geq 0.67\ m^2$
3 #	350 mg/m^2	$\geq 0.73\ m^2$

* Starting dose

RP2D. With declaration of the RP2D at Dose Level 3, the upper BSA restriction used for enrollment at Dose Level 3 during the dose finding phase has been lifted. During the expansion phases (PK and efficacy), patients with BSA $\geq 2.10\ m^2$ will receive 600 mg flat dose once a day.

Table of Contents

1 OBJECTIVES

1.1 Primary Objectives

1.1.1 To estimate the maximum tolerated dose (MTD) and recommend a Phase II dose of savolitinib administered orally daily in children with refractory, progressive, or recurrent primary CNS tumors.

1.1.2 To define and describe the toxicities of savolitinib in children with refractory, progressive, or recurrent primary CNS tumors.

1.1.3 To characterize the pharmacokinetics of savolitinib in children with refractory, progressive, or recurrent primary CNS tumors.

1.2 Secondary Objectives

1.2.1 To preliminarily define the antitumor activity of savolitinib within the confines of a Phase I study.

1.2.2 To perform a genomic analysis within the confines of a Phase I study to investigate correlation between response to treatment (as measured by objective response or PFS) and the presence of specific genomic alterations (e.g., *MET* or *HGF* amplification, *MET* mutations, or *MET fusion*) and/or specific subgroups of disease.

2 BACKGROUND

2.1 Study Disease

2.1.1 Overview of the HGF-MET Axis and its Role in Cancer

Paracrine hepatocyte growth factor (HGF) signaling regulates the development and homeostasis of several tissues including the kidneys, liver, mammary glands, muscles, and neurons.[1] Upon binding of HGF to the mesenchymal-epithelial transition receptor (c-MET), c-MET dimerizes leading to autophosphorylation and promotion of its intrinsic kinase activity. The downstream effects of c-MET signaling are then mediated through the activation of a multisubstrate docking site where several adapter proteins bind, including: growth factor receptor-bound protein 2 (GRB2), Src homology-2-containing (SHC), v-crk sarcoma virus CT10 oncogene homolog (CRK), and GRB2-asscoiated binding protein 1 (GAB1). In turn, the adapter proteins recruit a variety of signaling proteins forming a complex which provides effector functions of HGF-MET with downstream targets that include MAPK/ERK and PI3K/AKT.[2] By promoting proliferation, migration, survival, and differentiation, the HGF-MET axis plays a critical role in embryogenesis, organogenesis, and tissue repair.[3] HGF-MET signaling can also have pro-oncogenic effects since it promotes angiogenesis[4], metastasis[5], and tumor stem cell maintenance.[6]

Aberrant activation of HGF-MET is linked to oncogenic transformation in a spectrum of adult and pediatric cancers.[1] Tumorigenic activation of HGF-MET can occur through a variety of mechanisms. Activating point mutations of c-MET, particularly within the activation loop of the tyrosine kinase domain, can lead to constitutive activation of c-MET and are especially prevalent in sporadic and inherited papillary renal carcinomas.[7] MET may also be amplified with resulting overexpression and constitutive activation in tumors such as gastric and esophageal carcinomas, medulloblastoma, and gastric cancer.[2] The most common mechanism of c-MET activation in tumors is overexpression of c-MET as a consequence of transcriptional upregulation. In response to low concentrations of intracellular oxygen, hypoxia inducible factor 1 alpha (HIF1α) activates the c-MET promoter.[8] This phenomenon has been detected in a variety of tumor types including thyroid, colorectal, ovarian, pancreatic, lung, and breast malignancies.

2.1.2 HGF and c-MET Activity in Pediatric Brain Tumors

2.1.2.1 *Medulloblastoma*

There is accumulating evidence that the HGF/MET pathway is aberrantly activated in medulloblastoma. In a study looking at embryonal central nervous system (CNS) tumors, Li et al.[9] demonstrated that almost all medulloblastoma cell lines and primary human tumor samples expressed HGF (32/32) and c-MET (31/32). In addition, exogenous HGF was found to induce proliferation and anchorage independent growth of medulloblastoma cells. Amplification of the MET oncogene on chromosome 7q was detected by comparative genomic hybridization (CGH) in 38.5% of medulloblastoma tumors by Tong et al.[10] In large-cell anaplastic medulloblastoma, HGF was found to induce c-Myc mRNA and c-Myc protein via transcriptional and posttranscriptional mechanisms leading to cell cycle progression and proliferation.[11] More recently, a study done by Northcott et al. that profiled the genomic status of more than 1000 medulloblastoma of all four subgroups indicated a significant gain of the 7q31.1 segment, which includes the *MET* gene (Supplemental Table 14 located the noted citation), in Group 4

medulloblastoma (q value=0.0012593, GISTIC).[12] Finally, the RNA expression levels of c-MET correlate with poor outcome in medulloblastoma patients and were found to be an independent unfavorable prognostic factor.[9]

2.1.2.2 *High-Grade Glioma/Diffuse intrinsic pontine glioma (DIPG)*

HGF-MET signaling in high-grade gliomas (HGG) is often upregulated. c-MET signaling is involved in glioma stemness, growth and invasion and was associated with neurospheres expressing the gene signature of the mesenchymal and proneural subtypes of glioblastoma.[13] HGF and c-MET are expressed *in vitro* in glioblastoma multiforme (GBM) cell lines and HGF binding to MET in glioma cell lines leads to their proliferation, increased motility, and invasiveness.[14] Moreover, the degree of c-MET expression in malignant gliomas was found to correlate with tumor grade.[15] In a study of 32 gliomas, 100% of tumors expressed c-MET while 72% of the tumors co-expressed HGF.[14] MET and HGF co-staining was observed in 8 of 11 anaplastic astrocytomas, and in 13 of 15 GBM. Among 43 diffuse intrinsic pontine gliomas (DIPG), focal amplifications of genes within the RTK/PI3K signaling pathway were found in 47% of cases, 25.6% of them involved gains in *MET*.[16] An analysis of the submitted expression profiles compared to two normal brain samples obtained during autopsy shows that about half of DIPG samples expressed MET at clearly higher levels than normal samples (Figure 1). In addition, high levels of c-MET hold unfavorable prognostic value in patients with GBM.[17] More recently, Bender et al. performed an integrative genetic analysis of 53 pediatric GBM tumors and identified activating *MET* fusions in 10% of cases.[18]

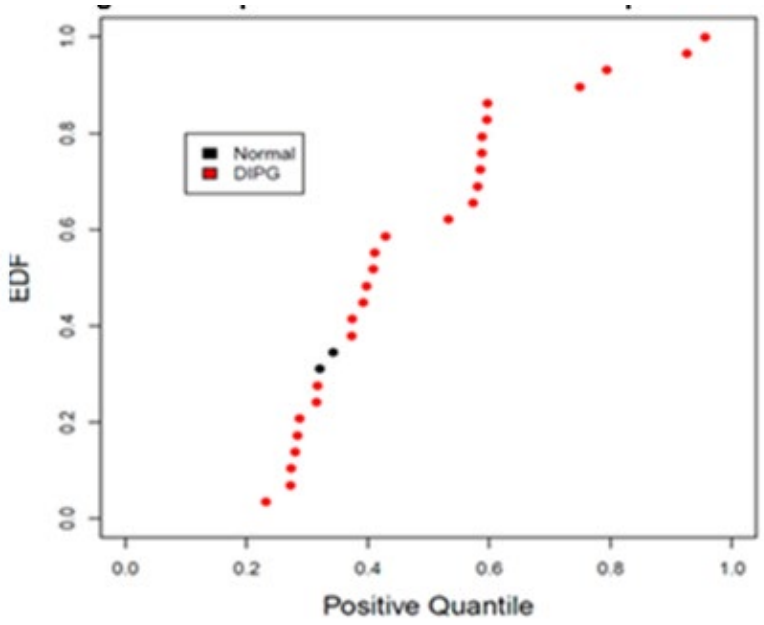


Figure 1. Empirical distribution of MET expression in DIPG

2.1.2.3 *Preclinical Studies of c-MET Inhibitors in CNS Tumors*

***In vitro* preclinical activity:**

c-MET inhibition in high-risk medulloblastoma cell lines with the small molecule inhibitor PHA665752 led to a dose-dependent decrease in proliferation and reduced motility and growth under anchorage-independent conditions.[19] These effects were shown to be at least partially mediated by inhibition of the RAS/MAPK and PI3K/AKT pathways. Using a different c-MET inhibitor, PF-02341066, Zhang et al. demonstrated a significant increase in cell death by apoptosis and decreased proliferation in different medulloblastoma and GBM cell lines especially when HGF was co-expressed.[20]

In vivo preclinical activity:

Therapy with foretinib, a multikinase inhibitor with high affinity to c-MET, was evaluated in 2 different medulloblastoma mice models with high c-MET expression and no underlying genomic aberrations in the MET gene.[21] DAOY hind flank xenografts implanted in nude mice responded to 2 doses of the drug. Following treatment for 9 days, tumor volumes were reduced by 37% and 46% with 60 and 100 mg/kg of foretinib, respectively. This was accompanied by significant changes in Ki-67 and activated caspase-3. In a genetically engineered metastatic SHH medulloblastoma mouse model (Ptch+/- /SB11/T2Onc), primary medulloblastoma tumors treated with foretinib displayed a less invasive phenotype and less metastasis. Moreover, foretinib treatment conferred longer survival in this aggressive mouse model (Figure 2).[21]

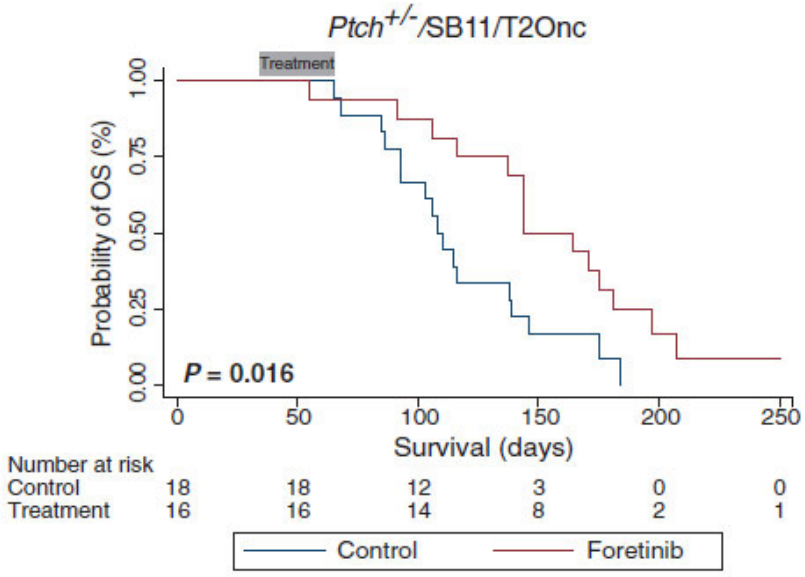


Figure 2. Kaplan-Meier survival curves of Ptch+/- /SB11/T2Onc mice treated with foretinib vs. control

In a GBM orthotopic xenograft mouse model using U87 cells implanted in the striatum of immunodeficient mice, treatment with the c-MET inhibitor SGX523 for 21 days lead to a significant decrease in tumor volume without any evident drug-related toxicities.[22] (Figure 3)

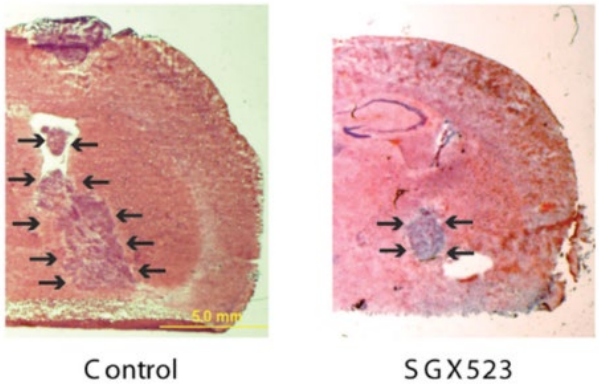


Figure 3. SGX523 leads to a significant decrease in tumor volume in GBM intracranial xenografts

2.2 Savolitinib

Biochemical and functional characterization of savolitinib has been fully described.[23] Savolitinib is a potent and selective small molecule inhibitor of c-MET kinase. It inhibits c-MET kinase at the cellular and enzymatic levels with an IC_{50} between 3–5 nM.

2.2.1 Preclinical Studies of Savolitinib in CNS Tumors

In vitro activity as single agent:
The U87MG glioma cell line with high c-MET expression was found to be responsive to savolitinib with an IC_{50} of 0.007 µm. This was enhanced in culture conditions with high HGF levels (0.1 % BSA), suggesting that the response to savolitinib is HGF-dependent in this model.[24]

In vivo activity as a single agent:
When administered to U87 tumor-bearing mice (nude mice bearing subcutaneous human GBM U87MG tumors and brain orthotopic xenografts), savolitinib significantly decreased tumor growth and prolonged median survival time in both models when compared to vehicle-treated mice. The compound lead to a dose-dependent tumor growth delay reaching up to 85% by day 22 in the subcutaneous xenograft model. In addition, its activity in the orthotopic xenograft model suggests that savolitinib crosses the blood brain barrier in these tumor-bearing mice.[24]

The activity of savolitinib has not been evaluated in pediatric cell lines nor *in vivo* models.

2.2.2 Adult Clinical Trials

Healthy Volunteer Studies:
In a study investigating the effect of food on single-dose pharmacokinetics (PK) of savolitinib in healthy volunteers, the drug was found to be rapidly absorbed with a median T_{max} around 1–3 hours. The mean t½ ranged between 3.6 to 6.8 hours across dose ranges. Mean AUC_{inf} was

estimated as 3034 h*ng/mL at the 100 mg dose. Food intake had a modest effect on PK that was determined unlikely to be clinically significant.

Phase I Studies of Savolitinib Monotherapy:
A phase I first-in-human dose escalation study of single-agent oral savolitinib in Australian patients with advanced solid tumors determined the maximum tolerated dose (MTD) of single-agent oral savolitinib as 800 mg/day and the recommended phase 2 dose (RP2D) as 600 mg/day. As of the data cut-off date of February 2017, a total of 245 patients had received savolitinib as monotherapy. Most patients (211/245 patients [86.1%]) had an adverse event (AE) that was considered related to savolitinib treatment. The most frequently reported causally-related AEs (≥ 10% of patients overall) were nausea (41.2%), vomiting (24.9%), fatigue (21.2%), peripheral edema (18%), decreased appetite (15.9%), diarrhea (10.6%).

A total of 100/245 patients (40.8%) had an AE of CTCAE Grade 3 and 20/245 (8.2%) had an AE of CTCAE Grade 4. The most frequent Grade 3 AE was fatigue, affecting 13/245 patients (5.3%). This was the only AE of CTCAE Grade 3 to affect > 5% patients. The most frequent Grade 4 AEs were ALT increased, anemia, drug induced liver injury, hyperkalemia all affecting 2/245 patients.

Limited data for efficacy is available at the current time. As of the data cut-off date of February 2017, in a Phase I, open-label, dose escalation study of the safety and PK of savolitinib in patients with advanced solid tumors, 3 patients with papillary renal cell carcinoma (PRCC) had achieved a partial response on savolitinib monotherapy. Hence the best overall response rate (ORR) for all patients overall was 6.3%. In addition, another patient with papillary renal cell carcinoma achieved a 25% tumor reduction. All 4 patients had *MET* alterations in their tumors.[24]

Phase II Study of Savolitinib in Patients with Advanced Papillary Renal Carcinoma:
The single-arm, multicenter, global, phase II study evaluated the safety and efficacy of savolitinib in patients with histologically confirmed locally advanced or metastatic PRCC[25]. In this trial, 109 patients were treated with savolitinib 600 mg once daily. Forty percent (40%) of patients had MET-driven PRCC, 42% were MET-independent and 17 % had unknown MET status. While objective responses were only achieved in MET-driven PRCC (18% had confirmed partial response), stable disease was seen in 22 patients (50%) with MET-driven disease and 11 (24%) with MET-independent disease. The most frequently observed AEs were consistent with prior savolitinib monotherapy trials and were nausea, vomiting, fatigue, and peripheral edema.

2.2.3 Pediatric Studies

No pediatric studies of savolitinib have been conducted.

2.3 Rationale for Proposed Pediatric Study

Pediatric patients with recurrent CNS tumors (such as recurrent medulloblastoma, DIPG, or high-grade glioma) have a poor prognosis, and there is a clear need to develop more effective therapies. In view of the preclinical activity of c-MET inhibitors in a variety of malignancies and CNS tumors, and the important role which the MET pathway plays in pediatric CNS tumors, we propose a Phase I study in pediatric patients with recurrent CNS malignancies that will define the toxicity profile in children, determine the MTD/RP2D in children, and will better describe the pharmacokinetics of savolitinib in this patient population. In an effort to look for an early signal

of efficacy, once the MTD/RP2D is determined we propose a small efficacy expansion cohort to enroll patients whose tumors harbor genetic *MET* activation as determined by testing performed at a CLIA-certified laboratory. Limited preclinical data suggest that savolitinib may be associated with physeal hyperplasia; the potential effect of savolitinib on bone development will therefore be monitored in this study by knee X-rays, and knee MRI if clinically indicated.

2.3.1 Primary Hypothesis

Savolitinib will have a similar toxicity profile in children with refractory or recurrent CNS tumors to the toxicity profile observed in adults. In this patient population, the MTD of savolitinib will be comparable to the adult MTD.

2.3.1 Secondary Hypothesis

Savolitinib will demonstrate anti-tumor activity in pediatric CNS tumors associated with HGF-MET aberrations.

2.4 Rationale for Amendment v7.0 (Protocol Version Date October 6, 2022) – Declaration of the RP2D and extension of the maximum number of courses

Following completion of the dose-finding phase, the RP2D has been established as Dose Level 3, 350 mg/m^2. All prospective patients enrolling onto this study in the PK and efficacy expansion phases will receive a dose of 350 mg/m^2. With the declaration of the RP2D at Dose Level 3, the upper BSA restriction used for enrollment at Dose Level 3 during the dose finding phase has been lifted. Patients with a BSA $\geq$ 2.10 m^2 will receive a 600 mg flat dose of savolitinib, once per day. Lastly, with this amendment, patients who show evidence of clinical benefit from the study drug may receive extended therapy beyond 39 courses with savolitinib. Provided that these patients continue to meet study criteria, study treatment may continue until all other subjects meet off-treatment criteria. Please see Section 5.1.1 for details.

2.5 Rationale for Amendment v8.0 (Protocol Version Date August 31, 2023) – Modification of eligibility criteria to allow CLIA-certified MET testing for enrollment on the efficacy cohort

In an effort to prevent tumor tissue exhaustion, treatment delays, and duplication of molecular testing, the protocol was amended to remove the requirement to have MET aberrations confirmed by an FDA-approved assay and will instead accept testing performed by a CLIA-certified laboratory for eligibility to the efficacy expansion cohort. Rapid review of local CLIA-certified sequencing laboratory reports will be performed by the Study Chair and qualified personnel from the Institute for Genomic Medicine at Nationwide Children's Hospital (NCH). Based on recent evidence showing that chromosome 7 gain is less predictive than *MET* amplification to correlate with sensitivity to MET inhibitors, this molecular eligibility criterion was removed. In addition, a clarification of acceptable *MET* mutations (kinase domain and exon 14) was added and revised to include well-characterized mutations that are associated with increased MET signaling. See Section 3.1.1 for details.

2.6 Rationale for Amendment v10 (November 14, 2024) – Clarification of exclusion criteria and management of savolitinib-related hepatotoxicity, hypersensitivity, and QTc prolongation

The protocol was amended upon AstraZeneca's request to further clarify exclusion criteria and management of savolitinib-related hepatotoxicity, hypersensitivity, and QTc prolongation.

2.7 Rationale for Amendment v11 (August 06, 2025) – Replacement of correlative study investigators for c-MET expression and c-MET amplification correlatives

The protocol was amended to reflect a change in correlative study investigators for the c-MET expression and c-MET amplification correlatives in Section 9.1.4. Two new investigators from the same institution, Cincinnati Children's Hospital Medical Center, have been appointed to streamline study execution and ensure continuity of the correlative analyses.

2.8 Correlative Studies Background

2.8.1 Rationale for Biology Studies and Genomics

Although understanding pharmacokinetics will be a primary objective of this Phase I study, biologic correlates will be investigated and are mandatory. We will assess whether tumor samples show evidence of c-MET expression. In addition, we will interrogate the c-MET pathway at the genomic level looking for specific aberrations that may lead to its activation (e.g., *MET* or *HGF* amplification, *MET* mutations, or *MET* fusions). We will also explore the relationship between c-MET status and anti-tumor response within the constraints of a Phase I trial. These data will be hypothesis generating.

2.8.2 Rationale for Pharmacokinetic Studies

Because the pharmacokinetics of savolitinib have not been explored in children, PK data collected from this trial will be analyzed to describe the interpatient variability in savolitinib PK parameters in this population. This information may be useful in evaluating toxicity, biologic activity, disease response, and for refining dose parameters. The information may help guide dose escalation beyond the proposed doses if no MTD is determined in the initial dose levels (as noted in Section 5.2.3). There is a possibility that patients' age may affect toxicity, PK parameters, and efficacy of this agent, and thus, at the MTD/RP2D as part of the PK expansion cohort, we will stratify enrollment to ensure at least 6 patients are treated at each of the following 2 cohorts based on age at the time of enrollment: patients < 12 years old and patients ≥ 12 years old.

2.8.3 Hypotheses

We hypothesize the PK parameters for savolitinib in children will be similar to those in adults. We also hypothesize that exposure will increase with increasing dose.

3 PATIENT SELECTION

All subjects must meet the following inclusion and exclusion criteria. No exceptions will be given. Imaging studies to establish eligibility must be done within 3 weeks prior to enrollment. All other clinical evaluations to establish eligibility must be done within 7 days prior to enrollment.

3.1 Eligibility Criteria for Enrollment

3.1.1 Diagnosis

- Patients with a histologically confirmed diagnosis of a primary CNS tumor (medulloblastoma, high-grade glioma, or DIPG) that is recurrent, refractory, or progressive. All tumors must have histologic verification at either the time of diagnosis or recurrence except patients with diffuse intrinsic brain stem tumors. These patients must have radiographic or clinical evidence of progression.

  Patients with a recurrent, progressive, or refractory primary CNS tumor with evidence of genetic activation of the MET pathway, regardless of histology, are also eligible to the Phase I component of this study. Refer to the efficacy expansion cohort section below for MET pathway activation definition and testing information.

  Note: Refractory disease is defined as the presence of persistent abnormality on conventional MRI imaging that is further distinguished by histology (biopsy or sample of lesion) or advanced imaging, OR as determined by the treating physician and discussed with the primary investigator prior to enrollment.

- Efficacy Expansion Cohort
  Patients must have a recurrent, progressive, or refractory primary CNS tumor with evidence of genetic activation of the MET pathway, regardless of histology. Specimens can be from diagnosis or recurrence and there is no time limit from when the specimen was obtained prior to enrollment onto the efficacy expansion cohort. Results from a CLIA-certified laboratory will be accepted for this eligibility criterion. Sites must provide a redacted copy of the local CLIA-certified sequencing laboratory report to the Study Chair via email prior to enrollment. See Section 4.4.2 for details.

  MET pathway activation is defined as:
  - *MET* mutations

  OR
  - *MET* or *HGF* amplification

  OR
  - *MET* fusion

  Acceptable *MET* mutations are listed in Appendix 15.4.

3.1.2 Available Pre-trial Tumor Tissue

Recurrent or refractory primary malignant CNS tumor patients must have adequate pre-trial frozen or FFPE tumor material available for the required correlative studies (Section 9.1.4 and 9.1.5). If target amounts of tissue or number of slides are not available, the site must obtain Study Chair/Co-Chair approval for adequacy of submitted tumor samples and prioritization of studies to be performed, prior to patient enrollment.

Patients with DIPG who have pre-trial tumor tissue available are requested to submit tissue; however, this is not required for eligibility.

3.1.3 Disease Status

Patients must have evaluable disease to be eligible. Evaluable disease is defined as the presence of at least one lesion that can be measured accurately in at least 2 (two) dimensions.

3.1.4 Age

Patients must be > 5 years and ≤ 21 years of age at the time of study enrollment.

3.1.5 BSA

- Patients enrolled on 75 mg/m^2/day (Dose Level 0) must have a BSA ≥ 1.00 m^2.
- Patients enrolled on 150 mg/m^2/day (Dose Level 1) must have a BSA ≥ 0.55 m^2.
- Patients enrolled on 240 mg/m^2/day (Dose Level 2) must have a BSA ≥ 0.67 m^2.
- Patients enrolled on 350 mg/m^2/day (Dose Level 3) must have a BSA ≥ 0.73 m^2.

3.1.6 Prior Therapy

Patients must have failed prior standard therapy for their tumor. Patients with medulloblastoma must have received radiation therapy in addition to platinum and alkylator-based chemotherapy. Patients with HGG and DIPG must have at least received radiation therapy.

Patients must have recovered from the acute treatment related toxicities (defined as ≤ Grade 1 if not defined in eligibility criteria) of all prior chemotherapy, immunotherapy, radiotherapy, or any other treatment modality prior to entering this study.

3.1.6.1 *Myelosuppressive chemotherapy*

Patients must have received their last dose of known myelosuppressive anticancer therapy at least 21 days prior to enrollment or at least 42 days if it included nitrosourea.

3.1.6.2 *Investigational/Biologic Agent*

- Biologic or investigational agent (anti-neoplastic):

Patients must have recovered from any acute toxicity potentially related to the agent and received their last dose of the investigational or biologic agent ≥ 7 days prior to study enrollment.

  - For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur.

- Monoclonal antibody treatment and agents with known prolonged half-lives:

Patients must have recovered from any acute toxicity potentially related to the agent and received their last dose of the agent ≥ 28 days prior to study enrollment.

3.1.6.3 *Radiation*

Patients must have had their last fraction of:

- Craniospinal irradiation or total body irradiation or radiation to ≥ 50% of pelvis > 12 weeks prior to enrollment.
- Focal irradiation > 4 weeks prior to enrollment

3.1.6.4 *Stem Cell Transplant*

Patients must be:

- ≥ 24 weeks since allogeneic stem cell transplant prior to enrollment with no evidence of active graft vs. host disease
- ≥ 12 weeks since autologous stem cell transplant prior to enrollment

3.1.7 Neurologic Status

- Patients with neurological deficits should have deficits that are stable for a minimum of 1 week prior to enrollment. A baseline detailed neurological exam should clearly document the neurological status of the patient at the time of enrollment on the study.
- Patients with seizure disorders may be enrolled if seizures are well controlled.
- Patients must be able to swallow whole tablets to be eligible for study enrollment.

3.1.8 Performance Status

Karnofsky Performance Scale (KPS for > 16 years of age) or Lansky Performance Score (LPS for ≤ 16 years of age) assessed within two weeks of enrollment must be ≥ 50.

- Patients who are unable to walk because of neurologic deficits, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

3.1.9 Organ Function

Patients must have adequate organ and marrow function as defined below:

- Absolute neutrophil count ≥ 1.0 x 10^9 cells/ L
- Platelets ≥ 100 x 10^9 cells/ L (unsupported, defined as no platelet transfusion within 7 days prior to enrollment)
- Hemoglobin ≥ 8 g/dL (hemoglobin should be unsupported, i.e., red blood cell transfusions are not allowed within 14 days prior to enrollment)
- Adequate liver function defined as:
  - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x the upper limit of normal (ULN) with Total Bilirubin ≤ 1x ULN
  OR
  - Total Bilirubin > ULN – ≤ 1.5 x ULN with ALT and AST ≤ 1 x ULN
- Albumin ≥ 2 g/dL
- Serum creatinine based on age/sex as noted in Table 1. Patients that do not meet the criteria in Table 1 but have a 24 hour Creatinine Clearance or GFR (radioisotope or iothalamate) ≥ 70 mL/min/1.73 m^2 are eligible.

Table 1.

Serum Creatinine for age/sex		
Age	**Maximum Serum Creatinine (mg/dL)**	
	Male	**Female**
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4
The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.		

- Coagulation parameters: INR < 1.5 x ULN and aPTT < 1.5 x ULN unless patients are receiving therapeutic anti-coagulation which affects these parameters.
- Patients with known tumor thrombus or deep vein thrombosis are eligible if clinically stable on low molecular weight heparin for ≥ 2 weeks.
- Cardiac Function:
  - Mean resting corrected QT interval (QTc Bazett) ≤ 450 msec on screening obtained from 3 electrocardiograms (EKGs)
- Pulmonary Function
  - Oxygen saturation as measured by pulse oximetry is > 93% on room air

3.1.10 Corticosteroids

Patients who are receiving corticosteroids must be on a stable or decreasing dose for at least 1 week prior to enrollment.

3.1.11 Growth Factors

Patients must be off all colony-stimulating factor(s) (e.g., filgrastim, sargramostim, or erythropoietin) for at least 1 week prior to enrollment. Two (2) weeks must have elapsed if patients received PEG formulations.

3.1.12 Pregnancy Prevention

- Patients of childbearing or child fathering potential must be willing to use a medically acceptable form of birth control, which includes abstinence, while being treated on this study.
- Women of child-bearing potential should use effective contraception from the time of enrollment until 4 weeks after discontinuing study treatment.
- Male study participants should use a condom with female partners of child-bearing potential during the study and for 24 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 24 weeks after discontinuing study treatment.

- Male study participants should avoid fathering a child and refrain from sperm donation from study start to 24 weeks after discontinuing study treatment.

3.1.13 Informed Consent

Ability to understand and willingness to sign a written informed consent document. Legally authorized representatives may sign and give informed consent on behalf of study participants.

3.2 Exclusion Criteria

3.2.1 Pregnancy or Breast-feeding Women

Pregnant women or nursing mothers are excluded from this study. Female patients of childbearing potential must have a negative serum or urine pregnancy test within 7 days prior to enrollment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Pregnant women are excluded from this study because there are unknown but potential risks to an unborn baby from savolitinib. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with savolitinib, breastfeeding should be discontinued if the mother is treated with savolitinib.

3.2.2 Concurrent Illness

- Patients with a known serious active infection including, but not limited to human immunodeficiency virus, and tuberculosis.
- Patients with a known active or resolved viral hepatitis infection.
- Patients with any clinically significant unrelated systemic illness or significant cardiac, pulmonary, hepatic, or other organ dysfunction), that in the opinion of the investigator would compromise the patient's ability to tolerate protocol therapy, put them at additional risk for toxicity or would interfere with the study procedures or results.
- Patients with uncontrolled hypertension (i.e., a blood pressure (BP) > 95th percentile for age, height, and sex, patients with values above these levels must have their blood pressure controlled with medication prior to starting study drug)
    - The normal blood pressure by height, age, and sex can be assessed by using the NIH Guidelines on the PBTC Member's website (*Protocols* → *Generic Forms and Templates* → *Normal Blood Pressure by Height and Age*)

- Patients with any of the following cardiac diseases:
    - Congestive heart failure (New York Heart Association ≥ Grade 2) (see Appendix 15.2)
    - Clinically significant cardiac arrhythmia
    - Mean resting corrected QT interval (QTc Bazett) > 450 msec on screening obtained from 3 electrocardiograms (EKGs) or
    - Factors that may increase the risk of QTc prolongation such as chronic hypokalemia 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 medication known to prolong the QT interval and cause Torsade de Pointes. Refer to Appendix 15.3 for a partial list of medications that are associated with QTc prolongation and Torsade de Pointes. These drugs must have been discontinued prior to the start of administration of study treatment in accordance with guidance provided in Table 5 of Appendix 15.3.
- Any clinically important abnormalities in rhythm, conduction, or morphology of resting EKG, e.g., complete left bundle branch block, third degree heart block, second degree heart block, PR interval > 250 msec.

- Patients with history of liver cirrhosis of any origin and clinical stage; or history of other serious liver disease or chronic disease with relevant liver involvement, with or without normal LFTs, including but not limited to:
  - Hemochromatosis
  - Alpha -1 Antitrypsin deficiency
  - Autoimmune hepatitis (AIH)
  - Primary sclerosing cholangitis (PSC)
  - Primary biliary cirrhosis (PBC)
  - Biopsy-confirmed Non-Alcoholic Steatohepatitis (NASH) with advanced fibrosis
  - Biopsy-confirmed Alcoholic Steatohepatitis with advanced fibrosis
  - Wilson's disease
  - Hepatocellular carcinoma

* Patients with liver metastases are eligible, provided they meet other eligibility criteria, including liver biochemistry criteria.

- Patients with a prior or concurrent malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment of the investigational regimen for this trial.

3.2.3 Concurrent Therapy

- Patients who are receiving any other anticancer or investigational drug therapy.
- Patients receiving strong inducers of CYP3A4, strong inhibitors of CYP3A4 or CYP1A2 or CYP3A4 substrates with a narrow therapeutic index within 2 weeks of the first dose of savolitinib (3 weeks for St John's Wort). Strong inducers of CYP3A4 and CYP3A4 substrates which have a narrow therapeutic range or CYP3A4 sensitive substrates should not be used during the trial or used with caution. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference. Appendix 15.6 (Patient Drug Information Handout and Wallet Card) should be provided to patients.
- Prior or current treatment with a MET inhibitor (e.g., foretinib, crizotinib, cabozantinib, or onartuzumab).

3.2.4 Herbal preparations/medicines

Patient is currently receiving any of the following herbal preparations or medications and cannot be discontinued 1 week (7 days) prior to enrollment (3 weeks for St. John's wort). These herbal medications include, but are not limited to: Cannabis products, St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng.

3.2.5 Surgical procedures

Patient has undergone major surgical procedure ≤ 28 days prior to beginning study drug or a minor surgical procedure ≤ 7 days prior to beginning study drug. No waiting is required following port-a-cath placement.

3.2.6 Inability to Participate

Patients who in the opinion of the investigator are unwilling or unable to return for required follow-up visits or obtain follow-up studies required to assess toxicity to therapy or to adhere to drug administration plan, other study procedures, and study restrictions.

3.2.7 Allergy

Patients with a history of allergic reactions attributed to compounds of similar chemical or biologic composition.

3.2.8 Prisoners

Prisoners will be excluded from this study.

3.3 Inclusion of Women and Minorities

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.

The PBTC remains committed to offering participation in our trials to subjects of all races and ethnic groups.

3.4 Treatment at the Primary Institution

All experimental protocol therapy must be dispensed and all on treatment imaging studies must be obtained at a PBTC institution. Laboratory studies, excluding pharmacokinetic and biologic assays, may be performed at a CLIA certified laboratory of the investigator's choice. Imaging utilized to determine eligibility may be performed at an outside institution if all required imaging sequences are included and the study is deemed of adequate quality by the treating team. All

required physical examinations and laboratory studies need to be performed at the primary PBTC institution during the dose finding period of the protocol.

3.5 Criteria to Start Treatment

- Subjects must start therapy within 7 days of enrollment.

- Laboratory values must be no older than 7 days prior to the start of therapy. If a test that is repeated post enrollment and prior to the start of therapy is outside the limits for eligibility, it must be rechecked within 48 hours prior to the start of therapy. If rechecks are still outside the limits for eligibility, the patient may not receive protocol therapy. The patient will be deemed ineligible and will go off study. See Section 5.4.4.

4 REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr/. The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes four person registration types that are applicable to this trial.

- Investigator (IVR): MD, DO, or international equivalent;
- Non-Physician Investigator (NPIVR): advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- Associate Plus (AP): clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges; and
- Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials

RCR requires the following registration documents:

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

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites in RCR to allow the following:

- Addition to a site roster;
- Selection as the treating, credit, or consenting person in OPEN;
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assignment of the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting or treating investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Refer to the NCI RCR page on the CTEP Website for additional information. 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 CTSU.

4.2.1 IRB Approval

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases. In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB prior to

March 1, 2019. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating through the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email (CTSURegPref@ctsu.coccg.org) or by calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval (applies to US and Canadian sites only) on at least one participating organization's roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

4.2.2 Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all applicable protocol-specific requirements (PSRs).

4.2.3 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (https://www.ctsu.org);
- Click on *Protocols* in the upper left of the screen
  - Enter the protocol number in the search field at the top of the protocol tree; or
  - Click on the By Lead Organization folder to expand, then select *PBTC* and protocol number *PBTC-049*.
- Click on *Documents*, *Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.4 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal, log in to the CTSU members' website, go to the *Regulatory section*, and select *Regulatory Submission*.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org in order to receive further instruction and support.

4.2.5 Checking Site Registration Status

Site registration status can be verified on the CTSU members' website.

- Click on the *Regulatory* at the top of the screen;
- Click on the *Site Registration*; and
- Enter the site's 5-character CTEP Institution Code and click on Go.
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. 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 Delegation of Tasks Log (DTL)

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application which is accessible via the Delegation Log link on the CTSU members' website or directly at https://dtl.ctsu.org. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and

enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and to activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and describe DTL task assignments, CI signature, and CTEP registration requirements, as well as include a Master Task List.

4.4 Patient Registration

4.4.1 OPEN

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs' registration/randomization systems for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- Active CTEP registration with credentials necessary to secure NCI/CTSU IT systems.
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type.
- If a DTL is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site.
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the Institutional Review Board (IRB) number used on the site's IRB approval on their Form Food and Drug Administration (FDA) 1572 in Registration and Credential Repository (RCR). If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

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

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Patient enrollment for this study will be facilitated using the Slot Reservation System in conjunction with the registration system in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

4.4.2 Special Instructions for Patient Enrollment on the Efficacy Expansion Cohort

For patients planning to enroll on the efficacy expansion cohort, rapid review of local CLIA-certified sequencing lab reports will be performed by the Study Chair and qualified personnel from the Institute for Genomic Medicine at Nationwide Children's Hospital (NCH) prior to enrollment. To facilitate this review, sites must provide a redacted copy of the local CLIA-certified sequencing laboratory report via email to ralph.salloum@dfci.harvard.edu and kathleen.schieffer@nationwidechildrens.org prior to enrollment. A copy of the correspondence with the Study Chair's confirmation should be uploaded to the Rave database as source documentation to support eligibility.

5 TREATMENT PLAN

Treatment will generally be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6.2. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Timing of protocol therapy administration and response assessment studies are based on schedules derived from the experimental design or on established standards of care. Minor unavoidable departures from protocol directed therapy and/or disease evaluations for valid clinical, patient and family logistical, or facility, procedure and/or anesthesia scheduling issues are acceptable.

5.1 Agent Administration

Savolitinib dosing will begin at 150 mg/m^2/dose which is approximately 40% of the revised adult RP2D of 600 mg daily as of April 2020 (Table 2). Only DLTs observed during the dose-finding period of therapy will be used to guide dose escalation. Dose escalation will be governed by the statistical design as described in Section 13.2 of the protocol.

Table 2.

Dose Escalation Schedule		
Dose Level	**Dose of savolitinib (mg/m^2 once a day)**	**BSA Requirements**
0	75 mg/m^2	$\geq 1.00\ m^2$
1*	150 mg/m^2	$\geq 0.55\ m^2$
2	240 mg/m^2	$\geq 0.67\ m^2$
3 #	350 mg/m^2	$\geq 0.73\ m^2$

* Starting dose
# With declaration of the RP2D at Dose Level 3, the upper BSA restriction used for enrollment at Dose Level 3 during the dose finding phase has been lifted. During the expansion phases (PK and efficacy), patients with BSA $\geq 2.10\ m^2$ will receive 600 mg flat dose once a day.

Please refer to the dosing tables in Appendix 15.5 for drug administration guidance. See Section 10 for the study calendar.

5.1.1 Savolitinib

Savolitinib is supplied as 100 mg and 200 mg tablets. Patients will receive savolitinib once a day orally on a continuous basis. Savolitinib tablets must be swallowed whole with water, not chewed or crushed. Twenty-eight (28) consecutive days (4 weeks) will constitute one course. Patients may continue to receive savolitinib for 39 courses (approximately 3 years). Patients may receive extended therapy beyond 39 courses with savolitinib if there is evidence of clinical benefit. Provided that the extended therapy patients continue to meet study criteria, treatment may continue until all other subjects meet off-treatment criteria. At that time, the extended therapy patients will be notified that they will be taken off treatment after their next scheduled MRI. The OBDMC will notify the treating institutions when this milestone is reached so that any extended therapy patients can be informed. Delays between courses for reasons other than toxicity may occasionally occur however dosing should follow the treatment plan as closely as possible.

Patients will be assigned a dose level at the time of enrollment. See Section 5.2.3 for details of dose escalation schedule. Duration of therapy is defined in Section 5.4.

Dosing should be adjusted based on BSA calculated at the beginning of each course of therapy for Courses 1–39, then every 3 courses (prior to course) for extended therapy patients. The dose prescribed should be rounded to the nearest deliverable dose based on the BSA adjustment and the available tablet sizes. Dosing tables which reflect this approach are available in Appendix 15.5. Patients should be provided with a Medication Diary for savolitinib (Appendix 15.7), instructed in its use, and asked to bring the diary as well as the remaining tablets and/or empty bottles with them to each appointment.

Savolitinib should be taken with food, using only water to swallow the tablets. Patients should be advised to drink plenty of water or take hydration fluids to avoid dehydration if diarrhea occurs. Patients are encouraged to take their dose of savolitinib at the same time each day. If the patient misses a dose, the patient should take the dose as soon as possible or within 12 hours after the missed dose. If the patient misses a dose by more than 12 hours, the dose should be withheld and

the patient should wait until the scheduled time for the next dose (i.e., patients should not make up the missed dose after 12 hours). The patient should then continue treatment with the original dosing schedule.

Patients who vomit a dose of savolitinib should NOT be re-dosed. Patients should take the next scheduled dose of savolitinib. Appropriate anti-emetic therapy should be implemented prior to the next scheduled dose. If vomiting persists despite anti-emetic therapy, patients should be advised to contact the treating physician.

5.1.2 Rechallenge for Dose Level 1 (Protocol Version 3.0)

As of September 2019, two DLTs have been documented at the first dose level of 150 mg/m^2/day; Grade 3 fatigue (n=1) and Grade 3 neutropenia causing a delay of > 7 days to start a subsequent cycle (n=1). Given that the 2 DLTs are from different classes of AEs and did not result in harm to patients, we propose an additional 6 patients be enrolled at Dose Level 1 (DL1) to better define the toxicities of this agent in children. This is also due to concerns from adult PK data[26] that Dose Level 0 (DL0) may be too low to achieve what is thought to be clinically efficacious exposures. Consequently, patients being treated at DL0 at the time of the amendment will be offered a dose-escalation to DL1 after completion of Course 1, provided that they have experienced no drug related toxicity of Grade 2 or higher.

5.1.3 Addition of Dose Level 2 and Dose Level 3 (Protocol Version 4.0)

As of March 2020, the adult R2PD of savolitinib has been revised to a flat dose of 600 mg daily. Based on the new definition of DLTs, only 1 out of 6 patients has experienced a DLT on DL1. Therefore, as long as the DLT rate at DL1 (based on revised definitions of DLTs) does not equal or exceed 33% in all evaluable subjects, we propose to enroll patients at DL2 (240 mg/m^2; adult equivalent of ~400 mg) and DL3 (350 mg/m^2; adult equivalent ~600 mg) if escalation criteria are met.

5.1.4 Efficacy Expansion Cohort

Once the MTD/RP2D is determined, a small efficacy expansion cohort will be opened to enroll patients whose tumors harbor genetic MET activation as determined by testing performed by a CLIA-certified laboratory. Refer to Section 3.1.1 for eligibility to the efficacy expansion cohort.

5.1.5 Criteria to start subsequent courses

A course may be repeated every 28 days if the patient does not meet off-treatment criteria (Section 5.4.2) and has again met eligibility laboratory parameters (Section 3.1.9). If a patient does not meet these parameters at the end of the treatment course, then savolitinib should be held until these parameters meet the eligibility criteria.

5.2 Definition of Dose Limiting Toxicity (DLT)

Management and dose modifications associated with adverse events are outlined in Section 6. DLT will be defined as any of the events listed in this section that are at least possibly related to savolitinib that occur during the dose-finding period regardless of expectedness.

- Any savolitinib-related adverse event during the first course of therapy that leads to a dose reduction or results in the permanent cessation of therapy will be considered dose limiting. All dose modifications in all courses are to follow the guidelines provided in Section 6.2.
- Any savolitinib related adverse event during the dose finding observation period that results in a delay of treatment > 14 days.

5.2.1 Non-hematologic dose limiting toxicity is defined as:

- Any Grade 4 non-hematologic toxicity
- Any Grade 3 non-hematologic toxicity with the exception of:
  - Grade 3 nausea or Grade 3 vomiting that is controllable with anti-emetics
  - Grade 3 infection
  - Grade 3 electrolyte abnormalities responsive to oral supplementation
- Hepatotoxicity that results in a dose reduction or permanent cessation of therapy in accordance with dose modifications for hepatotoxicity in Section 6.2.2.
- Any Grade 2 non-hematologic toxicity that persists for > 7 days AND is considered medically significant or sufficiently intolerable by the patient that the toxicity requires treatment interruption.
- Hypersensitivity reaction that does not respond to oral therapy and requires drug interruption.

5.2.2 Hematologic dose limiting toxicity is defined as:

- Grade 4 neutropenia
- Grade 3 or 4 thrombocytopenia

5.2.3 Dose-finding period

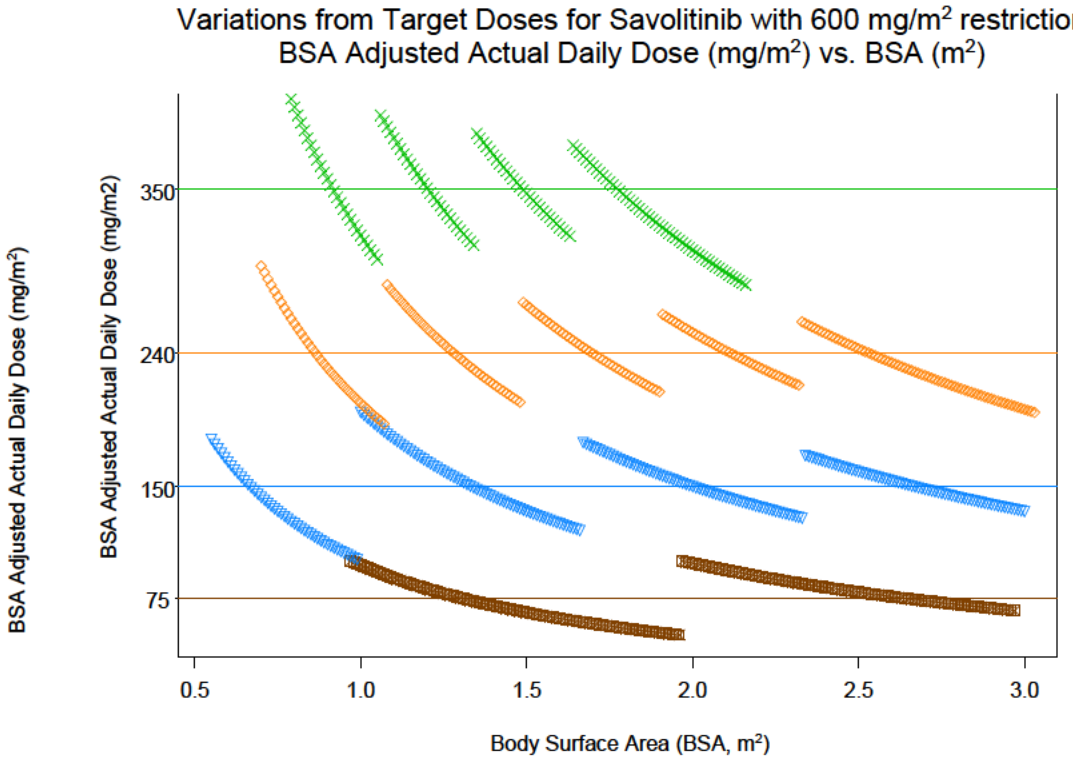
The dose finding period begins with the initial dose of savolitinib and ends on the last day of Course 1. Each course is 28 days. The DLT observation period or dose finding period for the purposes of dose-escalation will be the first course of therapy. **Should there be a delay starting the subsequent course, dose finding will complete on the start date of the subsequent course**.

5.2.4 Dose Escalation/De-escalation

Dose escalations will proceed within each cohort as follows:

Course 1 will be started with an initial cohort of 2–6 patients at the Dose Level 1 which is 150 mg/m^2/dose (see Table 2). Only DLTs observed during the dose-finding period of therapy will be used to guide dose de-escalation.

A plot of BSA adjusted doses based on a minimum 100 mg tablets is given below:



A "Rolling-6" Phase I design will be used to estimate the MTD and the first 28 days of treatment until initiation of Course 2 will be designated as the DLT observation period. Cohorts of 2–6 patients will be enrolled in each dose level and no intra-patient escalation will be allowed. See the Statistics Section 13.1 for details.

5.3 General Concomitant Medications and Supportive Care Guidelines

5.3.1 Drug Interactions

Savolitinib is a substrate of CYP 3A4/5 and 1A2. Avoid administration of strong CYP 3A4/5 and 1A2 inducers and inhibitors during study treatment. Savolitinib and its metabolites weakly and reversibly inhibited CYP450 1A2, 2C8, 2C9, 2D6 and 3A4/5 isoforms, and UGT1A1. 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. Savolitinib has the potential to inhibit P-gp, BCRP (breast cancer resistance protein), OATP1B1, MATE1, and MATE2K. Co-administration of substrates that are dependent on these drug transporter systems should be used with caution.

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. 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 15.6 (Patient Drug Information Handout and Wallet Card) should be provided to patients. Increase the frequency of INR tests if savolitinib and warfarin are used concomitantly,

as warfarin is a CYP2C9 substrate with a narrow therapeutic window and the savolitinib metabolites M2 and M3 inhibit CYP2C9.

5.3.2 Excessive sun 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; in addition, SPF30+ sunscreen should be used. Exposure to other sources of UV light including sun beds and tanning booths, etc. should be avoided.

5.3.3 Drugs that can cause potential QTc prolongation

Concomitant medications that are associated with QTc prolongation and Torsade de Pointes should NOT be used during the study. Please see Appendix Section 15.3 for a partial list of medications with the potential to prolong the QTc interval.

5.3.4 Analgesics and Antipyretics

Limit paracetamol/acetaminophen daily dose to a maximum of 3 g total dose for adolescents and adults (≥ 50 kg) and to a maximum daily dose of 50 mg/kg for children (≥ 2–12 years) and adolescents/adults < 50 kg due to the risk of hepatotoxicity associated with savolitinib.

5.3.5 Statins

Discontinue statins use unless considered essential, in which case, prescribe the lowest available dose and monitor for the effects of increased statin exposure.

5.3.6 Steroids

Corticosteroids should be used at the lowest dose to control symptoms of edema and mass effect, and discontinued, if possible. Use of corticosteroids should be recorded in the case report forms (CRFs).

5.3.7 Anticonvulsants

Anticonvulsants drugs should be used, if indicated. Use of anticonvulsants should be recorded in the case report forms (CRFs).

5.3.8 Growth Factors

Routine use of growth factors (i.e., G-CSF, GM-CSF, and erythropoietin) is not permitted. However, therapeutic use of G-CSF or GM-CSF in patients with serious neutropenic conditions, such as sepsis, may be considered at the investigator's discretion. This should also be discussed with the Study Chair. Use of growth factors should be recorded in the case report forms (CRFs).

5.3.9 Anti-emetics

The use of anti-emetics is highly recommended. Use of anti-emetics should be recorded in the case report forms (CRFs).

5.3.10 Herbal preparations/medicines

The use of herbal preparations including cannabis products is not permitted throughout the study.

5.3.11 Febrile neutropenia

Febrile neutropenia should be managed according to the local institutional guidelines.

5.3.12 Diarrhea

Diarrhea should be managed according to the local institutional guidelines. If diarrhea occurs, patients are advised to drink plenty of rehydration fluids to avoid dehydration. Medications such as loperamide are to be used with caution. Refer to the loperamide dosing guidelines in Table 3.

Table 3

Weight Specific Guidelines for Therapeutic Use of Loperamide			
Weight (kg)	Initial (Loading) Loperamide dose (mg)	Subsequent daytime loperamide dose	Subsequent nighttime loperamide dose
8–10	1	0.5 mg q 3h	0.75mg q 4h
10–20	1	1 mg q 3h	1 mg q 4h
20–30	2	1 mg q 3h	2 mg q 4h
30–42	2	1 mg q 2h	2 mg q 4h
42	4	2 mg q 2h	4 mg q 4h

5.3.13 Pneumocystis jiroveci pneumonia (PJP) prophylaxis

The use of medication (i.e., Bactrim) for PJP prophylaxis in patients on chronic steroids is recommended but it is at the investigator's discretion.

5.3.14 Neurosurgical or other surgical procedures

If a neurosurgical procedure or other surgical procedure is required for a reason other than tumor progression, these procedures should be documented, but will not constitute criteria for declaring the patient "off therapy." If possible, savolitinib should be held at least 2 days prior to a minor surgery and 7 days prior to a major surgery. Savolitinib will be resumed when the patient is clinically stable and has recovered from the acute effects of surgery and as per the treating physician's discretion.

5.3.15 Cardiac Monitoring

Patients must be monitored for prolonged QT interval. EKGs must be completed in triplicate at each time point described below and in Section 10. The mean of the 3 EKG readings should be documented in the patient's medical record and recorded in the database. Patients will have EKGs completed at eligibility, weekly 1–3 hours after the first dose of each week (Days 1, 8, 15, and 22), prior to each course through Course 39, then every 3 courses (prior to course) for Courses 40+ in extended therapy patients, and at the discontinuation of treatment for all patients. If an EKG assessment performed at the discontinuation of treatment is abnormal, a follow-up EKG is required 28 days after the off-treatment date to confirm reversibility of the abnormality.

Patients who develop QT prolongation should be managed according to the recommended management for cardiac adverse events described Section 6.2.4.

5.4 Duration of Therapy

In the absence of treatment delays due to adverse event(s) or disease progression, treatment may continue for 39 courses (approximately 3 years) or until one of the Off Treatment Criteria noted in Section 5.4.2 is met. Patients may receive extended therapy beyond 39 courses with study drug if there is evidence of clinical benefit. Provided that the extended therapy patients continue to meet study criteria, treatment may continue until all other subjects meet off-treatment criteria (see Section 5.1.1). At that time, the extended therapy patients will be notified that they will be taken off treatment after their next scheduled MRI. The OBDMC will notify the treating institutions when this milestone is reached so that any extended therapy patients can be informed.

5.4.1 On Study Data Submission Schedule

Pre-treatment, on-study, and off-treatment data, as well as patient response data are to be recorded in the electronic case report forms (eCRFs) in the Rave database. See the Required Data and Timetable for Submission form located on the PBTC-049 Protocol Webpage for the schedule. For assistance, contact the PBTC Protocol Coordinator listed on the cover page.

5.4.2 Off Treatment Criteria

At the discontinuation of treatment, the "Off Treatment Date" is to be recorded in the eCRF and is to be consistent with the reason given for going off treatment. The "Last Treatment Date" is defined as the last date that the patient received protocol-based therapy. Date of "off treatment" must be the greatest of the date of last treatment, date of procedure, date of patient assessment, notification of patient/family decision, or decision made by the physician that resulted in the patient being taken off protocol treatment. The reason for discontinuation of treatment must be documented by the attending investigator in the medical record and recorded in the eCRF.

Patients will be considered Off Treatment for the following reasons:

- Development of unacceptable toxicity as outlined in Section 5.2. See Section 7.3 for specific reporting requirements.
- Progressive disease (PD) as described in Section 11.3.
- Development of a medical or psychiatric illness that in the investigator's judgment renders the patient incapable of further therapy on this protocol or the treating physician determines continuation on this study is not in the patient's best interest.
- The patient, parent, or legal guardian refuses further treatment on this protocol. In this case the investigator should clarify if the family also wishes to withdraw consent for continued participation for data collection purposes.
- Completion of all protocol-defined treatment
- Pregnancy
- Non-compliance that in the opinion of the investigator does not allow for ongoing participation.
- Termination of the study by the sponsor

Patients who are off protocol therapy must be followed until an "Off Study Criterion" is met.

5.4.3 Data Submission Schedule for Patients Off Treatment

All patients must be followed for a minimum of 30 days from the last treatment date. Toxicities that are considered at least possibly related to the study treatment and are ongoing at the end of day 30 of last treatment date will be followed until resolution or return to baseline unless consent is withdrawn for further data submission or follow-up.

Patients in off treatment follow-up will continue to be followed for up to 2 years from the completion of protocol treatment until an off study criterion is met to document any unexpected later developing toxicities or other morbidity and to document disease progression and survival. Any required data collected during the follow-up period should be submitted quarterly in the Rave database. The required follow-up data includes:

- Any adverse events that are possibly, probably, or definitely related to the study drug (see Section 7 for specific reporting timelines) should be reported as soon as possible.
- Dates of any disease assessments and results of the associated disease assessments (i.e., tumor measurements and overall response) up to and including the first disease progression following study treatment.
- Date of first disease progression on study
- Date of commencement of new anticancer therapy
- Date of most recent contact including imaging uploads requested in Section 9.2.1.
- Date of death

5.4.4 Criteria for Removal from Study

Patients who are off protocol therapy will be followed until they meet criteria for removal from study. The date and reason for the patient coming off study must be documented in the eCRF and the Operations, Biostatistics, and Data Management Core (OBDMC) must be notified according to standard reporting guidelines (see Section 5.4.5, Section 7, Section 12.2, and the Required Data and Timetable Submission form located on the PBTC-049 Protocol Webpage).

Ongoing AEs, or AEs that emerge after the patient is removed from protocol therapy but within 30 days of the last dose of study treatment, must be followed and reported via Rave and CTEP-AERS (if applicable). Toxicities that are at least possibly related to the study treatment and are ongoing at the end of day 30 of last treatment date will be followed until resolution or return to baseline, whichever is longer.

Patients will be considered Off-Study for the following reasons:

- Patient has completed study follow-up which is defined as 2 years from completion of treatment. All required data elements must be submitted before declaring the patient as off-study.
- Patient determined to be ineligible.
    - If the patient was found to be ineligible after starting treatment, follow-up should continue for 30 days from the last administration of study drug or until the toxicity resolves or returns to baseline, whichever is longer unless the patient commences a different anti-cancer therapy.
- Patient did not initiate treatment on study.

- Parent, patient, or guardian withdraws consent for further required observations or data submission.
- Patient death while on study. The IRB, Investigational Drug Branch (IDB), Study Chair, and OBDMC must be notified as per Section 7.3.3.
- Patient has started another anti-cancer therapy. Follow-up must still be completed for 30 days following the last treatment date.
- Lost to follow-up
    - Sites must make every attempt to continue follow-up of patients during the study period as specific in Section 5.4.1. Multiple attempts must be made and documented to obtain required study data before the patient can be declared lost to follow-up. The study Protocol Coordinator and Study Chair must be notified before a subject is declared lost to follow-up.
- Progressive Disease
    - If PD occurs within less than 30 days of last treatment date then follow-up should continue until 30 days from off-treatment date or until commencement of additional anticancer therapy, whichever occurs first.
    - If the off treatment reason is toxicity and the patient is subsequently found to have PD, then follow-up should continue for 30 days of last treatment date or until the toxicity resolves or returns to baseline, whichever is longer.

5.4.5 Data Submission for Patients Off study

No data will be collected documenting treatment or reporting events or disease status that occur subsequent to the official "off study" date with the exception of adverse events with an attribution of possible, probable, or definite that occur after the "off study" date for agents being studied under a CTEP IND (see Section 7).

6 DOSING DELAYS/DOSE MODIFICATIONS

6.1 Notification of the Study Chair

The Study Chair or Co-Chair must be notified of any dosage modifications, prior to the implementation of the dose modification. Patients receiving 100 mg daily and who meet criteria for a dose reduction must be removed from protocol therapy.

6.2 Hematologic and Non-hematologic Adverse Events and Management

6.2.1 Dose Modification for Non-hematologic Toxicity excluding Savolitinib-related Hepatotoxicity, Hypersensitivity or QTc prolongation

For the management of savolitinib-related hepatotoxicity; hypersensitivity, or QTc prolongation, follow the specific guidelines below:

Non-hematologic toxicity	Management/Next Dose for Savolitinib
≤ Grade 1	No change in dose
Grade 2	No change in dose
Grade 2 that persists for >7 days AND is considered sufficiently medically significant or sufficiently intolerable by patients that it requires treatment interruption	Hold savolitinib. If the toxicity resolves to meet on study parameters within ≤ 14 days of drug discontinuation, the patient may resume treatment at the next lower dose level*. For patients enrolled at Dose Level 1, the dose should be reduced to Dose Level 0. Patients already receiving Dose Level 0 at the time of dose limiting toxicity must be removed from study. Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose. • If toxicity does not resolve to meet on study parameters within 14 days of drug discontinuation, the patient must be removed from protocol therapy. • If a dose-limiting toxicity occurs in a patient who has resumed treatment at a reduced dose, the patient must be removed from protocol therapy.
Grade 3 or 4 (dose limiting)	Hold savolitinib. If the toxicity resolves to meet on study parameters within ≤ 14 days of drug discontinuation, the patient may resume treatment at the next lower dose level*. For patients enrolled at Dose Level 1, the dose should be reduced to Dose Level 0. Patients already receiving Dose Level 0 at the time of dose limiting toxicity must be removed from study. Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose. • If toxicity does not resolve to meet on study parameters within 14 days of drug discontinuation, the patient must be removed from protocol therapy.

	• If a dose-limiting toxicity occurs in a patient who has resumed treatment at a reduced dose, the patient must be removed from protocol therapy.

*If patients do need dose interruption in the first 6 weeks of savolitinib, restarting savolitinib should be done in the hospital and under controlled conditions (as detailed in Section 6.2.3).

6.2.2 Dose Modifications for Hepatotoxicity

Promptly evaluate patients with elevated LFTs during study treatment for alternative etiologies (for example, elevated serum ALP indicating cholestasis, viral hepatitis, or another suspect drug), and discontinue potential contributing concomitant medications or causal agents and treat alternative etiologies, if appropriate.

Toxicity	Management/Next dose of Savolitinib
• ALT or AST > 8x ULN or • ALT or AST > 5x ULN for > 2 weeks or • ALT or AST > 3x ULN and Total bilirubin > 2x ULN or INR > 1.5 if not on anticoagulants that elevate the INR • ALT or AST > 3x ULN with new onset of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or new onset of eosinophilia above the normal reference range, or significant change in pre-existing eosinophilia.	Discontinue savolitinib.
• ALT or AST > 5x but ≤ 8x ULN without Total bilirubin elevation above baseline or ULN	Withhold savolitinib. Repeat liver function testing twice a week for 1 week. • If improved to < Grade 1 or baseline in 1 week, resume savolitinib at the reduced dose* with liver function testing twice a week for 6 weeks. • If not improved, discontinue savolitinib.
• ALT or AST > 3x ULN and concurrent Total bilirubin > 1.5x but ≤ 2x ULN	Withhold savolitinib. Repeat liver function testing twice a week for 1 week. • If ALT, AST and Total bilirubin improve to < Grade 1 or baseline in 1 week, resume savolitinib at the reduced dose* with liver function testing twice a week for 6 weeks. • If not improved, discontinue savolitinib.

Toxicity	Management/Next dose of Savolitinib
• ALT or AST > 3x but ≤ 5 x ULN without Total bilirubin elevation above baseline or ULN	Continue dosing at current dose level and repeat liver function testing every week. • If ALT or AST improves to < Grade 1 or baseline in 1 week, continue at the same dose with liver function testing every week for 6 weeks. • If ALT or AST is trending upward, withhold dosing and repeat liver function testing twice a week for 1 week. • If ALT or AST improves to < Grade 1 or baseline in 2 weeks, resume at the reduced dose* with liver function testing every week for 6 weeks. • Discontinue savolitinib if not improved to < Grade 1 or baseline in 2 weeks.
• Recurrent ALT or AST > 5x ULN or • Recurrent ALT or AST > 3x but ≤ 5x ULN and Total bilirubin > 1.5x but ≤ 2x ULN	Discontinue savolitinib.
• Recurrent ALT or AST > 3x but ≤ 5x ULN without Total bilirubin elevation above baseline or ULN	Withhold savolitinib. Repeat liver function testing twice a week for 1 week. • If improved to < Grade 1 or baseline in 1 week, resume at the reduced dose* and repeat liver function testing every week for 6 weeks. • If not improved, discontinue savolitinib.
If a patient discontinues due to liver function testing abnormality, liver function monitoring should continue until resolved to Grade 1 or baseline or an apparent plateau has been reached.	

*If patients do need dose interruption in the first 6 weeks of savolitinib, restarting savolitinib should be done in the hospital and under controlled conditions (as detailed in Section 6.2.3).

6.2.3 Dose Modification and Guidance for Specific Toxicities

6.2.3.1 *Hypersensitivity*

A case of Stevens-Johnson syndrome (SJS) has been reported in temporal association savolitinib. Patients who show symptoms or signs suggesting emerging Stevens-Johnson syndrome (SJS) while on 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 may manifest as a constellation of symptoms such as (but not limited to) pyrexia, chills, flu-like symptoms, allergic skin reactions (including rash and/or pruritis), peripheral or facial edema, increased liver enzymes, cytopenias, eosinophilia, myalgia and/or arthralgia. The presentation may mimic infection and a high index of suspicion is required for diagnosis of hypersensitivity. Microbial confirmation of infective aetiology is recommended in order to distinguish hypersensitivity

reactions from true infections. Pyrexia is a prodromal feature of the majority of cases of hypersensitivity and in some cases of hepatotoxicity. The majority of hypersensitivity reactions have occurred in the first 6 weeks of therapy, but some have been recorded a year after the first dose. Participants with suspected savolitinib-related hypersensitivity may be managed with corticosteroids, antihistamines, and antipyretics (doses and duration of treatment according to local practice at the discretion of the investigator).

Dose interruption with savolitinib should be avoided, if possible; (depending on the benefit: risk profile of the individual patient) for example, in situations considered ***unlikely*** to be due to hypersensitivity, such as upper respiratory tract infections without fever, chills, or cytopenias, in patients who are deriving benefit from therapy.

Some participants who experienced an initial hypersensitivity reaction have reported severe acute hypersensitivity reactions, including anaphylaxis, upon restarting savolitinib treatment following a short period of interruption. Therefore, if the participant experiences a severe, acute hypersensitivity or anaphylactic reaction, immediate intervention must be initiated and treatment with savolitinib must be permanently discontinued.

- Also note that as per Section 6.2.2, permanent discontinuation of savolitinib must occur in cases of ALT or AST > 3 × ULN with the appearance of fever, rash and/or new onset of eosinophilia above the normal reference range, or significant change in pre-existing eosinophilia.

6.2.3.2 *Restarting Savolitinib*

Any recommendations regarding hypersensitivity management guidelines or pre-treatment should be used as guidelines only. Final decisions concerning management of individual patients reside with the investigator or the treating physician.

If patients do need dose interruption, restarting savolitinib must be done only after consideration of the benefit: risk profile of the individual patient. It is recommended to restart savolitinib only if the initial reaction was considered *unlikely* to be due to hypersensitivity. Consultation with, and approval from, the study chair is recommended before restarting savolitinib. Savolitinib should be restarted at a reduced dose, and with the following management:

- Treatment:
  - Pre-treatment with systemic corticosteroids should be started at least 24 hours before the restart of savolitinib;
  - Pre-treatment with antipyretics and antihistamines on the day of restart of savolitinib.
  - Doses of antihistamines, corticosteroids, and antipyretics should be according to labelling instructions/product information.
    - These medications should be continued daily for at least a week, but doses of steroids may subsequently be tapered according to local practice.
  - The restart of savolitinib should be performed in the hospital/institution where the clinical study is carried out with medical equipment readily available for resuscitation and management of anaphylaxis.

- Vitals should be recorded (BP, temperature, respiratory rate, heart rate, etc.) before administration of savolitinib, every 15 minutes after savolitinib dosing for the first hour, every 30 minutes for the next hour, hourly for a total of at least 4 hours, and every 2 to 4 hours thereafter.
- Participant should be observed in the hospital/institution for at least 24 hours before discharge.
- Should the symptoms recur, or an acute anaphylactic reaction occurs, immediate intervention must be instituted for appropriate management of event and savolitinib must be permanently discontinued.

6.2.4 Dose Modifications for Savolitinib-related Cardiac Toxicity

QTc Prolongation	
NCI CTCAE Toxicity Grade	**Action**
Grade 0, 1, or 2	None
Grade 3 • Patients with QTc prolongation to >500 msec or > 60 msec increase from baseline on at least two separate EKGs • If the toxicity resolves to QTc < 481 msec within 21 days • If the toxicity does not resolve to QTc < 481msec within 21 days	Hold dosing and follow algorithm below: • Consult with a cardiologist to validate EKG finding. Perform additional EKGs weekly or more frequently as clinically indicated. • Restart drug at one reduced dose level*. Patients already receiving Dose Level 0 at the time of dose limiting toxicity must be removed from protocol therapy. • Discontinue study drug and consult with a cardiologist for further management as clinically indicated.
Grade 4 • Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrythmia	Discontinue study drug and consult with a cardiologist for further management as clinically indicated.

*If patients do need dose interruption in the first 6 weeks of savolitinib, restarting savolitinib should be done in the hospital and under controlled conditions (as detailed in Section 6.2.3).

6.2.5 Dose Modifications for Hematological Toxicity

Thrombocytopenia	Management/Next Dose for Savolitinib
≤ Grade 1	No change in dose.
Grade 2	No change in dose.
Grade 3 or 4 (dose limiting)	Hold savolitinib. Counts should be checked twice weekly during this time. If the toxicity resolves to meet on study parameters within 14 days of drug discontinuation, the patient may resume treatment at the next lower dose level*. For patients enrolled at Dose Level 1, the dose should be reduced to Dose Level 0. Patients already receiving Dose Level 0 at the time of dose limiting toxicity must be removed from protocol therapy. Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose. • If toxicity does not resolve to meet on study parameters within 14 days of drug discontinuation, the patient must be removed from protocol therapy. • If a dose-limiting toxicity occurs in a patient who has resumed treatment at a reduced dose, the patient must be removed from protocol therapy.

Neutropenia	Management/Next Dose for Savolitinib
≤ Grade 1	No change in dose.
Grade 2	No change in dose.
Grade 3	No change in dose.
Grade 4 (dose limiting)	Hold savolitinib. Counts should be checked twice weekly during this time. If the toxicity resolves to meet on study parameters within 14 days of drug discontinuation, the patient may resume treatment at the next lower dose level*. For patients enrolled at Dose Level 1, the dose should be reduced to Dose Level 0. Patients already receiving Dose Level 0 at the time of dose limiting toxicity must be removed from protocol therapy. Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose. • If toxicity does not resolve to meet on study parameters within 14 days of drug discontinuation, the patient must be removed from protocol therapy. • If a dose-limiting toxicity occurs in a patient who has resumed treatment at a reduced dose, the patient must be removed from protocol therapy.

*If patients do need dose interruption in the first 6 weeks of savolitinib, restarting savolitinib should be done in the hospital and under controlled conditions (as detailed in Section 6.2.3).

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 (Section 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. The coding of attribution in the Rave database pertains to adverse events related to savolitinib.

- *Baseline Abnormalities*

Any baseline (pretreatment) abnormalities observed during the initial physical examination should be recorded in the CRFs. For lab abnormalities, only those with defined CTCAE terms should be recorded unless otherwise specified below.

- *Treatment or within 30 days of treatment*

Only record adverse events Grades 1 and 2 if the attribution is at least **possibly** related to savolitinib. Record all adverse events Grades 3 through 4 and deaths), regardless of attribution on the electronic case report forms.

7.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Savolitinib (AZD6094, NSC 785348)

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' for further clarification at https://dctd.cancer.gov/research/ctep-trials/for-sites/adverse-events/reporting-requirements.pdf. *Frequency is provided based on 662 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.

7.1.1 CAEPR for Savolitinib (NSC 785348)

Version 2.5, July 25, 2024[1]

Adverse Events with Possible Relationship to Savolitinib (AZD6094) (CTCAE 5.0 Term) [n= 662]			**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			
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)***
	Generalized edema		***Generalized edema (Gr 2)***
HEPATOBILIARY DISORDERS			
Hepatobiliary disorders - Other (hepatotoxicity)[2]			***Hepatobiliary disorders - Other (hepatotoxicity)[2] (Gr 2)***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[3]		***Allergic reaction[3] (Gr 2)***
		Anaphylaxis[3]	
INVESTIGATIONS			
Alanine aminotransferase increased[2,4]			***Alanine aminotransferase increased[2,4] (Gr 2)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
Aspartate aminotransferase increased[2,4]			***Aspartate aminotransferase increased[2,4] (Gr 2)***
	Blood bilirubin increased[2]		***Blood bilirubin increased[2] (Gr 2)***
	Creatinine increased		***Creatinine increased (Gr 2)***
		Electrocardiogram QT corrected interval prolonged	***Electrocardiogram QT corrected interval prolonged (Gr 1)***
	GGT increased		***GGT increased (Gr 2)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 2)***
	Platelet count decreased		***Platelet count decreased (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
Hypoalbuminemia			***Hypoalbuminemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
		Arthralgia	
		Myalgia	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Stevens-Johnson syndrome[3]	
VASCULAR DISORDERS			
		Hypotension	

[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 (ALT), Aspartate aminotransferase increased, Alkaline phosphatase increased (ALT), Blood bilirubin increased (Bili)), hepatic function abnormal, and drug-induced liver injury (DILI). If Gr 2 ALT, AST, and Gr 3 Bili occur simultaneously, report as DILI and/or possible Hy's Law and not as the individual adverse events.

[3]Allergic reactions (including anaphylaxis and Stevens-Jonson syndrome) may cause a range of signs/symptoms including fever, chills, flu-like symptoms, peripheral or facial oedema (swelling), itching, rashes or more severe skin conditions. Blood tests showing liver damage or low / high blood cell counts (cytopenias or eosinophilia), or general pain in the muscles and joints.

[4]In accordance with Hy's Law, the SPEER exception can apply only for Alanine aminotransferase increased and Aspartate aminotransferase increased if isolated, and not in the setting for any concomitant increases in bilirubin.

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; Constipation; Dyspepsia; Gastritis; Gastrointestinal disorders - Other (abdominal incarcerated hernia); Gastrointestinal disorders - Other (GI [anastomic] perforation); Ileus; Mucositis oral; Small intestinal obstruction; Upper gastrointestinal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Edema face; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatic pain; Hepatobiliary disorders - Other (cholestasis); Hepatobiliary disorders - Other (hepatic encephalopathy); Hepatobiliary disorders - Other (hepatic lesion); Hepatobiliary disorders - Other (hepatomegaly)
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 - Lymphocyte 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
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; 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 website https://dctd.cancer.gov/research/ctep-trials/for-sites/adverse-events#ctep-ctcae.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (i.e., those listed in the SPEER column, Section 7.1.1) 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 Rave-CTEP-AERS Integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) Integration enables evaluation of Adverse Events (AEs) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting. **Sites must initiate all AEs for this study in Medidata Rave.**

Treatment emergent AEs: All AEs that occur after the start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period and is used to collect AEs that start during the period or persist from the previous reporting period. AEs that occur 30 days after the Last Administration of Investigational Agent/Intervention are collected using the Late Adverse Events form.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query-free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form (i.e., checking the box *Send All AEs for Evaluation* and save the form). Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form. Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com if you have any issues submitted an expedited report in CTEP-AERS.

In the rare occurrence that 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 that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU members' website:

- Study specific documents: *Protocols > Documents > Protocol Related Documents: Adverse Event Reporting*; and
- Additional resources: *Resources > CTSU Operations Information > User Guides & Help Topics*.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://dctd.cancer.gov/research/ctep-trials/for-sites/adverse-events/reporting-requirements.pdf

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 the responsible Protocol Coordinator at the PBTC, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

The following must be copied on expedited reports (24-hour notification and the complete report) submitted via CTEP-AERS:

Study Chair:
Ralph Salloum, MD
Dana Farber Cancer Institute
450 Brookline Ave.
Boston, MA 02215
Telephone: 617-632-3889
Email: ralph_salloum@dfci.harvard.edu

PBTC OBDMC:
Rachel Chon DNP, MPH, RN
St. Jude Children's Research Hospital
Department of Biostatistics
262 Danny Thomas Place
Memphis, TN 38105
Telephone: 901-481-5848
Fax: 901-595-4585
Email: rachel.chon@stjude.org

Study Co-chair:
Maryam Fouladi, MD
Nationwide Children's Hospital
700 Children's Drive
Columbus, OH 43205
Telephone: 614-722-5758
Fax: 614-722-3369
Email: maryam.fouladi@nationwidechildrens.org

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 <u>both</u> routine and expedited reporting, regardless of causality, as long as the death occurred within 30 days after the last administration of the investigational agent. 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 (SAEs), whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).

An AE is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening AE
3) An AE 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 SAEs that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Grade 1-2 Timeframes	Grade 3-5 Timeframes
24-Hour notification, 10 Calendar Days	24-Hour notification, 5 Calendar Days

NOTE: Protocol specific exceptions to expedited reporting of SAEs 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 SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "24-hour notification, 10 Calendar Days" – The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 10 calendar days of the initial 24-hour report.

[1]SAEs 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 notifications are required for all SAEs followed by a complete report

- Within 5 calendar days for Grade 3-5 SAEs
- Within 10 calendar days for Grade 1-2 SAEs

[2]For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT, or PET), the SAE 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: August 30, 2024

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must <u>also</u> 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 https://dctd.cancer.gov/research/ctep-trials/for-sites/adverse-events/reporting-requirements.pdf) 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 such as 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. The Adverse Event eCRF should be updated with the appropriate description within 1 week of learning of the secondary malignancy.

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 AGENT INFORMATION

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

8.1 Savolitinib (AZD6094) (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 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 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 is off-white to yellow crystalline powder.

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

- 100 mg yellow, plain, round (9 mm)
- 200 mg yellow, plain, oval (7.25 x 14.5 mm)

Savolitinib 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 tablets at controlled room temperature (20°C–25°C). Brief excursions are permitted between 15°C and 30°C.

If a storage temperature excursion is identified, promptly return savolitinib 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 tablets with food. Swallow whole with water.

Potential Drug Interactions: According to in vitro studies, savolitinib 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 study treatment. Savolitinib is a P-glycoprotein (P-gp) substrate.

In vitro, savolitinib 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 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 has little induction potential for major CYP isoforms.

In vitro studies demonstrate that savolitinib and its major metabolite inhibit a number of drug transporters to varying degrees. The manufacturer cautions that when administered at clinically relevant doses, savolitinib 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 24 weeks after discontinuing study treatment. Also advise men to avoid fathering a child and refraining from sperm donation from study start to 24 weeks after discontinuing study treatment. Refer to the protocol for specific guidance.

Advise patients to avoid prolonged sun exposure and use protective clothing, hats and SPF30+ sunscreen during study treatment and for 4 weeks after the last dose. Consult the protocol document for any dose modification necessary if sunburn occurs.

8.2 Agent Ordering and Accountability

8.2.1 Agent Ordering

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 investigator at that institution.

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

Submit agent requests through the PMB AURORA application. Access to AURORA requires the establishment of credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems, maintenance of an “active” account status, a “current” password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time or use the dialog function in AURORA to communicate with PMB staff. Refer to the PMB’s website for specific policies and guidelines related to agent management.

8.2.2 Agent Dispensing

Savolitinib tablets are supplied in 24-count per bottle. The research pharmacist (or the authorized designee) is recommended to open the manufacturer bottles and destroy extra tablets that are not required for the course in order to provide an exact count. Destruction should be documented on the DARF.

8.2.3 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.

Product Quality Complaint (PQC): A product quality complaint is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a study subject. Lot or batch numbers are of high significance and need to be provided where and when possible. PQC must be reported to the PMB as soon as the PQC is identified. Report PQC to PMB at PMBAfterHours@mail.nih.gov or by using the dialog function in AURORA to communicate with PMB staff.

8.2.4 Material Safety Data Sheets

The current versions of the material safety data sheets (MSDS or SDS) for PMB-distributed agents will be accessible to site investigators and research staff through the PMB AURORA application. Questions about MSDS access may be directed to the PMB at PMBAfterHours@mail.nih.gov or by using the dialog function in AURORA to communicate with PMB staff.

8.2.5 Investigator Brochure Availability

The current versions of the IB will be accessible to site investigators and research staff through the PMB AURORA application. Access to AURORA 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.

8.2.6 Useful Links and Contacts

- CTEP Forms, Templates, Documents: https://dctd.cancer.gov/research/ctep-trials/trial-development
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: https://dctd.cancer.gov/research/ctep-trials/for-sites/agent-management
- PMB AURORA application: https://ctepcore.nci.nih.gov/aurora/login
- 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

This section contains the collection, shipping and handling information for all planned biomarker and exploratory correlative studies, and neuropathology review. The table below identifies the tests, sample type and amount, analyzing laboratory and whether it is required or optional. For additional details, please review the associated section below.

Tissue Prioritization: If there is limited FFPE tissue to complete all mandatory assays, tissue prioritization will be as follows:

1. Genomic analysis of c-MET signaling axis and related cancer genes
2. c-MET expression & amplification
3. PBTC CRB

Test Name	Sample Type and Amount Collected	Required or Optional	Receiving Laboratory
Section 9.1.3 Pharmacokinetics	Plasma – 2 mL per sample	Required	Center for Translational Pharmacology (CTP)
Section 9.1.4 c-MET expression (IHC) & c-MET amplification (FISH)	FFPE tissue from original diagnosis, relapse, or any subsequent resections or biopsies prior to treatment • 7 FFPE unstained slides + 1 H&E stained slide Note: If c-MET amplification was previously tested, tissue for IHC will only be needed.	Required	PBTC CRB
Section 9.1.5 Genomic analysis of c-MET signaling axis and related cancer genes	FFPE or frozen tissue from original diagnosis, relapse, or any subsequent resections or biopsies prior to treatment. Blood in a purple top tube. See Section 9.1.5.1 for more details.	Required	PBTC CRB
Section 9.1.1 PBTC CRB Repository Samples	20 unstained slides and blood for future research, 1 H&E stained slide	Optional	PBTC CRB

9.1 Pathology and Exploratory Correlative Studies

The Pathology Central Review and Biorepository (PBTC CRB)'s function is to collect, distribute, and store specimens for central pathology review and planned correlative studies which support the laboratory objectives of this protocol. Samples submitted to the PBTC CRB may be used for planned correlative studies in consenting patients. **If a patient consents to both the PBTC CRB and planned correlative studies that use the PBTC CRB, samples should be processed according to instructions in the specific correlative study section.**

The CRB will also serve as a central repository for specimens collected for future research and leftover specimens (tumor tissue or blood) returned to the repository following the planned analysis from patients who consent to future research studies. These samples will be stored in the repository for undefined future studies which support the mission of the PBTC. **If the patient does not consent to future research, remaining correlative study samples will be destroyed once the PBTC-049 analysis is complete.**

9.1.1 PBTC CRB Submission Guidelines

If the patient consents to provide slides for submission to the repository at the time of participation in a PBTC trial the following should be submitted:

- Tumor material

Slides from the original and/or recurrent surgery should be prepared for storage. The site should provide up to twenty (20) unstained sections cut at 4 µm in thickness on (+) slides from the most representative section. Fewer unstained sections may be submitted based on size and availability of tissue. Preference is for tissue that has not previously been frozen. The corresponding pathology report(s) including immunohistochemical, special stains, and molecular/genetic results is to be uploaded to the PBTC using the secure File Upload system. These reports will be made available to the pathologist via a link in ProtoLab.

Suitability of sections would be established by preparing one (1) H&E to ensure that the sections meet the following criteria:

- histologically representative of the reported lesion
- contain at least 60% viable tumor
- no more than 40% necrosis

- Peripheral Blood Mononuclear Cells (PBMC)

PBMC may be collected by processing a 2–5mL whole blood specimen with Ficoll or collecting the specimen in a BD Vacutainer™ CPT™ Cell Preparation Tube with Sodium Citrate or similar tube which is available locally. Once separated, all pellets must be snap frozen and stored at least at -20°C prior to dry ice shipment

9.1.1.1 *Specimen Collection*

- *Processing by Ficoll tube*

1. Collect 2–5mL of fresh blood into an EDTA tube.
2. Transfer blood into a sterile 50-mL tube and add double the amount of PBS. MIX GENTLY.
3. Set up another tube containing half of its total volume of Ficoll. For example, if there is 15 mL of blood + PBS, then use 7.5 mL of Ficoll (2:1 ratio).
4. At very slow pace (approx. 2 mL/minute), layer the blood + PBS mixture onto the Ficoll so that the solutions DO NOT MIX. Spin the blood/Ficoll at 750 g in slow mode for 30 minutes @ 25ºC. After spin you will see four distinct layers: Plasma (top layer), white fluffy ring (2nd layer), Ficoll (3rd layer), and blood (bottom layer).
5. Remove plasma layer down to about 1 mL above the white fluffy ring and discard.
6. Collect the entire white fluffy ring. If ring is hard to see, also take extra liquid above. Then discard everything else.
7. Place this fraction of white blood cells into a fresh 50 mL sterile tube with 20 mL of PBS. Spin down for 10 minutes @ 25ºC, 750 g in fast mode. Remove the supernatant. Add back to pellet 1 mL of PBS and spin for 5 min. at 4°C at 10000rpm. Remove supernatant.
8. Freeze the pellet of WBCs in a 2 mL cryovial and store at -80ºC until shipment. Cryovials larger than 2 mL cannot be accepted by the PBTC CRB.
9. Please ensure that the labeling system used is designed to withstand temperatures down to -80oC. Samples should be stored at -80ºC until shipment. For short term storage (2–3 weeks) -20ºC is acceptable. NOTE 4ºC IS NOT ACCEPTABLE STORAGE.

If it is not possible to collect the PBMC by Ficoll gradient then separation of PBMC can be conducted using CPT tube separation as an alternative. However, the PBMC pellet MUST BE frozen immediately and stored at -80ºC.

- *Collection and Processing by CPT tube*

1. Peripheral blood should be collected in a BD Vacutainer CPT™ Cell Preparation Tube with Sodium Citrate. 8 mL and 4 mL CPT tubes can be obtained from Fisher Scientific (Cat# 02-685-125, 02-688-81) or Becton-Dickinson (BD No.362761, 362760). The 8 mL tubes have a 6 mL minimum draw and the 4 mL tubes have a 3 mL minimum draw.
2. Centrifuge the CPT™ tube at 1500 x g for 30 minutes at room temperature (20o C to 25o C). DO NOT APPLY THE BREAK ON THE CENTRIFUGE. Use acceleration 5, brake 0 (“slow mode”).
3. It may be necessary to spin the tube longer to ensure that all of the red blood cell components have been separated from the plasma layer through the polyester gel barrier.
4. The tube should be removed immediately from the centrifuge. The mononuclear layer and plasma lie above the polyester gel plug.
5. Using a sterile pipette, remove as much of the plasma component (upper half of the CPT tube) without disturbing the mononuclear layer if possible and discard.
6. Transfer mononuclear cell layer (and some residual plasma layer) to a labeled 15 mL conical centrifuge tube and add 5 mL sterile room temperature magnesium or calcium-free phosphate buffered saline (PBS) to fill the conical tube and recap.
7. Centrifuge at 450 x g for 10 minutes at room temperature (20o C to 25o C). Use acceleration 9, brake (“fast mode”).

8. Remove supernatant, being careful not to aspirate the cellular pellet at the bottom of the tube.
9. Add 1 mL of sterile PBS to the pellet and gently re-suspend by pipetting up and down. Transfer the entire suspended pellet to the labeled 2 mL cryovial. Cryovials larger than 2 mL cannot be accepted by the PBTC CRB.
10. Centrifuge the cryovial at 450 x g for 5 minutes (or spin down the microcentrifuge tube at 1300 x g for 5 minutes) at room temperature. Discard the supernatant. Store the cell pellet cryovial frozen at -80ºC. For short term storage (2–3 weeks) -20°C is acceptable.

9.1.1.2 *Handling of Specimens*

All samples should be labeled with the following:

- Patient PBTC Accession #
- PBTC Study #
- Collection date
- Sample type
- Slide number (For slides only; designate as "PBTCR #" where the # is assigned from 1 to 20 or the highest number of unstained sections prepared sequentially, **or** "PBTCR H&E" for the H&E stained section.)

Slides, scrolls, and Formalin Fixed, Paraffin Embedded (FFPE) tumor material should be shipped at room temperature. PBMCs should be shipped with a generous amount of dry ice enclosed to safeguard against shipping delays.

9.1.1.3 *Shipment of Specimens*

Refer to the PBTC CRB Specimen Transmittal Form posted on the PBTC-049 Protocol Webpage for shipping and contact information. The sample collection, shipment date, and other specimen-specific information must be documented in the eCRF. Samples collected for the repository should be shipped to the PBTC CRB for delivery Monday through Thursday by completing the Internet form at http://www.fedex.com/us/. The FedEx user ID and password for pathology shipping can be found on the PBTC-049 Protocol Webpage. Weekend and holiday deliveries are not permitted. Sites should notify the PBTC CRB staff via email when samples are shipped. It is recommended that samples are shipped as soon as possible after enrollment.

9.1.2 Pathology Central Review

Retrospective central pathology review will be completed from the slides submitted to the PBTC CRB if the patient consents to the CRB. Pathologist review will include the following elements:

- Examination of H&E stained slides. For each subject one (1) H&E stained slide per one representative block from the brain tumor, removed either at initial diagnosis or relapse, should be submitted for review.
- Review of the corresponding pathology report(s) of the immunohistochemical, special stains, and molecular/genetic results from current and/or original primary tumor
- If necessary, review of immunohistochemical or special stained slides. Slides submitted to the PBTC CRB will be digitized to 40X. H&E stained sections will be retained and filed at the CRB. Original immunohistochemical or special stain slides will be returned to the submitting institution.

9.1.3 Plasma Pharmacokinetics

Plasma pharmacokinetic (PK) studies will be obtained from all patients (including efficacy expansion cohort patients) enrolled on this study. Sites expecting to enroll a patient on PBTC-049 should request a PK kit by emailing the Center for Translational Pharmacology (CTP) at CTPLogistics@stjude.org. Please allow at least 2-3 business days for the kit to arrive.

Analysis of savolitinib and two metabolites (M2 and M3) in plasma will be performed at Covance using appropriate validated bioanalytical method. Full details of the analytical method used will be described in separate bioanalytical report. All samples within the known stability of the analytes of interest at the time of receipt by the bioanalytical laboratory will be analyzed.

9.1.3.1 *Sampling Strategy*

Sampling Strategy for Pharmacokinetic Study

On Day 1 of Course 1, serial blood samples for savolitinib pharmacokinetic studies will be collected at the following times: Pre-dose and 30 min (±5 min), 1 hr (±0.25 hrs), 2 hrs (±0.25 hrs), 4 hrs (±0.5 hrs), 8 hrs (±1 hrs), and 24 hrs (±4 hrs) after the oral dose.

The serial blood samples for savolitinib pharmacokinetic studies will also be collected on Day 8 (±2 days) of Course 1 at the following times: Pre-dose, 30 min (±5 min), 1 hr (±0.25 hrs), 2 hrs (±0.25 hrs), 4 hrs (±0.5 hrs), 8 hrs (±1 hrs), and 24 hrs (±4 hrs) after the dose.

For children less than 13 kg, contact the CTP (CTPLogistics@stjude.org) for a sampling strategy with reduced blood requirements.

9.1.3.2 *Collection and Handling of Specimens*

Please refer to the PBTC-049 Pharmacy Operations Manual (POM) posted on the PBTC-049 Protocol Webpage for more detailed information regarding the collection, processing, and shipment of PK samples for this study.

At each time point, 2 mL of blood should be collected into an appropriately labeled sodium heparin tube. Two (2) mL of blood is needed to provide approximately 1 mL plasma for pharmacokinetic analysis. The PK Data Collection Form (located in the POM) should be completed with the exact time that the sample is drawn as well as the exact time that the drug is administered. The samples should be labeled with the PBTC study number, Patient PBTC Accession number and the Course, Day, and the collection time for each sample.

Within 1 hour of collecting the whole blood sample, centrifuge at 1500 x g at 4°C for 10 minutes (note: If a refrigerated centrifuge is not available, please refer to the POM for further instructions). The plasma should be stored in amber screw top tubes in an upright position at -80°C within 1 hour of plasma preparation and kept at this temperature until shipment.

9.1.3.3 *Shipping of Specimens*

Samples should be shipped via Priority Overnight to ensure they will be delivered to the CTP only on Tuesday through Friday. Shipments should be packed with a generous amount of dry ice enclosed to safeguard against shipping delays. Weekend and holiday deliveries must be avoided.

In order for sites to receive cost reimbursement, PK samples must be shipped to the CTP within 30 days of the collection of the last sample. The site should use the PBTC-049 PK FedEx account details posted on the PBTC-049 Protocol Webpage. Ship all pharmacokinetic samples on dry ice along with the completed PK Data Collection Forms to the address provided on the PBTC-049 Protocol Webpage.

Sites should contact the CTP at St. Jude Children's Research Hospital, at CTPLogistics@stjude.org when samples are shipped. The sample collection and shipping dates must be documented in the eCRF.

9.1.4 c-MET expression and c-MET amplification

Tissue from original diagnosis, relapse or any subsequent resections or biopsies prior to treatment will be analyzed for c-MET expression using IHC and c-MET amplification using FISH. The IHC method will detect membranous c-MET expression; relative expression will be scored as: Negative, weak, moderate or strong. The relationship between c-MET expression and c-MET amplification and response to therapy will be explored within the constraints of a Phase I trial. These data will be hypothesis generating.

Note: If c-MET amplification was previously tested, FFPE tissue submission will only be needed for c-MET expression.

9.1.4.1 *Collection of Specimen(s)*

Seven (7) unstained slides from formalin-fixed paraffin-embedded (FFPE) tumor material will be collected along with one H&E stained slide prepared from the same block. The following will be collected from a representative tumor tissue for both c-MET expression and amplification:

- 7 unstained FFPE slides cut at 4 µm in thickness on (+) slides from the same tissue tumor block (IHC 5 unstained slides + FISH 2 unstained slides)
- 1 H&E stained slide from the same tissue tumor block
- Pathology report with tumor percentage in the area if available

If c-MET amplification was previously tested, the following will be collected from a representative tumor tissue for c-MET expression:

- 5 unstained FFPE slides cut at 4 µm in thickness on (+) slides from the same tissue tumor block
- 1 H&E stained slide from the same tissue tumor block
- Pathology report with tumor percentage in the area if available

Note: It is important that H&E and unstained FFPE slides come from the same block.

9.1.4.2 *Handling of Specimen(s)*

Samples should be labeled with the following:

- PBTC Accession number
- PBTC Study number
- Collection date
- Sample type (e.g., FFPE, H&E)

9.1.4.3 *Shipping of Specimen(s)*

Samples should be shipped to the PBTC CRB. **Refer to the PBTC CRB Specimen Transmittal Form posted on the PBTC-049 Protocol Webpage for shipping and contact information.** The sample collection date, shipment date, and other specimen-specific information must be documented in the eCRF. All samples should be shipped for delivery Monday through Thursday by completing the internet form at http://www.fedex.com/us/. FedEx user ID and password for shipping can be found on the PBTC-049 Protocol Webpage. Weekend deliveries are not permitted. Sites should inform the PBTC CRB staff via e-mail when samples are shipped.

Specimens should be shipped at room temperature along with a completed PBTC CRB Specimen Transmittal Form located on the PBTC-049 Protocol Webpage.

9.1.4.4 *Site Performing Correlative Studies*

Slides will be shipped from PBTC CRB to CCHMC for c-MET IHC and c-MET FISH analysis. All slides will be initially received by the CCHMC Pathology Lab contact below, then distributed to the appropriate lab for analysis. All stained slides will be centrally reviewed by Dr. Daniel Leino.

c-MET expression:

Daniel Leino, M.D, MPH
Cincinnati Children's Hospital Medical Center
3333 Burnet Ave., MLC 1035
Cincinnati, OH 45229
Telephone: 513-803-2361
Fax: 513-636-3924
Email: daniel.leino@cchmc.org

c-MET amplification:

Stephanie Balow, PhD
Cincinnati Children's Hospital Medical Center
Genetics and Genomics Diagnostic Laboratory
3333 Burnet Ave., MLC 7016
Cincinnati, OH 45229
Telephone: 513-803-4474
Fax: 513-636-4373
Email: stephanie.balow@cchmc.org

Lab contact person for questions:

Jaime Reuss
Cincinnati Children's Hospital Medical Center
Pathology Laboratory
3333 Burnet Ave., MLC 1035
Cincinnati, OH 45299
Telephone: 513-803-3338
Fax: 513-636-3924
Email: jaime.reuss@cchmc.org

9.1.5 Genomic analysis of c-MET signaling axis and related cancer genes

As an ancillary/exploratory study, genomic analyses will be performed to investigate the correlation between response to savolitinib treatment and the presence of specific genomic alterations and/ or specific disease subgroups. Tumor tissue in the form of frozen tissue and formalin fixed paraffin embedded (FFPE) tumor material, if available, from any previous surgical excision/biopsy of the primary tumor or recurrent tumor(s), will be studied. Assays performed on FFPE will include:

- Assays with DNA extracts will include the somatic disease/germline comparator (SDGC) assay, done in the research setting, using the Claret library construction kit for NGS library preparation. For patient samples with a comparator normal available, mutations will be evaluated from the SDGC assay. For those without a comparator normal, variants will be called using an alternative pipeline. Both types of patient samples (matched and unmatched) will be evaluated for copy number alterations, with a specific focus on *MET* amplification and extent.
- From the RNA extracts, RNAseq will be performed using a standard approach (TruSeq Stranded RNAseq) and evaluated for fusions and internal tandem duplications (ITDs) through the Ensemble pipeline. RNAseq data will be evaluated using Ingenuity Pathway Analysis to evaluate or elevated *MET* and associated pathways.
- Results for each patient will be evaluated from DNA and RNA evidence to compile data that may be helpful in the context of patient response and outcomes.

9.1.5.1 *Collection of Specimens*

The following samples must be collected for this correlative study:

- 1 H&E stained section
- 5 unstained slides of FFPE tissue
- If available, 20 mg of fresh frozen tumor sample OR 250 ng of genomic DNA (if genomic DNA has already been extracted from tumor material, this can be submitted in lieu of fresh frozen tumor)
- 5 mL of blood collected in a purple top tube, prior to treatment (to be used as a normal control for targeted sequencing studies)

Samples should be processed using the method described in Section 9.1.1 for PBTC CRB Repository samples.

9.1.5.2 *Handling and Shipping of Specimens*
All samples should be labeled with the following:

- Patient PBTC Accession number
- PBTC Study number
- Collection Date
- Sample Type
- Slide number (For slides only; designate as "PBTCR #" where the number is assigned from 1 to 20 or the highest number of unstained sections prepared sequentially, **or** "PBTCR H&E" for the H&E stained section).

Slides, scrolls, and Formalin Fixed, Paraffin Embedded (FFPE) tumor material should be shipped at room temperature. Fresh Frozen Tumor (FFT) and PBMC samples must be shipped on dry ice.

Refer to the PBTC CRB Specimen Transmittal Form posted on the PBTC-049 Protocol Webpage for shipping and contact information. The sample collection date, shipment date, and other specimen-specific information must be documented in the eCRF. Receipt and processing of samples will be recorded in ProtoLab, as appropriate, by staff at the PBTC CRB. Samples should be shipped for delivery Monday through Thursday by completing the internet form at http://www.fedex.com/us/. FFT and PBMC samples must be shipped via FedEx Priority Overnight. The FedEx user ID and password for shipping can be found on the PBTC-049 Protocol Webpage. Weekend and holiday deliveries are not permitted. Sites should notify the PBTC CRB staff via when samples are shipped.

9.1.5.3 *Site(s) Performing Correlative Study*

Kathleen M. Schieffer, PhD, FACMG
Institute for Genomic Medicine
Nationwide Children's Hospital
575 Children's Crossroad
Columbus, OH 43215
Telephone: 614-355-2894
Fax: 614-938-2090
Email: kathleen.schieffer@nationwidechildrens.org

9.2 Neuroimaging Studies

Patients will have MRI Brain with and without contrast performed prior to therapy, then every 8 weeks until Course 6 (after Courses 2, 4, 6), then every 12 weeks until Course 24 (after Courses 9, 12, 15, 18, 21, 24), then every 16 weeks until Course 39 (after Courses 28, 32, 36, 39). For patients allowed to extend therapy past Course 39, imaging should be done every 36 weeks (after Courses 48, 57, 66, etc.). All patients will have imaging performed at the completion/discontinuation of treatment until time of progression or completion of treatment. MRI Spine should be performed prior to therapy and at the same time points as standard MRI Brain, if clinically indicated.

Standard MR imaging will include Sagittal T1 MPRAGE, axial DWI, axial T2 FLAIR, axial T2, and post gadolinium sagittal T1 MPRAGE (with reconstructions) images. The standard MR parameters are listed on the PBTC NIC web page located at http://www.childrenshospital.org/research/centers-departmental-programs/pediatric-brain-tumor-consortium-neuroimaging-center under Neuroimaging Studies/ Specific MR Imaging Sequences- Open PBTC Protocols. There is also a link to the same PBTC-NIC webpage from the PBTC-049 Protocol Webpage.

Volumetric analyses will be done at the Neuroimaging Center (NIC, Children's Hospital Boston) via the Vitrea (Vitrea™) workstation, from the axial T2 FLAIR and T1-weighted post-contrast brain images.

9.2.1 Neuroimaging Review

Local review of MR imaging studies at each site and central review of the MR imaging studies will be conducted through the PBTC Neuroimaging Center (NIC). NIC review will include assessment of response to therapy (as feasible). The director and one neuroradiologist of NIC will review the imaging studies at study completion. If the local and central review are not in agreement the NIC neuroradiologist will confer with the participating site to determine why there is a discrepancy via conference call.

For patients showing a partial or complete response (PR or CR), the following scans should be uploaded to PBTC at the time response is sustained:

- The baseline scan
- The first scan showing a partial or complete response (PR or CR)
- The confirmation scan obtained approximately 8 weeks later (if available)

Once scans are uploaded, they will be electronically transferred to the PBTC NIC for central review at the completion of the study. Additional scans may be requested from the sites (e.g. at a later timepoint) if the patient's response cannot be confirmed by the NIC. All patient specific data are stripped from the images and replaced with PBTC Accession numbers prior to transmitting the images to the NIC. All image data transfer is accomplished using PGP (pretty-good-privacy) 128-bit encryption which meets industry standard for secure communication.

10 STUDY CALENDAR

Data is to be submitted according to the Data submission timelines located on the PBTC-049 Protocol Webpage.

	Eligibility	Course 1	Courses 2–39	Courses 40+ (extended therapy patients)	Completion/ Discontinuation of Treatment
Physical Assessments					
Medical history	X	Weekly	Prior to each course	Every 3 courses Prior to course	X
Physical exam / height/weight/BSA [A]	X	Weekly	Prior to each course	Every 3 courses Prior to course	X
Vital signs	X	Weekly	Prior to each course	Every 3 courses Prior to course	X
Performance status	X	Weekly	Prior to each course	Every 3 courses Prior to course	X
Neurologic exam	X	Weekly	Prior to each course	Every 3 courses Prior to course	X
Smoking Status[A]		X			
Pulse Oximetry	X				
Laboratory Evaluations					
CBC WBC, HgB, Platelets, ANC, ALC [B]	X	Weekly	Prior to each course	Every 3 courses Prior to course	X
Serum Chemistry Sodium, Potassium, Bicarbonate, Chloride, Calcium, BUN, Creatinine, Glucose, Phosphorous, Magnesium, Albumin, Total Protein [B]	X	Weekly	Prior to each course	Every 3 courses Prior to course	X
Coagulation (PT, INR, aPTT) [B, I]	X	Weekly	Prior to each course	Every 3 courses Prior to course	X
SGPT(ALT), SGOT(AST), Total Bilirubin [B, C]	X	Weekly	C2–C3: Weekly C4–C39: Prior to each course	Every 3 courses Prior to course	X
Serum or Urine pregnancy test (for females of childbearing potential) [D]	X	Prior to each course	Prior to each course	Every 3 courses Prior to course	X
CSF cytology (if clinically indicated)	X				

	Eligibility	Course 1	Courses 2–39	Courses 40+ (extended therapy patients)	Completion/ Discontinuation of Treatment
Other Assessments					
EKG (All EKGs taken should be in triplicate.)	**X**	**1–3 hours after the first dose of each week (e.g., Days 1, 8, 15, 22)**	**Prior to each course**	**Every 3 courses Prior to course**	**X[H]**
Right knee X-ray[E]	**X**		**Every 3 courses After course**	**Every 3 courses Prior to course**	**X**
Imaging Assessments					
Brain MRI (standard)[F]	**X**		**X**	**X**	**X**
Spinal MRI (if clinically indicated)[G]	**X**		**X**	**X**	**X**
Image Upload	Refer to Section 9.2.1 for image upload timepoints				
Correlative Laboratory Studies					
Refer to the sample collection table in Section 9.0.					

A. Height/weight/BSA and smoking status required only once, prior to treatment, for Course 1.
B. To be done more frequently throughout the duration of treatment if required to monitor toxicities.
C. To be done every week during each course for the first 3 courses. Collect prior to each course for Courses 4–39 and then collect every 3 courses thereafter (prior to Courses 42, 45, 48, etc.). Collect for all patients at the completion/discontinuation of treatment.
D. To be done within 24 hours prior to each course. Pregnancy test should be repeated prior to Course 1 if the test used for eligibility is > 24 hours old prior to the start of treatment.
E. Obtain pre-treatment tibial x-ray (AP and lateral views) of the right knee, to be repeated every 3 courses (after Courses 3, 6, 9, etc.). If abnormalities are detected on routine X-rays, MRI scan of both knees should be performed.
F. Standard imaging is to be done every 8 weeks until Course 6 (after Courses 2, 4, 6), then every 12 weeks until Course 24 (after Courses 9, 12, 15, 18, 21, 24), then every 16 weeks until Course 39 (after Courses 28, 32, 36, 39), then perform every 36 weeks thereafter (after Courses 48, 57, 66, etc.). Collect for all patients at the completion/discontinuation of treatment.
G. MRI Spine should be done at the same time points as the standard MRI brain, if clinically indicated.
H. A 28-day follow-up EKG assessment is required 28 days after the off-treatment date if an EKG assessment is abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality.
I. Increase the frequency of INR tests if savolitinib and warfarin are used concomitantly.

11 MEASUREMENT OF EFFECT

Although the clinical benefit of savolitinib has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. For the purposes of this study, patients should be re-evaluated every 8 weeks for the first 6 courses (after Courses 2, 4, 6), then every 12 weeks until Course 24 (after Courses 9, 12, 15, 18, 21, 24), then every 16 weeks until Course 39 (after Courses 28, 32, 36, 39). After Course 39, patients will be re-evaluated every 36 weeks thereafter (after Courses 48, 57, 66, etc.). All patients will be evaluated at the completion/discontinuation of treatment. In addition to a baseline scan, confirmatory scans will also be obtained 8 weeks following initial documentation of an objective response.

11.1 Antitumor Effect Definitions

11.1.1 Definitions

- Evaluable for Toxicity

Patients who receive at least 1 dose of savolitinib and are removed from treatment for toxicity during the dose-finding period (first 4 weeks of treatment) are evaluable for estimating the MTD.

Patients who receive approximately 85% (24 or more doses) of prescribed therapy during the dose-finding period but who progress prior to completing the course may be considered evaluable for estimating the MTD, as long as no additional anti-cancer therapy or supportive care that would confound the interpretation of any observed toxicity or side effect is given. Patients must have completed all of the clinical and laboratory monitoring requirements specified by the protocol up to the time of disease progression for them to be considered evaluable for MTD estimation.

Patients who have completed all therapy during the dose-finding period but who failed to comply with all the specified clinical and laboratory monitoring requirements for the first course may be considered inevaluable for estimating the MTD and replaced.

Patients who receive less than 24 doses of the protocol specified therapy for reasons other than toxicity (e.g., dosing error, progressive disease, withdrawal of consent etc.) during the dose finding period will be considered inevaluable for estimating the MTD and will be replaced.

- Evaluable for Efficacy

All patients who receive at least 1 dose of the agent will be considered evaluable for efficacy analyses and will be assessed based on the criteria described below.

11.2 Disease Parameters

In order to completely document the assessment of response, the measurements of the longest tumor dimension, and its perpendicular, of all target lesions upon which the assessments of tumor response are based should be explicitly noted in the radiology report for the baseline and all subsequent follow-up exams. Reports for the follow-up exams should reiterate the measurements obtained at baseline for each target lesion. Non-target lesions or newly occurring lesions should

also be enumerated in these reports, and changes in non-target lesions should be described. 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.

Tumor response criteria are determined by changes in size using the longest tumor dimension, and its perpendicular. FLAIR, T2 or post contrast T1 weighted images may be used—whichever gives the best estimate of tumor size.

Since many tumors contain non-enhancing components (or, in some cases, the tumor may not enhance at all), both the enhancing and the non-enhancing components must be evaluated—on post contrast T1 weighted images and on FLAIR/T2 weighted images respectively. Increase in enhancement on T1 weighted images without accompanying increase in disease bulk on T2 or FLAIR images is not considered tumor progression. In turn, enlarging areas of non-enhancing tumor (defined as mass effect/tissue thickening) are evidence of tumor progression. Conversely, decrease in enhancing tumor component without decrease in overall FLAIR/T2 extent may represent change in tumor permeability (commonly observed with antiangiogenic therapies) rather than represent tumor response.

11.2.1 Method

The following section describes the methodology. (See Figure 4 below for illustration.)

- For MRI imaging (preferred), the longest measurement of the tumor (or width, W) should be determined. It can be measured from the axial plane or the plane in which the tumor is best seen or measured, provided the same plane is used in follow ups. Longest diameter of target lesion(s) should be selected in the axial plane only for CT.

- The measurement (transverse (T)) perpendicular to the width in the selected plane should be determined. NOTE: A measurable lesion should have a minimal transverse measurement that is at least twice the combined thickness of the image slice and the inter-slice gap. For example, with a 4 mm slice and a 0.4 mm gap, minimal measurable lesion diameter is 8.8 mm. Smaller lesions would not be measurable for study purpose.

- The cystic or necrotic components of a tumor are not considered in tumor measurements. Therefore, only the solid component of cystic/necrotic tumors should be measured. If cysts/necrosis composes the majority of the lesion, the lesion may not be "measurable." Options:
  - if the cyst/necrosis is eccentric, the W and T of the solid portion should be measured, the cyst/necrosis excluded from measurement
  - if the cyst/necrosis is central but represents a small portion of the tumor (< 25%), disregard and measure the whole lesion
  - if the cyst/necrosis is central but represents a large portion of the tumor, identify a solid aspect of the mass that can be reproducibly measured

- Leptomeningeal tumor spread is usually not a target lesion, and usually cannot be measured accurately. Presence and location of leptomeningeal tumor spread should be noted and change in extent/thickness assessed on follow up studies.

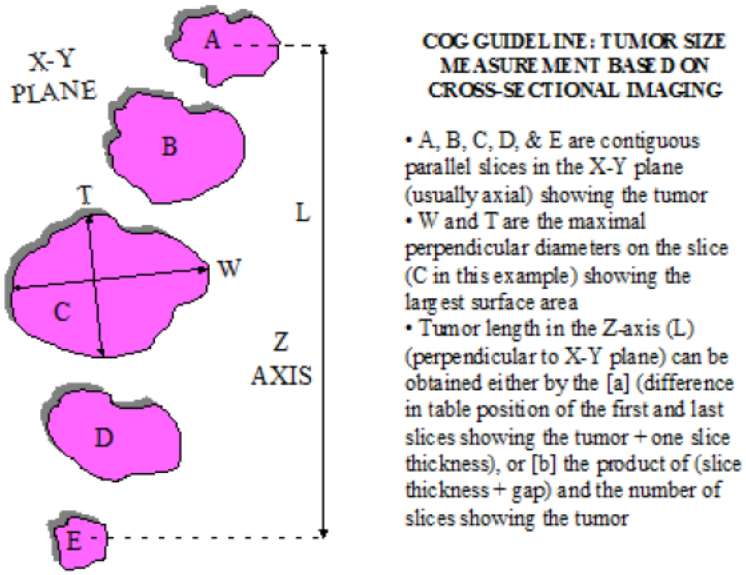


Figure 4. Tumor size measurement based on cross-sectional imaging

11.2.2 Overall Response Assessment

The overall response assessment takes into account response in both target and non-target lesion, and the appearance of new lesions, where applicable, according to the criteria described in the table below.

Overall Response Assessment

Target Lesions	New Lesions*	Overall Response
CR	No	**CR**
PR	No	**PR**
SD	No	**SD**
PD**	Yes or No	**PD**
Any	Yes	**PD**
CR – Complete Response; PD – Progressive Disease; PR – Partial Response; IR – Incomplete Response; SD – Stable Disease *If CSF cytology becomes positive when previously negative at study entry, it will be considered a new lesion and progressive disease. **This includes progression of non-target lesions as well as appearance of new lesions even in the absence of PD in the target lesion.		

11.2.3 Selection of Target and Non-target Lesions

- For most CNS tumors, only one lesion/mass is present and therefore is considered a "target" for measurement/follow up to assess for tumor progression/response.
- If multiple measurable lesions are present, a minimum of the 2 largest lesions should be measured; a maximum of 5 should be selected as "target" lesions. Target lesions should be selected on the basis of size and suitability for accurate repeated measurements. All other lesions will be followed as non-target lesions.

- The lower size limit of the target lesion(s) should be at least twice the thickness of the slices showing the tumor to decrease the partial volume effect (e.g., 8 mm lesion for a 4 mm slice).
- Non-target lesions are assessed for disease and count towards progressive disease.

11.3 Tumor Response Criteria

11.3.1 Complete Response (CR)

Complete disappearance on MR of all evaluable tumor and mass effect, on a stable or decreasing dose of corticosteroids (or receiving only adrenal replacement doses), accompanied by a stable or improving neurologic examination. Complete response will be confirmed if it is maintained for at least 8 weeks. If CSF was positive, it must be negative.

11.3.2 Partial Response (PR)

Greater than or equal to 50% reduction in tumor size by bi-dimensional measurement, as compared with the baseline measurements, on a stable or decreasing dose of corticosteroids, accompanied by a stable or improving neurologic examination. Partial response will be confirmed if it is maintained for at least 8 weeks.

11.3.3 Stable Disease (SD)

Neurologic exam is at least stable and maintenance corticosteroid dose not increased, and MR/CT imaging meets neither the criteria for PR nor the criteria for Progressive Disease. If this category is to be reported as of possible clinical benefit, Stable Disease status must be maintained for 16 weeks (4 courses).

11.3.4 Progressive Disease (PD)

- Progressive neurologic abnormalities or worsening neurologic status not explained by causes unrelated to tumor progression (e.g., anticonvulsant or corticosteroid toxicity wean, electrolyte disturbances, sepsis, hyperglycemia, etc.), OR
- A greater than 25% increase in the bi-dimensional measurement of any measurable lesion, taking as a reference the smallest disease measurement recorded since the start of protocol therapy, OR
- A greater than 25% increase in the sum of the bi-dimensional measurements of all measurable lesions, taking as reference the smallest sum of the disease measurements recorded since the start of protocol therapy, OR
- The appearance of a new tumor lesion., OR
- For non-measurable disease there is a clear increase in size of tumor from smallest appearance since the start of protocol therapy. Development of new disease or progression/relapse in any established lesion(s) (including target and non-target), regardless of response in other lesions (e.g., when multiple lesions show opposite responses) will be considered progressive disease.

Increasing doses of corticosteroids required to maintain stable neurological status should be strongly considered as a sign of clinical progression unless in the context of recent wean or transient neurologic change.

11.3.5 Progression-free Survival (PFS)

Interval of time between date of initiation of protocol treatment and minimum date of documentation of PD, second malignancy, death due to any cause, or date of last follow-up.

11.3.6 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.

12 STUDY OVERSIGHT AND DATA REPORTING/ REGULATORY REQUIREMENTS/ CONFIDENTIALITY

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7).

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.

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 Pediatric Brain Tumor Consortium's (PBTC) data safety monitoring plan.

12.2 Data Reporting

Medidata Rave is the clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- Active CTEP registration with credentials necessary to access secure NCI/CTSU IT systems; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.
  - Rave role requirements:
    - Rave CRA or Rave CRA (Lab Admin) role must hold a minimum of an Associate Plus (AP) registration type;
    - Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and
    - Rave Read Only role must have at a minimum an Associates (A) registration type.
- Refer to https://dctd.cancer.gov/research/ctep-trials/for-sites/registration for registration types and documentation required.
- DTL Rave CRA task assignment requirements (for write access):
  - Corresponding role (Rave CRA or Rave CRA (Lab Admin) on the site roster.

Upon initial site registration approval for the study in Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. No action will be required; each study invitation will be automatically accepted and study access in Rave will be automatically granted. Site staff 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 eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Action will be required by site staff (to activate their account) who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application. Account activation instructions are located on the CTSU website in the *Data Management* section under the Data Management Help Topics > Rave resources > Medidata Account Activation and Study Invitation (to activate your iMedidata account). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management Rave Resources section or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

12.2.1 Method

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis, either by FTP burst of data or via the CDS web application. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (https://dctd.cancer.gov/research/ctep-trials/trial-development).

NOTE: If your study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS.

12.2.2 Responsibility for Data Submission

The OBDMC for the PBTC is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

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" (https://dctd.cancer.gov/research/ctep-trials/trial-development/agents-agreements) 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: https://dctd.cancer.gov/programs/ctep.

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 (https://dctd.cancer.gov/research/ctep-trials/trial-development/agents-agreements#intellectual-property-and-the-ctep-ip-option). 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 Participant and Data Confidentiality

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict

confidence. No information concerning the study and the data will be released to an unauthorized third party without the prior written approval of the Pediatric Brain Tumor Consortium (PBTC).

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

Source documents which are the original records of clinical findings, observations, or activities in a clinical trial are to be maintained at each participating site. Sites must upload all source documentation which supports the eligibility, DLT, or dose finding and evaluability of the participant to the PBTC via the RAVE database. In the event the patient experiences unexpected events, additional source documentation may be requested to complete the event review. These documents may include but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, and radiographic images.

Study participant study related data, which is for purposes of statistical analysis and scientific reporting will be transmitted to the Pediatric Brain Tumor Consortium electronically via the RAVE database. This will not include the participant's contact or identifying information. Rather, research participants and their research data will be identified by a unique study identification number assigned at the time of screening or registration. The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and institutional regulations.

The study data entry and study management systems used by clinical sites and by the PBTC will be secured and password protected. At the end of the study, all study data is maintained on a secure server.

After the study is completed, the data collected will be maintained on a server and may be used by other investigators, including those outside the study. With the participant's approval and as approved by local IRBs, biological samples labeled only with the participant's protocol specific identification number will be stored at the PBTC Central Review and Biorepository and could be made available to other investigators for future unspecified research. Investigators conducting future studies will not have access to the key for stored data collected while the participant is on study. Clinical data will be de-identified before it is shared with other investigators.

If the participant agrees to submit a repository sample, those samples contain genetic information that may be used for research related to brain tumors and their treatment. They may also be used to develop tests/assays to improve diagnosis and treatment of these diseases in the future. Genetic research may consist of the analysis of one or more genes or the analysis of genetic markers throughout the genome.

13 STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a phase I study and we will use the Rolling-6 design for dose finding.

A "Rolling-6" Phase I design will be used to estimate the maximum tolerated dose (MTD) and recommend a phase II dose (MTD/RP2D) of savolitinib, where dose escalations are planned in cohorts of two-six (2–6) patients. Dose escalation will be initiated at Dose Level 1. No intra-patient escalation will be allowed.

The Rolling-6 design was recently introduced by Skolnik et al.[27] motivated by the observation in Lee et al.[28] that most pediatric Phase I trials in oncology have not produced excessive toxicities. A possible explanation for this could be that pediatric trials are often preceded by their adult counterparts and the knowledge gained in the latter is utilized towards ensuring safety in the former. The Rolling-6 design aims to shorten the duration of pediatric Phase I trials by minimizing the time the trial would be closed to accrual for toxicity monitoring. This is achieved by enrolling anywhere from 2 to 6 patients at a dose level without requiring that the DLT status of the patients already assigned to the same dose level are known; hence reducing the number of patients who would be turned away due to unavailability of open slots. The simulations in Skolnik et al. as well as PBTC's own simulations[29] indicate that this approach decreases the duration of a Phase I trial compared to the traditional method without increasing the overall toxicity percentage.

13.2 Dose Escalation/De-Escalation Rules

The Rolling-6 design allows for accrual of two to six patients concurrently onto a dose level. Decisions as to which dose level to enroll a patient are based on the number of patients currently enrolled and evaluable, the number of patients experiencing dose-limiting toxicities (DLT), and the number of patients still at risk of developing a DLT at the time of new patient entry. Dose escalation occurs if 0 out of 3–6 or at most 1 out of 6 evaluable patients experience a DLT while being treated at a dose level; otherwise if 2 of 2–6 patients experience DLTs the dose is declared too toxic and thus above the MTD. Once a dose is determined to be too toxic, then escalation to higher dose levels is not allowed. The MTD is empirically defined as the highest dose level at which six patients have been treated with at most one patient experiencing a DLT and the next higher dose level has been determined to be too toxic. Dose escalation will begin with Dose Level 1.

The following table enumerates all possible scenarios and describes escalation/de-escalation rules for a Rolling-6 design.

Dose Escalation/De-Escalation Rules for the Rolling-6 Design					
				Decision when Next Patient is Enrolled	
# Pats Enrolled	# Pats with DLTs	# Pats w/o DLT	# Pats with Toxicity Data Pending	Not at the Highest Dose Level	At the Highest Dose Level
2	0, 1	Any	Any	Stay	Stay
2	2	0	0	De-escalate	De-escalate
3	0	0, 1, 2	3, 2, 1	Stay	Stay
3	0	3	0	Escalate	Stay
3	1	0, 1, 2	2, 1, 0	Stay	Stay
3	≥ 2	Any	Any	De-escalate	De-escalate
4	0	0, 1, 2, 3	4, 3, 2, 1	Stay	Stay
4	0	4	0	Escalate	Stay
4	1	0, 1, 2, 3	3, 2, 1, 0	Stay	Stay
4	≥ 2	Any	Any	De-escalate	De-escalate
5	0	0, 1, 2, 3, 4	5, 4, 3, 2, 1	Stay	Stay
5	0	5	0	Escalate	Stay
5	1	0, 1, 2, 3, 4	4, 3, 2, 1, 0	Stay	Stay
5	≥ 2	Any	Any	De-escalate	De-escalate
6	0	0, 1, 2, 3, 4	6, 5, 4, 3, 2	Suspend	Suspend
6	0	5, 6	1, 0	Escalate	MTD not determined
6	1	0, 1, 2, 3, 4	5, 4, 3, 2, 1	Suspend	Suspend
6	1	5	0	Escalate	MTD not determined
6	≥ 2	Any	Any	De-escalate	De-escalate

Based on the above-outlined escalation rules, if Dose Level 0 is found to be too toxic, then the trial will be closed to accrual and the merits of amending or closing the trial permanently will be reconsidered. On the other hand, if the maximum dose level proposed for the study is deemed to be safe, then the MTD will not have been determined and consideration may be given to investigate higher dose levels. Otherwise the highest dose level may be recommended as the Phase II dose. Accrual will be suspended for any Grade 5 AE *or* any two Grade 4 AEs that occur in 2 separate subjects (rather than 2 Grade 4 AEs that occur within the same subject) which are at least possibly attributable to savolitinib. Only Grade 4 AEs that meet the DLT definitions will be counted towards this monitoring rule. If the suspension threshold is reached, the toxicity data and all associated information will be reviewed by the study committee, the PBTC toxicity monitoring committee, CTEP, and by the FDA prior to a deliberate decision to resume accrual.

As part of routine analyses, toxicities will be summarized by dose level, by grade, and by attribution. These analyses will also take into account the actual dosage received by subjects to ensure that large deviations in dosage that will likely occur due to limitations in savolitinib formulation do not lead to safety concerns. For the same reason, with each completed dose level we will assess the toxicity data to determine if the observed higher grade toxicities were more likely in patients who received higher than targeted dosages. Furthermore, at the end of the study, we will explore associations between PK parameters (such as C_{max} and AUC) and higher grade toxicities that may help identify and safety trends.

13.3 Special Considerations for Protocol Version 3.0

As of September 2019, 2 DLTs were observed at Dose Level 1 and the dose was de-escalated to Dose Level 0. However, due to concerns that Dose Level 0 may be too low to achieve what is thought to be clinically efficacious exposures and the fact that the 2 DLTs observed were from 2 different AE classes, following discussions with the PBTC DSMB, CTEP, and AstraZeneca, a decision was made to re-challenge Dose Level 1.

Once protocol Version 3.0 is activated, 6 additional slots will be opened at Dose Level 1 and if 2 or more patients experience DLTs (of any toxicity class) among these 6 subjects, then Dose Level 1 will be considered too toxic and de-escalation to Dose Level 0 will occur. Otherwise (i.e., if no more than 1 subject with a DLT is observed in these 6 subjects which would result in 3 DLTs in 12 subjects treated at this dose) we will proceed to the expansion cohorts described below at Dose Level 1.

Subjects who have initiated treatment at Dose Level 0 will be given the option to escalate to Dose Level 1 at the time of Course 2 or later if they are further along in their treatment course.

Furthermore, as of protocol Version 3.0, Dose Level 2 is eliminated based on guidance from the drug sponsor that the adult RP2D has been revised to 300 mg/day as the maximum dose.

13.4 Special Considerations for Protocol Version 4.0

Based on the guidance received as of protocol Version 4.0, the adult recommended phase 2 dose for savolitinib was revised to 600 mg/day. Thus, with version 4.0, Dose Level 2 has been re-inserted as a proposed dose level and Dose Level 3 was added.

At the time of the activation of protocol version 4.0, if the DLT rate at Dose Level 1 remains under 33%, enrollment to the study will be temporarily stopped until all patients currently on treatment are assessed for the dose finding period. If the observed DLT rate at Dose Level 1 is below 33% (e.g., 2 DLTs in 8 subjects, etc.) then escalation to Dose Level 2 will occur and the remaining slot openings will follow the Rolling 6 design for Dose Levels 2 and 3.

13.5 Expansion Cohorts

13.5.1 PK Expansion

Once the MTD has been estimated or the recommended phase 2 dose has been determined, up to 6 additional patients (to reach a total of 12) will be treated at that dose level to better describe the toxicity profile of the agent. There is a possibility that patients' age may affect PK parameters, toxicity and potential efficacy of this agent and thus at the MTD we will stratify enrollment to ensure at least 6 patients are treated at each of the following 2 cohorts based on age at the time of enrollment:

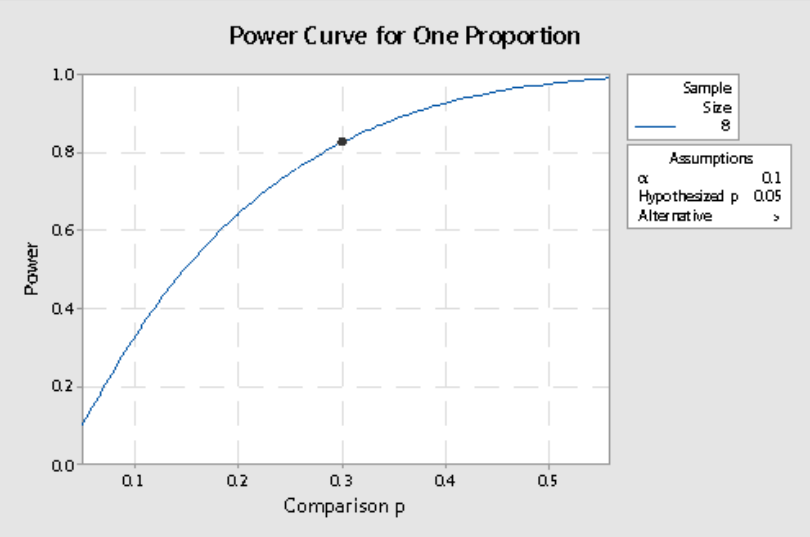
- Patients under 12 years old
- Patients 12 or older

If excessive number of toxicities is observed at the MTD following the enrollment of the PK expansion cohort (i.e., > 33%) or if the observed data suggests that the dose is intolerable in one or both of the age-defined strata above then the initial MTD estimate may be revised and a lower dose than the originally declared MTD may be further studied in the entire cohort or a subset of it (e.g., younger patients) to better define an MTD/RP2D in this cohort.

13.5.2 Efficacy Expansion

In an effort to look for an early signal of efficacy, once the MTD/RP2D is determined, we propose a small efficacy expansion cohort to enroll up to 8 patients whose tumors harbor genetic MET activation as determined by CLIA tests performed at participating sites. Patients who are treated at the MTD or as part of the PK expansion cohort will also count towards this efficacy expansion if they are known to have tumors with MET activation.

For the efficacy expansion cohort, with 8 patients and using single proportion binomial test, we will be able to test with 10% type 1 error and 82% power between an unacceptable response rate of 5% vs. a desirable response rate of 30%. If at least 2 patients respond, we will consider savolitinib promising in this patient population.



13.5.3 Contingency

In the event of a single fatal toxicity, the OBDMC will suspend enrollment, pending discussion with the Study Chair, IDB, and others as necessary.

13.6 Sample Size/Accrual Rate

Since the Rolling-6 design allows for up to 6 patients at each dose level and given the broad eligibility criteria for this trial, we anticipate that we will enroll 6 patients per dose level. With the expectation that up to 4 dose levels will be studied and that the cohort at the MTD will be expanded to 12 patients, we anticipate maximum enrollment of 36 evaluable patients for the dose finding component. Taking into account the planned efficacy expansion and assuming that none of the previously treated patients will be eligible for the efficacy expansion cohort, we may enroll a total of 44 eligible and evaluable patients. It is typical to encounter eligible patients who enroll on a Phase I trial but turn out to be inevaluable for assessing toxicity due to their inability to complete the DLT observation period. Thus we expect we may have to enroll 5–6 additional patients due to inevaluability for a total sample size of 50 patients.

13.6.1 Projected Accrual Ranges and Study Duration

The projected accrual rate for this study is 1–2 patients per month, based on knowledge of the member institutions and their commitment to the Consortium. With 2 possible dose levels, the total sample size and the study duration are expected to be 36 and about 1–2 years, respectively, if two dose levels are investigated.

Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	1	0	0	0	**1**
Asian	1	3	0	0	**4**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	3	1	0	0	**4**
White	12	15	7	5	**39**
More Than One Race	1	1	0	0	**2**
Total	**18**	**20**	**7**	**5**	**50**

13.7 Analysis of Secondary Endpoints

13.7.1 Imaging Correlates

Any objective responses (CR+PR) which may be observed in this trial will be described by dose and by histology. Prolonged stable diseases will also be reported in a descriptive fashion. Similarly, data from molecular analyses of tumors will be reported descriptively.

13.7.2 Statistical Analysis of Pharmacokinetics

Plasma drug concentrations and pharmacokinetic parameters will be presented in tabular and graphical form. Pharmacokinetic parameters of interest, such as apparent volume of the central compartment (Vc/F), elimination rate constant (Ke), half-life ($t_{1/2}$), apparent oral clearance (CL/F), and area under the plasma concentration time curve (AUC) will be estimated using compartmental methods. Dose proportionality in pharmacokinetic parameters will be investigated by performing one-way analysis of variance (ANOVA) on dose-normalized parameters.

In addition to estimating individual pharmacokinetic parameters, we will also estimate the population parameters using nonlinear mixed effects modeling methods (NONMEM). This method estimates the population parameters and both the inter- and intra-subject variability. Once the population parameters and corresponding covariance matrix are estimated, individual estimates can be obtained using post hoc analysis.

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15 APPENDICES

15.1 Performance Status Criteria

MODIFIED LANSKY SCORE (Score as 0 – 100)

A. Normal Range

100 = Fully active
90 = Minor restrictions in physically strenuous play
80 = Restricted in strenuous play, tires more easily, otherwise active

B. Mild to moderate restriction

70 = Both greater restrictions of and less time spent in active play
60 = Ambulatory up to 50% of time, limited active play with assistance/supervision
50 = Considerable assistance required for any active play; fully able to engage in quiet play

C. Moderate to severe restriction

40 = Able to initiate quiet activities
30 = Needs considerable assistance for quiet activity
20 = Limited to very passive activity initiated by others (e.g., TV)
10 = Completely disabled, not even passive play
0 = Unresponsive, coma

KARNOFSKY SCALE

100 = Normal; no complaints
90 = Able to carry on normal activities; minor signs or symptoms of disease
80 = Normal activity with effort
70 = Cares for self. Unable to carry on normal activity or to do active work
60 = Requires occasional assistance but able to care for most of his/her needs
50 = Requires considerable assistance and frequent medical care
40 = Disabled; requires special care and assistance
30 = Severely disabled; hospitalization indicated though death not imminent
20 = Very sick. Hospitalization necessary. Active support treatment necessary.
10 = Moribund
0 = Dead

15.2 New York Heart Association Classification

Functional Capacity	Objective Assessment
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	**A.** No objective evidence of cardiovascular disease.
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	**B.** Objective evidence of minimal cardiovascular disease.
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	**C.** Objective evidence of moderately severe cardiovascular disease.
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	**D.** Objective evidence of severe cardiovascular disease.

Based on: The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

15.3 Medications Which May Cause QTc Prolongation

The following table presents a list of drugs that may prolong the QTc. These drugs should NOT be used during the study. Providers should consult a frequently-updated drug information reference for a complete list.

Table 4. Drugs that prolong QTc interval

Alfuzocin	Foscarnet	Ondansetron
Amantadine	Fosphenytoin	Pentamidine
Amiodarone (cordarone)	Gatifloxacin	Pimozide
Amitriptyline	Gemifloxacin	Procainamide
Arsenic trioxide	Grepafloxacin	Protiptyline
Azithromycin	Halofantrine	Quetiapine
Bepridil	Haloperidol	Quinidine
Chloral hydrate	Hydroxychloroquine	Quinine
Chloroquine	Ibutilide	Risperidone
Chlorpromazine	Imipramine	Salmeterol
Cisapride	Indapamide	Sotalol
Clarithromycin	Isradipine	Sparfloxacin
Cloroquine	Levofloxacin	Sumatriptan
Desipramine	Levomethadyl	Tacrolimus
Disopyramide	Lithium	Tamoxifen
Dofetilide	Mesoridazine	Telithromycin
Dolesetron	Methadone	Thioridazine
Domperidone	Moexipril/HCTZ	Tizanidine
Doxepin	Moxifloxacin	Vardenifil
Droperidol	Naratriptan	Venlaflaxine
Erythromycin	Nicardipine	Voriconizole
Felbamate	Nortriptyline	Ziprasidone
Flecainide	Octreotide	Zolmitriptan
	Ofloxacin	

Drugs with a known risk of Torsades de Pointes
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.

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.

Table 5. 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	16 weeks
Amiodarone, chloroquine	1 year

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

15.4 Eligible MET Activating Alterations for the Efficacy Expansion Cohort

MET pathway activation is defined as:

- *MET* kinase mutations

OR

- *MET* or *HGF* amplification

OR

- *MET* fusion

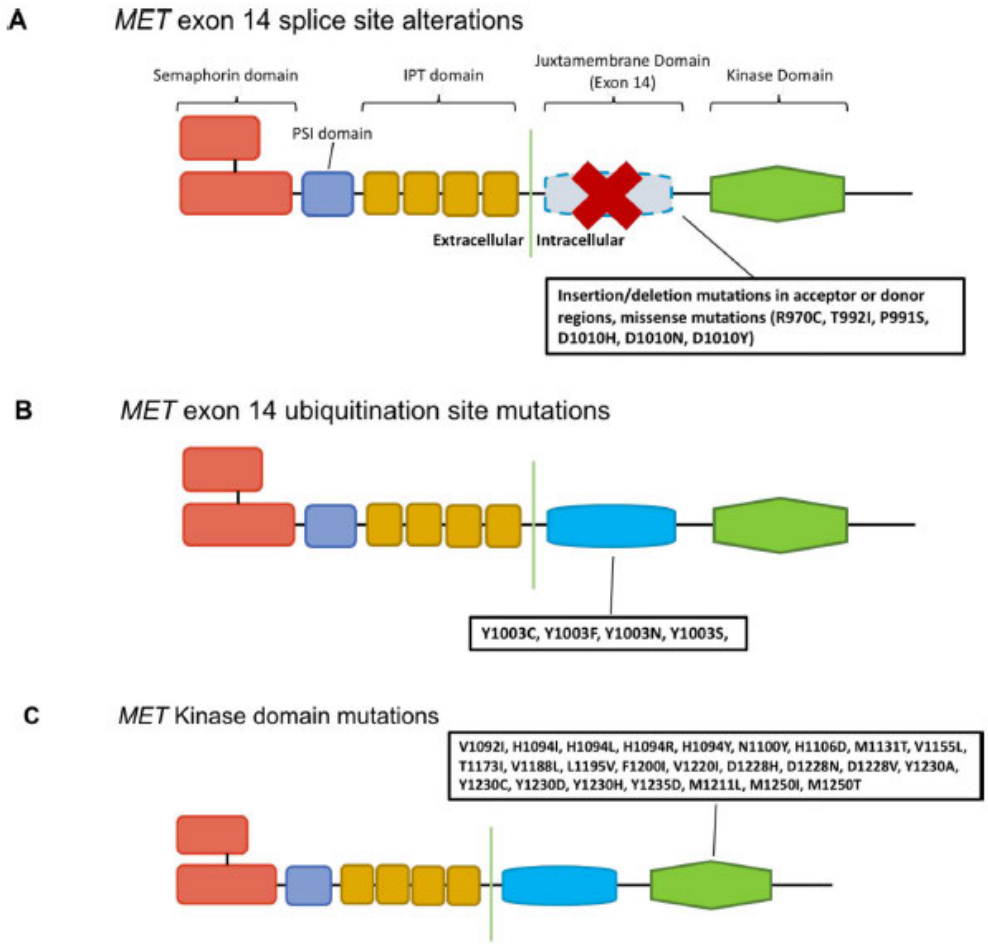

Figure 5: *MET* mutations[30]

15.5 Dosing Tables for Savolitinib

Dose Level 0: 75 mg/m^2/day
BSA must be ≥ 1.00 m^2

	Total Daily Dose (mg)	BSA Range		Tablets Required	
		low	high	100 mg	200 mg
Dose Level 0 75 mg/m^2/day	100	1.00	1.99	1	0
	200	2.00	3.00	0	1

Dose Level 1: 150 mg/m^2/day
BSA must be BSA ≥ 0.55 m^2

	Total Daily Dose (mg)	BSA Range		Tablets Required	
		low	high	100 mg	200 mg
Dose Level 1 150 mg/m^2/day	100	0.55	0.99	1	0
	200	1.00	1.66	0	1
	300	1.67	2.33	1	1
	400	2.34	3.00	0	2

Dose Level 2: 240 mg/m^2/day
BSA must be BSA ≥ 0.67 m^2

	Total Daily Dose (mg)	BSA Range		Tablets Required	
		low	high	100 mg	200 mg
Dose Level 2 240 mg/m^2/day	200	0.67	0.99	0	1
	300	1.00	1.45	1	1
	400	1.46	1.87	0	2
	500	1.88	2.29	1	2
	600	2.30	3.00	0	3

Dose Level 3 (RP2D): 350 mg/m^2/day #
BSA must be BSA ≥ 0.73 m^2

	Total Daily Dose (mg)	BSA Range		Tablets Required	
		low	high	100 mg	200 mg
Dose Level 3 350 mg/m^2/day	300	0.73	0.99	1	1
	400	1.00	1.28	0	2
	500	1.29	1.57	1	2
	600	1.58	2.10	0	3
	600	> 2.10		0	3

With declaration of the RP2D at Dose Level 3, the upper BSA restriction used for enrollment at Dose Level 3 during the dose finding phase has been lifted. During the expansion phases (PK and efficacy), patients with BSA ≥ 2.10 m^2 will receive 600 mg flat dose once a day.

15.6 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.** 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 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 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 inhibits CYP 3A4, 3A5, 1A2, 2C8, 2C9, 2D6 and UGT1A1 and may affect other drugs that are substrates of these enzymes.
- Savolitinib 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.

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

Savolitinib 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 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 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.

- 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.
- 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 _____.

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STUDY DRUG INFORMATION WALLET CARD	
You are enrolled on a clinical trial using the experimental study drug **savolitinib.** This clinical trial is sponsored by the NCI. Savolitinib 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. ➢ You may need to be monitored more frequently if you are taking any drugs that have narrow therapeutic ranges, such as warfarin.	➢ Savolitinib 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 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 _____.

15.7 Medication Diary

Patient ID: _____ **Drug: Savolitinib**

Course Number: _____ **Start Date:** ____/____/ ____ **End Date:** ____/ ____/ ____ **Total Daily Dose:** _____**mg**

A total of_____100 mg tablets, and/or_____200 mg tablets are dispensed for Course ____.

EXAMPLE			Number of tablets taken		Comments
	Date	Time	100 mg	200 mg	
Day 1	*10 / 15 / 18*	8:30 AM ~~PM~~		*1*	He felt nauseated an hour after taking the drug, but did not vomit.

1. Complete one form for each course of treatment.
2. You will take **savolitinib** once a day orally. Take **savolitinib** tablets with food. Savolitinib tablets must be swallowed whole with water, not chewed or crushed. Store the savolitinib tablets at controlled room temperature (20°C-25°C).
3. **It is very important that you follow the instructions that come with savolitinib**.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring this form and your bottles of **savolitinib** when you return for each appointment. All medication bottles (including empty ones) are to be brought to clinic at each appointment.

Day	Date	Time of dosing		Number of tablets taken		Comments
				100 mg	200 mg	
1			**AM or PM**			
2			**AM or PM**			
3			**AM or PM**			
4			**AM or PM**			
5			**AM or PM**			
6			**AM or PM**			
7			**AM or PM**			
8			**AM or PM**			
9			**AM or PM**			
10			**AM or PM**			
11			**AM or PM**			
12			**AM or PM**			
13			**AM or PM**			
14			**AM or PM**			
15			**AM or PM**			
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25			**AM or PM**			
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27			**AM or PM**			
28			**AM or PM**			