A Phase II Study of Sitravatinib in Metastatic, Pre-Treated, Triple Negative Breast Cancer

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1. SCHEMA

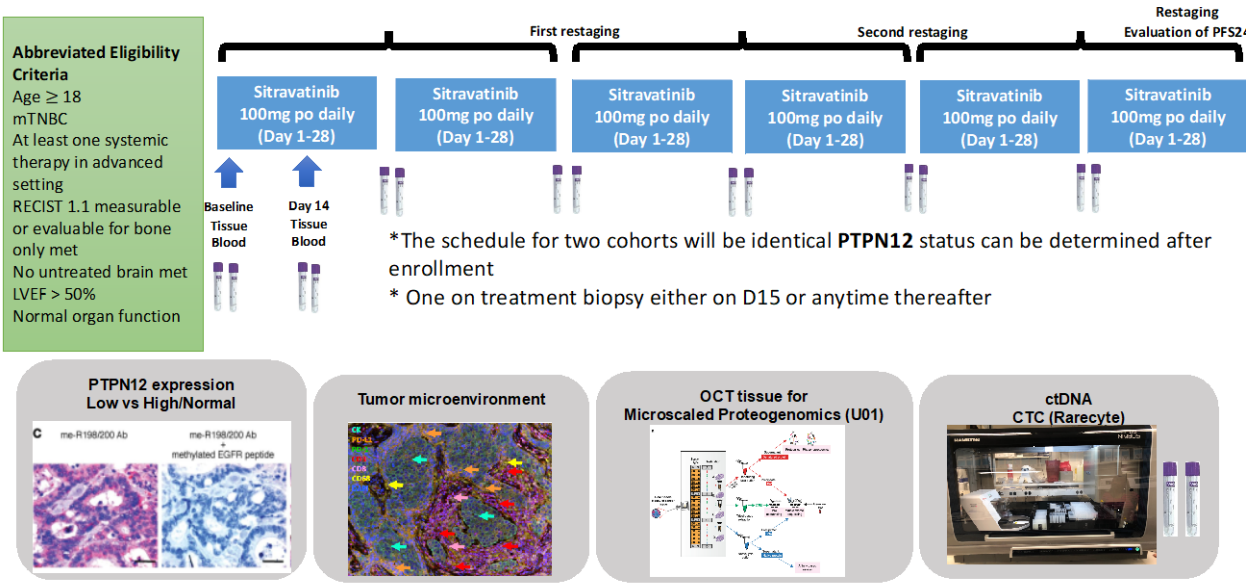

Figure 1: Treatment schema and correlative endpoints that will determine a) whether CTC analysis can contribute to an assessment of PTPN12 status and response to treatment b) whether acute changes in ddPCR assessent of ctDNA can predict the outcome of subsequent response determined radiologically and c) conduct proteogenomic analysis of snap frozen OCT-embedded tumor biopsies to analyze the TNBC kinome and purtubations induced by treatment with sitavatinib.

2. STUDY DESIGN/SUMMARY

This is a phase II, two cohort trial designed to evaluate the efficacy of sitravatinib in patients with metastatic triple-negative breast cancer (mTNBC) after treatment with at least one line of chemotherapy for advanced disease. The drug, sitravatinib at 100 mg, will be dosed daily at the initiation of the study and continued until progression or unacceptable toxicity.

The study will employ a modified optimal Simon's two stage design. Participants will be recruited into two cohorts: Protein Tyrosine Phosphatase, Non-Receptor Type 12 (PTPN12) low or PTPN12 high/normal cohorts simultaneously and independently. Seven participants will be enrolled to each arm during the first stage. After the first stage, depending on the observed number of responses, the study will proceed to the second stage utilizing an adaptation of the Jones and Holmgren approach [1]. The primary endpoint is progression-free survival status at 24 weeks (PFS24) and the secondary endpoints will include: Time to Progression (TTP), Objective Response Rate (ORR), Clinical Benefit Rate (CBR), and grade 3 or higher adverse events. The maximum accrual needed is 25 participants. This study approach will have 90% power to detect PFS24 rate of 30% in the PTPN12*low* stratum, or 85% power to detect a PFS24 rate of 25% in the unselected population.

3. OBJECTIVES

3.1 Primary Objective

To evaluate the efficacy of sitravatinib as measured by progression-free survival at 24 weeks (PFS24), as evaluated by RECIST version 1.1, in participants with mTNBC that have been treated with at least one line of chemotherapy.

3.2 Secondary Objectives

3.2.1 To evaluate Time to Progression (TTP), defined as the duration of time from initiation of treatment until progression according to RECIST 1.1 criteria

3.2.2 To evaluate Objective Response Rate (ORR), defined as the proportion of participants who achieve a Complete Response (CR) or Partial Response (PR) to treatment per RECIST 1.1 criteria

3.2.3 To evaluate the Clinical Benefit Rate (CBR), defined as the proportion of participants who achieve CR, PR, or stable disease (SD) per RECIST 1.1 criteria

3.2.4 To evaluate the number of participants with grade 3 or higher adverse events as per the NCI Common Terminology Criteria for Adverse Events version 5.0 (CTCAEv5)

3.3 Exploratory Objectives

3.3.1 To examine the relationship between Circulating Tumor Cell (CTC) expression of PTPN12 and tumor tissue expression to determine if CTC analysis can contribute to an assessment of PTPN12 status and response to treatment

3.3.2 To examine the relationship between acute changes in digital droplet PCR-based ctDNA mutant allele frequencies in the first month of treatment and subsequent radiological response evaluations

3.3.3 To evaluate the effect of sitravatinib on the drug bead-based tumor kinome profiling and mass spectrometry-based phosphoproteomics through examination of protein

extracts from tumor biopsy material before and during treatment, performed on OCT-embedded snap frozen tissue biopsy from patients with disease accessible by core needle biopsy

3.3.4 To evaluate immune biomarkers to explore the effects of sitravatinib on the immune microenvironment and the influence of tumor infiltrating lymphocytes on response

4. BACKGROUND

4.1 Scientific Background and Rationale

4.1.1 Triple-Negative Breast Cancer

Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer diagnosed in more than 200,000 women each year across the world [2]. There are currently no targeted therapies available for this disease and after relapse prognosis is extremely poor, although recently a PD-L1 inhibitor atezolizumab with nab paclitaxel has been shown to prolong progression free survival as first line treatment [3]. After progression on first line treatment there is no consensus treatment and no other therapies that are definitively helpful, except treatment with a PARP inhibitor in the uncommon setting of a germline BRCA mutation [4].

4.1.2 Targeted Therapy in TNBC

Inhibitors of oncogenic receptor tyrosine kinases (RTK) comprise a substantial fraction of the targeted therapies in various cancer types. The precise application of these inhibitors has been largely guided by RTK mutations, amplification, and chromosomal translocations in human cancers including HER2-amplified breast cancer. However, most cancers, like TNBC, do not harbor frequent mutations in RTKs that can account for aberrant receptor signaling, thus obfuscating the rational use of RTK inhibitors in these malignancies. Indeed, while TNBCs harbor multiple hyperactive RTKs, therapeutic targeting of single RTKs, for example epidermal growth factor receptor (EGFR), have been largely ineffective in TNBC patients [5]. Work from our collaborative team has discovered that rather than mutational activation of RTKs, TNBCs often lose feedback control of RTKs, thus locking these receptors in a chronically active or constitutive state. In particular, Dr. Westbrook and his colleagues have discovered that approximately 45-55% of TNBCs are driven by the concerted activity of Hepatocyte Growth Factor Receptor (HGFR) precursor, MET, and Platelet-Derived Growth Factor Receptor (PDGFR) [6, 7]. Importantly, in a pre-clinical trial of patient derived xenografts (PDX) from 14 independent TNBC patients, therapeutic targeting of MET and PDGFR elicits robust regressions in more than half of the models from chemorefractory patients [7]. These receptors share a common negative regulator called PTPN12. Baylor investigators have shown that PTPN12- deficient TNBCs may be responsive to combined RTK inhibition. Restoring PTPN12 protein levels restrains signaling from RTKs, including PDGFR and MET, and impairs TNBC cell survival. However, the repertoire of RTKs that are restrained by PTPN12 in human cells has not been systematically explored. By methodically identifying the suite of RTK substrates (MET, PDGFR, EGFR and others) inhibited by PTPN12, the team has rationalized a combination RTK-inhibitor therapy that induces potent tumor regression across heterogeneous models of TNBC. In contrast with single agents, combined inhibition of PDGFR and MET receptors have shown to induce apoptosis in TNBC cells *in vitro* and *in vivo*. This therapeutic strategy resulted in tumor regressions in chemo-refractory PDX TNBC

models. Notably, response was found to correlate with PTPN12 deficiency, suggesting that impaired receptor feedback may establish a combined addiction to these proto-oncogenic receptors. Taken together, this data provided the scientific rationale for combining RTK inhibitors in TNBC that lack receptor-activating mutations. Notably, this was the underlying premise of the CRIZENT clinical trial (NCT02074878), a phase I two-drug combination of crizotinib and sunitinib in different doses across three arms in metastatic TNBC. The trial stopped accrual and closed early due to intolerable toxicity of the two drug combination.

4.1.3 **Sitravatinib**

An alternative to combining several tyrosine kinase inhibitors is to use a single broad spectrum inhibitor that is effective against the relevant targets. Sitravatinib (MGCD516) is a spectrum-selective RTK inhibitor that has so far been tested in 3 phase II trials and an ongoing phase III trial in combination with nivolumab (NCT03575598, NCT03606174, NCT02954991, NCT03680521, NCT03906071) with a favorable toxicity profile. Sitravatinib is a potent inhibitor of the TAM family (TYRO3, AXL, MERTK), Vascular Endothelial Growth Factor Receptor (VEGFR) family, Platelet Derived Growth Factor Receptor (PDGFR) family, KIT Proto-Oncogene Receptor Tyrosine Kinase (KIT), RET Receptor Tyrosine Kinase (RET), and MET with additional immunomodulatory effects including depletion of regulatory T cells (Treg) or suppressor T cells, Myeloid-Derived Suppressor Cells (MDSC) and enhancement of M1 tumor macrophage profile.

A phase 1 trial of 32 patients established the 150 mg daily dosing as the maximum tolerated dose (MTD). However, an assessment of longer term tolerability for patients starting at the 120 mg dose of sitravatinib, together with data from patients who were dose reduced from 150 mg to 120 mg suggests the 120 mg dose has better tolerability beyond the first cycle of treatment; therefore, 120 mg is considered the recommended phase 2 dose. However, that formulation subsequently changed to malate base with dosing of 100 mg daily, which is equivalent to 120 mg of free base dosing. Notable grade 3 and higher toxicities included hypertension (20%), diarrhea (11.7%), fatigue (10%), vomiting and mucosal inflammation (3.3%), loss of appetite and nausea (1.7%). No grade 4 toxicities were reported.

The rationale for this protocol is based on the activity of sitravatinib in PTPN12*low* TNBC models derived from patients with chemotherapy refractory disease. Sitravatinib effectively inhibits tumor growth and induces tumor regression in a similar pattern previously observed with the crizotinib and sunitinib combination (Figures 2 and 3). This study will therefore evaluate the efficacy and safety of sitravatinib in metastatic TNBC given this supportive preclinical data.

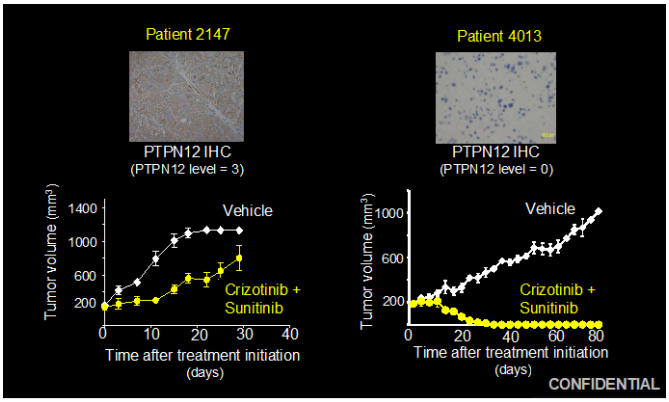

Figure 2. Crizotinib + sunitinib confers tumor regression in PDXs from TNBC patients

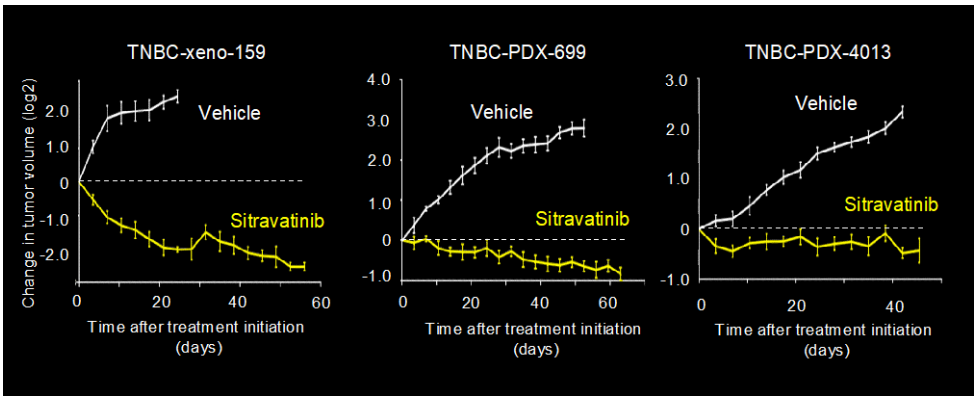

Figure 3. Sitravatinib inhibits the growth of PTPN12-deficient TNBC PDX

4.2 Correlative Science Background

Orthogonal approaches have revealed that PTPN12 is recruited to inhibit several RTK receptors after ligand stimulation, thereby serving as a feedback mechanism to limit receptor signaling. Response to combination RTK inhibition is correlated with PTPN12 deficiency, suggesting that impaired receptor feedback may establish a combined addiction to these proto-oncogenic receptors. Cancer-associated mutation of PTPN12 or reduced PTPN12 protein levels diminish this feedback mechanism, leading to aberrant activity of these receptors. PTPN12 deficiency in TNBC is largely secondary to absent protein rather than mutation, and low PTPN12 levels have been reported in 62% of all TNBC. Inactivating PTPN12 mutations account for only 3% of PTPN12 deficiency.

A highly specific PTPN12 monoclonal antibody has been developed at Baylor College of Medicine for PTPN12 analysis. An immunohistochemistry (IHC) assay will be used to detect the level of this protein in primary and metastatic breast cancer tissue. This assay will be used to place patients into the two cohorts of the study. Additionally this antibody will be used to measure PTPN12 in CTCs by immunofluorescence to address whether CTC PTPN12 status will be a useful biomarker in future studies if the CTC status correlates well with tissue PTPN12 status. RTK signaling in cancer cells contributes to shape the immune microenvironment by regulating tumor secretomes. In addition we will collaborate with the Clinical Proteomic Tumor Analysis Consortium to analyze any OCT-embedded frozen specimens that are generated in the

protocol. We will analyze them using mass-spectrometry-based proteomics and also conduct RNA sequencing and Whole Exome Sequencing for a full proteogenomic profile [8]. We have recently adapted these techniques to interrogate fresh frozen core biopsy material embedded in OCT [9].

Recent data indicate that sitravatinib may impair myeloid-derived suppressor cells (MDSCs) and other immunosuppressive compartments, thus raising the provocative hypothesis that Sitravatinib may have both tumor-autonomous and non-autonomous immunostimulatory effects. Prompted by this knowledge, we will assess important constituents of the tumor immune microenvironment using established assays, and correlate the results to PTPN12 status. Sitravatinib's effects on the microenvironment will be examined by comparing pre- and post-treatment biopsies. Although the results may be preliminary and limited by sample size, important insights may be derived to inform future clinical trials. Tumor-infiltrated lymphocytes will be determined by morphology following previously established guidelines [10]. IHC assays of the following molecules will be performed to quantitate major immune cell types/pathways (see Table 1).

Table 1: Exploratory Immune Biomarkers

Marker	Cell type	Function	Reference (PMID)
CD8	CD8 T cells	Anti-tumor cytotoxicity	[11]
FOXP3	Regulatory T cells	Inhibit CD8 T cell-mediated cytotoxicity	[12]
LOX-1	Neutrophils (MDSCs)	Immunosuppressive myeloid cells that may confer resistance to immunotherapies.	[12]
CD15	Neutrophils (MDSCs)		[12]
S100A8/MRP8	Neutrophils (MDSCs)		[13]
CD66b	Granulocytes		[14]
CD68	Tumor Associate Macrophages (TAMs)		[14]
CD163	Tumor Associate Macrophages (TAMs)		[14]
CD20	B cells	Potential roles in regulating responses to check point blockade	[14]
Granzyme B	Activated CD8 T cells	T cell activation/ anti-tumor	[14]
PDCD1 (PD-1)	T cells	Check point molecules indicative of T cell functions and targeting agents available.	[14]
PD-L1	Various cell types		[3]
Tim3	T cells and Dendritic cells		[15]
LAG3	T cells and Dendritic cells		[16]
Arg1	Various cell types	Important metabolic enzymes with known immunosuppressive functions	[17]
iNOS	Various cell types		[18]
IDO1	Various cell types		[19]

4.3 Investigational Agent

Sitravatinib is an orally-available, potent small molecule inhibitor of a closely related spectrum of tyrosine kinases including MET, TAM (TYRO3, AXL, MERTK) family, VEGFR family, PDGFR family, KIT, FLT3, TRK family, RET, DDR2, and selected EPH family members. This subset of tyrosine kinases is involved in a number of processes implicated in human cancer

including regulation of tumor growth and cell survival pathways, tumor invasion and metastatic progression, as well as tumor angiogenesis. Anti-tumor activity of sitravatinib has been observed over several human tumor xenograft models exhibiting genetic alterations in receptor tyrosine kinase (RTK) targets, providing rationale for evaluating sitravatinib monotherapy in tumors driven by these pathways in the clinical setting.

Additionally, based on its tyrosine kinase target profile, sitravatinib may modulate effects on the tumor microenvironment to overcome resistance to checkpoint inhibitors by effects on relevant immune cell populations. Inhibition of TAM RTKs (MERTK, TYRO3 and AXL) expressed by macrophages and dendritic cells may enhance the innate, M1 macrophage pro-inflammatory cytokine response and suppress M2 macrophage anti-inflammatory cytokine production, while inhibition of AXL and MERTK on natural killer (NK) cells may abrogate negative regulation of anti-tumor NK cell activity. Inhibition of the split kinase receptors may enhance anti-tumor immunoreactivity by depletion of regulatory T-cells (through VEGFR2) and myeloid-derived suppressor cells (MDSCs) (through KIT and VEGFR family members), resulting in the expansion and migration of anti-tumor cytotoxic T-cells, and their infiltration into tumor tissue. Inhibition of MET may inhibit expansion of MDSCs and restore antigen-presenting cell function. Together, these effects are predicted to complement and augment the activity observed with checkpoint inhibitor therapy (CIT).

Nonclinical pharmacokinetic (PK) and toxicology studies support clinical evaluation of sitravatinib. It is metabolized to eight putative metabolites (M1-M8) in mouse, rat, dog, monkey and human hepatocytes and to 13 putative metabolites (M1-M7 and M9-M14) in vivo in dog and rat plasma samples, with studies using human liver microsomes and recombinant human P450 enzymes suggesting that multiple enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP2E1, and CYP3A4) are involved in the metabolism of sitravatinib. Toxicology studies with repeated dosing of sitravatinib for 7 days and 4 weeks demonstrated no target organs identified in the dog, despite overt decreases in body weight and food consumption, while VEGF-related target organs were identified in the rat, including the adrenal gland, Brunner's glands in the duodenum, femur and sternum (bone and bone marrow), spleen, lymph nodes, thymus, ovary, kidney (glomerulopathy, tubule necrosis, increased basophilic tubules), pancreas, and tongue. All effects in rats, except those in the kidney and pancreas, either recovered or showed partial recovery.

In clinical trials sitravatinib was administered as a single agent in the first-in-human Study 516-001 and in combination with the PD-1 inhibitor nivolumab in patients with advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) who have experienced disease progression either on or after prior treatment with a checkpoint inhibitor therapy (CIT-experienced) or after treatment with a platinum-based doublet chemotherapy (CIT-naïve) in Study MRTX-500. Study 516-001 is a multi-center, Phase 1/1b clinical trial characterizing the safety, PK, metabolism, pharmacodynamic (PD) and clinical activity of sitravatinib in patients with advanced solid tumor malignancies. The primary objective of the Phase 1 was the determination of the maximum tolerated dose, while Phase 1b objectives included assessment of safety and clinical activity in patients with certain tumor types (e.g., renal cell carcinoma [RCC]) or with tumors characterized by certain genetic alterations; sitravatinib monotherapy was administered orally once daily, and based on the Phase 1 results, the starting dose in Phase 1b was 150 mg daily, which was subsequently changed to 120 mg during the trial. Study MRTX-500 is a parallel Phase 2 study of glesatinib, sitravatinib or mocetinostat in combination with

nivolumab administered at a dose of 240 mg intravenously every two weeks, with sitravatinib 120 mg administered once daily after the safety of this dose was confirmed in the lead-in portion of the study.

Pharmacokinetic evaluation in Study 516-001 shows that after single dose administration, sitravatinib reaches peak concentration in a median time of approximately 3 to 9 hours, and C_{max} and AUC are approximately dose proportional with single doses up to 200 mg. Median elimination half-life varies between 43 and 58 hours, and the steady state PK is reached in a mean time of 11 to 15 days. After multiple dose administration, drug accumulation ranged from 1.6- to 4.2-fold for C_{max} and 2.0- to 5.1-fold for AUC_{0-24}. Steady-state C_{max} to C_{min} mean ratio was 1.50 to 1.88.

As of 26 Jun 2021, a total of 1,106 subjects with advanced/metastatic solid malignancies have received at least one dose of sitravatinib in 8 clinical studies. Of these subjects, 220 have received treatment with sitravatinib as a single agent, approximately 565 have received sitravatinib in combination with the PD-1 inhibitor nivolumab, 300 have received sitravatinib in combination with the PD-1 inhibitor tislelizumab, 13 have received sitravatinib in combination with pembrolizumab and the antibody drug conjugage enfortumab vedotin-ejfv, and 10 have received sitravatinib in combination with nivolumab and ipilimumab.

Among the 1,106 subjects with solid malignancies who were treated with sitravatinib, 1,012 (92%) experienced at least one sitravatinib-related AE. Sitravatinib-related AEs reported in ≥ 5% of these subjects are presented in Table 2. Among the 1,106 subjects, sitravatinib-related Grade 3 events were reported in 485 subjects (44%) overall. Sitravatinib-related Grade 3 events reported in ≥ 5% of subjects were hypertension (16%), diarrhea (7%), and fatigue (5%). Sitravatinib-related Grade 4 AEs were reported in 26 subjects (2%). The only Grade 4 sitravatinib-related events occurring in more than 1 subject by Preferred Term were amylase increased, hyperuricemia, and cerebrovascular accident in 2 subjects each (0.2%), and lipase increased in 5 subjects (0.5%). Sitravatinib-related Grade 5 AEs were reported in 12 subjects, including death in 6 subjects, cardiac arrest in 2 subjects, and cardiac failure, hepatic encephalopathy, ischemic stroke and respiratory failure in 1 subject each.

Among the 1,106 subjects with solid malignancies, a total of 501 (45%) experienced at least one AE regardless of causality. No healthy subjects experienced an SAE. Among the 1,106 subjects with solid malignancies, sitravatinib-related SAEs were reported in 194 subjects (18%). Related SAEs reported in 5 or more subjects (≥ 5%) included diarrhea (3.0%), vomiting (1.2%), nausea and pulmonary embolism (1.0%), fatigue, hepatobiliary disorders, and hypertension (0.7%), and cardiac failure, pancreatitis, death, hepatic function abnormal, acute kidney injury, pneumonitis, deep vein thrombosis, and embolism (0.5% each).

Among the 1,106 treated subjects with solid malignancies across all studies, the most common sitravatinib-related AEs leading to discontinuation of sitravatinib were diarrhea and nausea (19 subjects each [0.8%]), fatigue (13 [1.2%]), vomiting and hypertension (7 subjects each [0.6%]), and lipase increased and pneumonitis (5 subjects each [0.5%]).

For this study, the malate formulation of sitravatinib at 100 mg will be used, which is equivalent to 120 mg of free base sitravatinib.

Table 2: Sitravatinib-related Adverse Events Reported in ≥ 5% of Subjects with Solid Malignancies (all studies combined)

Adverse Event **Preferred Term**, n (%)	**Subjects (N=1,106)**
Any Sitravatinib-Related AE	1,012 (91.5)
Diarrhoea	526 (47.6)
Fatigue	362 (32.7)
Hypertension	348 (31.5)
Decreased appetite	309 (27.9)
Nausea	298 (26.9)
Alanine aminotransferase increased	281 (25.4)
Aspartate aminotransferase increased	275 (24.9)
Palmar-Plantar Erythrodysaesthesia Syndrome	252 (22.8)
Vomiting	214 (19.3)
Dysphonia	200 (18.1)
Weight decreased	197 (17.8)
Hypothyroidism	150 (13.6)
Proteinuria	144 (13.0)
Stomatitis	134 (12.1)
Platelet count decreased	90 (8.1)
Dry mouth	88 (8.0)
Anaemia	87 (7.9)
Lipase increased	87 (7.9)
Rash	79 (7.1)
Abdominal pain	77 (7.0)
Dysgeusia	76 (6.9)
Constipation	73 (6.6)
Blood alkaline phosphatase increased	60 (5.4)
Blood thyroid stimulating hormone increased	60 (5.4)
Dizziness	60 (5.4)
Hypoalbuminaemia	57 (5.2)

5. PARTICIPANT SELECTION

5.1 Inclusion Criteria

5.1.1 Women or men age 18 and older

5.1.2 Metastatic or locally advanced inoperable breast cancer (beyond curative management) that is measureable according to RECIST 1.1 criteria.

NOTE: Patients with bone-only disease are eligible if there is at least one lytic lesion that can be followed for response.

5.1.3 Tumor is ER-negative and PR-negative per ASCO/CAP Guidelines of 2010

5.1.4 Tumor is HER2neu-negative per ASCO/CAP Guidelines of 2018

5.1.5 Patient has archival tissue from metastatic or locally advanced breast cancer for the analysis of PTPN12 status.

NOTE: For patients who do not have archival tissue available, a research biopsy of the locally advanced or metastatic breast tumor is required.

5.1.6 At least one prior line of chemotherapy with or without a PD-L1 or PD-1 antibody in the metastatic setting

5.1.7 ECOG performance status ≤ 2 (Karnofsky ≥ 60%)

5.1.8 Normal organ and hematologic function as defined below:

- Absolute neutrophil count — > 1000/mcL
- Hemoglobin — > 11 g/dL
- Platelets — ≥ 100,000/mcL
- Total bilirubin — ≤ 1.5 x normal institutional limits
- AST (SGOT)/ALT (SGPT) — ≤ 2.5 x institutional ULN or ≤ 5.0 × ULN for patients with documented liver metastases.
- Creatinine — within normal institutional limits
- Creatinine clearance — ≥ 30 mL/min
- Normal LVEF function defined as normal LV wall motion and ejection fraction of ≥ 50%

5.1.9 If patient has brain metastasis, documented treatment and stability for at least 30 days by scans and off steroids at the time of enrollment

5.1.10 Women of child-bearing potential and actively menstruating must have a negative pregnancy test prior to starting study treatment

5.1.11 If sexually active in a way that could lead to pregnancy, participant must agree to use a highly effective method of birth control starting at the time of informed consent and continuing throughout the study and for at least 3 months after the final dose of sitravatinib. Highly effective methods of birth control include:

- Intrauterine device
- Condoms with spermicide
- Bilateral tubal occlusion/ligation

- Vasectomy (for male participants) or vasectomized partner (for female participants)
- Sexual abstinence when it is the preferred and usual lifestyle choice of the participant

5.1.12 Ability to understand and the willingness to give informed consent

5.2 Exclusion Criteria

5.2.1 Uncontrolled hypertension, defined as systolic blood pressure > 150 and/or diastolic blood pressure > 100, on two or more occasions within 30 days prior to enrollment

5.2.2 Imaging suggestive of lymphangitic carcinomatosis in the lung, or use of home O_2

5.2.3 Untreated brain metastases

5.2.4 Women who are pregnant or nursing

5.2.5 Concurrent metastatic disease of another tumor type

5.2.6 Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of sitravatinib

5.2.7 History of stroke, pulmonary embolus (PE), or myocardial infarction (MI)

5.2.8 Known proteinuria of ≥ 2 g urinary protein/24 h

5.2.9 HIV-positive participants

5.2.10 History of Hepatitis C or Hepatitis B infection

5.2.11 History of congestive heart failure (CHF), and/or LVEF < 50%

5.2.12 Concurrent use of medications that prolong QTc (listed in Section 9, Table 11) . These medications need to be discontinued at least 2 weeks prior to starting study treatment.

5.2.13 Concurrent medical condition that, in the sole judgment of the principal investigator, would make the patient inappropriate for trial participation

5.3 Inclusion of Underrepresented Populations

Individuals of all races and ethnic groups are eligible for this trial. There is no bias towards age or race in the clinical trial outlined. This trial is open to the accrual of women and men.

6. REGISTRATION PROCEDURES

All consented participants will be registered in the online collaborative research environment (OnCore), a Clinical Trials Management System available at Baylor College of Medicine Dan L. Duncan Cancer Center. Prior to study enrollment, the eligibility data must be reviewed and verified by a delegated member of the study team. After eligibility status is confirmed, the participant will be assigned a unique subject identification number. If the participant does not meet all eligibility criteria (i.e., is a screen failure), he/she will be given a status of Ineligible in OnCore, and the reason will be recorded appropriately.

NOTE: OnCore is also being used for electronic data collection (i.e., completion of case report forms) for this study.

7. STUDY PROCEDURES

7.1 Screening Phase

Participants who have a diagnosis of triple-negative metastatic or inoperable locally advanced breast cancer, post-progression on at least one line of chemotherapy in the metastatic setting, will be evaluated for eligibility to enroll in the trial. Those who meet eligibility criteria will be identified by the investigator and study staff, and will be asked to provide a signed informed consent form prior to any study-related activities.

Participants who signed an informed consent form but are found ineligible for any reason will be considered screen failures.

7.1.1 Collection of Demographics and Other Baseline Characteristics

The data that will be collected on participant characteristics at screening includes:

- Demographics (date of birth and initials, sex, race, ethnicity, source of patient referral)
- Diagnosis and extent of cancer (including staging at study entry and histology/cytology)
- Medical history (e.g., important medical, surgical, and allergic conditions from the patient's medical history which could have an impact on the patient's evaluation) / current medical conditions (e.g., all relevant current medical conditions present at the time of signing informed consent).
- ER, PR and HER2 status
- All prior antineoplastic therapies including surgical interventions and chemo-, biologic-, immunologic- and radiation-therapies provided as treatment for cancer prior to the administration of study drug.
- All medications and significant non-drug therapies taken within 28 days before starting study treatment

7.1.2 Pre-Study Screening Assessments

The following assessments will be performed as part of screening within 28 days prior to starting study treatment:

- Vital signs (including height and weight)
- Physical examination and performance status (ECOG)
- Laboratory evaluations (hematology, biochemistry, TSH, urine protein/creatinine ratio,

and pregnancy test for women of childbearing potential)
- Echocardiogram (LVEF assessment)
- Tumor assessments (radiographic imaging or clinical exam as appropriate)
- Blood collection for CTC and ctDNA analysis
- Collection of archival tissue from primary tumor and metastatic/locally advanced site (if available)
- If archival tissue from metastatic/locally advanced site is unavailable, a biopsy is required (optional for participants who do have archival tissue available)

7.2 Treatment Phase

Once registered/enrolled, participants will start treatment with sitravatinib 100 mg once daily until disease progression (assessed by RECIST 1.1), unacceptable toxicity, death or discontinuation from treatment for any other reason. Each cycle is 28 days in length. Study assessments, and efficacy and safety monitoring will continue as outlined in the study calendar.

All assessments must be performed prior to the administration of study treatment unless otherwise specified. The following windows apply:

- On-study assessments for all cycles must be performed within +/- 3 days of Day 1, unless otherwise indicated.
- Re-staging scans for tumor evaluations should continue on schedule if treatment is held or delayed.

7.2.1 Study Treatment and Agent Administration

For this study, the term "study treatment" refers to sitravatinib. All dosages prescribed and dispensed to the participant and all dose changes during the study must be documented. Participants will receive a 28-day supply at every monthly visit. Participants should take 2 capsules of 50 mg once daily for the full 100 mg dose. An additional number may be dispensed at the discretion of the study site to provide for holidays or inclement weather. The number of bottles and capsules dispensed should be documented by research pharmacy staff using an IP Accountability Log. Sitravatinib capsules should be taken during the morning hours, and at least 1 hour before breakfast. Sitravatinib capsules should be taken with at least 200 mL (1 cup) of water. Dose should be skipped if missed or vomited.

Compliance with study treatment will be assessed by study staff at each visit. Participants will be asked to bring their bottle(s) of sitravatinib, along with all unused capsules, to each visit. Compliance will be assessed by counting the number of remaining capsules, and using that to evaluate how many days the study treatment was taken as prescribed. Repeated pill counts indicating less than 75% adherence to study treatment may result in removal from the study, as judged by the treating physician and/or Principal Investigator.

7.2.2 Discontinuation of Study Treatment

Study treatment must be discontinued under the following circumstances:

- Adverse event or laboratory abnormalities, that, in the opinion of the treating physician, would preclude further participation in the study
- Study treatment delay ≥ 28 days
- Progressive Disease

- Pregnancy
- Lost to follow-up
- Physician decision
- Participant/guardian decision
- Death
- Study terminated by sponsor
- Repeated protocol deviations or non-compliance where continued participation would jeopardize the participant's safety or the integrity of the study, as judged by the Principal Investigator or treating physician.

7.2.3 Withdrawal of Consent

Participants may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a participant does not want to participate in the study any longer, and does not want any further visits or assessments or further study-related contact. All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

If a participant withdraws consent, the investigator (or designee) must make every effort (e.g., telephone, e-mail, letter) to determine the primary reason for this decision and record this information. Study treatment must be discontinued and no further assessments conducted. Further attempts to contact the participant regarding the study related follow-up are not allowed unless safety findings require communication or follow-up.

7.3 Follow-up

7.3.1 Survival Follow-up

All participants will be followed for survival status once every 3 months after treatment discontinuation regardless of discontinuation reason (except if consent is withdrawn) until death, lost to follow-up, or withdrawal of consent for survival follow-up. Additional survival assessments may be performed outside of this schedule if a survival update is required for an interim assessment to meet safety or regulatory needs. Survival information can be obtained via phone and documented in source documents.

7.3.2 Follow-up for Safety Evaluations

All participants who discontinue study treatment, including those who refuse to return for an end of treatment visit, will be contacted for safety evaluations (i.e., assessment of adverse events and/or Serious Adverse Events, concomitant medications) between 30-45 days after the last dose of study treatment. Participants whose treatment is interrupted or permanently discontinued due to an adverse event, including abnormal laboratory value, must be followed until resolution or stabilization of the event, whichever comes first.

If participants refuse to return for safety evaluation visits or are unable to do so, every effort should be made to contact them by telephone to determine their status. Attempts to contact the participant should be documented in source documents (e.g., dates of telephone calls, registered letters, etc.).

7.4 Lost to Follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show due diligence by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the participant (e.g., dates of telephone calls, registered letters, etc.). A participant should not be considered lost to follow-up until due diligence has been completed.

8. STUDY CALENDAR

Test/Procedure	Pre-Study[1]	C1D1	C1D14	Subsequent Cycles Day 1	End of Treatment	Safety Follow-Up[11]	Survival Follow-Up
Informed Consent	X						
Participant Demographics	X						
CLINICAL EVALUATIONS							
History and Physical Exam	X	X	X	X	X		
Height	X						
Vital signs and weight	X	X	X	X	X		
Performance Status	X	X	X	X	X		
LABORATORY/RADIOLOGIC EVALUATIONS							
CBC/differential	X		X	X	X		
Comprehensive Metabolic Panel	X		X	X	X		
TSH	X		X	X[4] **(odd cycles)**	X		
Urine Protein/Creatinine Ratio	X		X	X[4] **(odd cycles)**	X		
Pregnancy test	X[2]						
Tumor Assessments	X			X[5]	X		
Echocardiogram	X			X[6]			
TREATMENT DISPENSATION							
Sitravatinib		X		X			
CORRELATIVE							
ctDNA collection	X		X	X[7]	X		
CTC collection	X		X	X[7]	X		
Tumor/Tissue Biopsy[8]	X[10]		X[3]		X		
Archival tissue	X[9]						
ADDITIONAL INFORMATION							
Concomitant Medications	X		X	X	X	X	
Adverse Events/Toxicity Assessment				X	X	X	
Compliance Assessment				X	X		
Assess vital status							X[12]

NOTE: The schedule may be modified +/- 3 days due to scheduling delays or conflicts (e.g. holidays, inclement weather, vacations, etc.)

1. All pre-study assessments, with the exception of the informed consent, must be performed within 28 days prior to starting study treatment, unless otherwise indicated.
2. Urine or serum pregnancy test is acceptable; to be performed for women of child-bearing potential only
3. May be performed any time between Cycle 1, Day 14 and Cycle 3, Day 14
4. To be performed prior to dosing on C3D1, then prior to dosing on Day 1 of every odd-numbered cycle thereafter (e.g., C5D1, C7D1, etc.)
5. Clinical and radiological tumor assessments will be performed by CT, PET or MRI scan at baseline and then every 2 cycles (i.e., within 7 days prior to Cycles 3, 5, 7, and 9) until disease progression. The same testing modality should be used for each evaluation. Responses of CR or PR should be confirmed with a second assessment no earlier than 4 weeks, but no later than the next scheduled scan, per protocol. Brain MRI and bone scan should be performed if clinically indicated (e.g., participants with known history of bone or brain mets). Results must be reviewed for each scan prior to dosing at next cycle
6. To be performed within 7 days prior to C4D1. Further echocardiograms may be performed as clinically indicated.
7. To be collected on C2D1, C3D1, then on Day 1 of each odd-numbered cycle thereafter (e.g., C5D1, C7D1, etc.)
8. Applies only to participants with accessible disease. For these participants, each biopsy is optional, but encouraged.
9. Archival tissue must be from a metastatic or locally advanced disease site. If locally advanced, disease must not be amenable to curative management.
10. Baseline biopsy required for participants in the event that archival tissue from a metastatic site is not available. Otherwise, this biopsy is optional, and will be offered only to participants with accessible disease. Archival tissue from the primary tumor should be requested, but is not mandatory for enrollment.
11. To be completed 30-45 days after last dose of sitravatinib.
12. To be completed every 3 months from EOT date, via phone call or review of clinic notes.

9. TOXICITY MANAGEMENT – DOSE MODIFICATIONS

9.1 Sitravatinib-Related Adverse Events

In general, non-hematologic AEs should be managed using standards of care. Dose interruption should be considered for sitravatinib-related toxicities ≥ grade 3 until resolution to ≤ grade 1 or baseline. In the event of symptomatic sitravatinib-related AEs, dose reduction to a level that can be administered continuously is preferred over continuing dosing until interruption becomes necessary.

Symptomatic grade 2 non-hematologic sitravatinib-related AEs occurring any time on study, particularly early in treatment (e.g., Cycle 1, Day 15 or Cycle 2, Day 1), are recommended to be managed using dose reduction to the next lower dose level rather than treatment interruption. If the toxicity is adequately managed by routine supportive care (e.g., anti-emetics, anti-diarrheals, electrolyte supplementation), or if the event is grade 3 fatigue, or asymptomatic amylase or lipase elevation, treatment may be resumed at the same dose; otherwise, treatment may be resumed at one or more levels below the dose level where toxicity was observed (Table 3). Recurrence of the toxicity may be managed similarly. Similar dose interruptions and reductions should be considered for grade 3/4 hematologic toxicities that cannot be adequately managed with supportive care. If treatment is interrupted for ≥ 28 days, sitravatinib must be permanently discontinued.

Based on reported experience with sitravatinib and similar agents, and non-clinical data with sitravatinib, guidance to the investigator is provided for selected AEs.

Table 3: Dose Modifications for Non-Hematologic Sitravatinib-Related Toxicities

Toxicity Grade	Interruption	Reduction
Grade 1	Continue treatment unchanged.	
Grade 2, asymptomatic	May be implemented based on investigator discretion.	
Grade 2, symptomatic	May be implemented based on investigator discretion. *Dose reduction by one dose level is recommended over treatment interruption.*	
Grade 3 or 4	Hold until ≤ Grade 1 or return to baseline.	Resume at one or more dose levels below that which induced the toxicity.*

* Participants may resume at the same dose in the following cases:

- Grade 3 or 4 electrolyte abnormality that is not clinically complicated and resolves spontaneously or with conventional medical treatment within 72 hours;
- Grade 3 amylase or lipase elevation that is not associated with symptoms or clinical manifestations of pancreatitis.

Table 4: Sitravatinib Dose Level Reduction Table

Sitravatinib Dose Level	Dose and Schedule	Number of Capsules and Strength
Starting Dose	100 mg once daily	2 x 50 mg capsules
Dose Level 1 (DL1)	70 mg once daily	2 x 35 mg capsules
Dose Level 2 (DL2)	50 mg once daily	1 x 50 mg capsule
Dose Level 3 (DL3)	35 mg once daily	1 x 35 mg capsule

9.1.1 Hypertension

Hypertension up to grade 3/4 has been reported with sitravatinib. Participants taking sitravatinib should undergo regular blood pressure monitoring and receive treatment with standard anti-hypertensive therapy if necessary. Dihydropyridine calcium channel blockers such as nifedipine, amlodipine, and nicardipine may be considered if anti-hypertensive therapy is required. In cases of clinically significant grade 3 increases in blood pressure (such as an increase of ≥ 30 mmHg in systolic BP to ≥ 180 mmHg or increase of ≥ 20 mmHg in diastolic BP to ≥ 110 mmHg, confirmed with repeated testing after at least 5 minutes), temporary suspension of sitravatinib dosing is recommended until blood pressure is controlled. Treatment with sitravatinib may resume at the same or a lower dose at the discretion of the investigator. If significant hypertension recurs, options include change in medical management, reduction of sitravatinib dose to DL2 or DL3, or discontinuation of study treatment, at the discretion of the investigator. In the event of grade 4 hypertension, sitravatinib should be permanently discontinued (see Table 5).

Table 5: Dose Modifications for Hypertension

Toxicity Grade	Interruption	Reduction*
Grade 1 or 2 hypertension	Investigator discretion	
Grade 3, hypertension without clinically significant increases in BP as defined below	Investigator discretion. Consider anti-hypertensives per above paragraph.	
Grade 3, hypertension with clinically significant increases in BP *defined as* either an increase of ≥ 30 mmHg in systolic BP to ≥ 180 mmHg *or* increase of ≥ 20 mmHg in diastolic BP to ≥ 110 mmHg, confirmed with repeated testing after at least 5 minutes	Hold until ≤ Grade 2 or return to baseline	Investigator discretion
Grade 4 hypertension	Discontinue sitravatinib	Discontinue sitravatinib

* For dose reductions from 100 mg, reduce to 70 mg (DL1); if further dose reduction required, reduce to 50 mg (DL2).

9.1.2 Fatigue

Fatigue, defined as physical and/or mental exhaustion, occurs in patients with advanced stage tumors and long-term survivors, with a prevalence of approximately 30%. It has been reported in higher proportions of patients receiving chemotherapy and radiotherapy, with a prevalence between 59% and 96% and between 65% and 100%, respectively [20]. Asthenia, defined as loss of strength and energy, or weakness, is an event term that is frequently used to characterize the

same condition but is used more frequently among investigators outside of the US. Fatigue is also listed among the most common AEs observed in patients being administered other kinase inhibitors of VEGFR. Given that fatigue has been reported as a suspected adverse reaction (SAR) more than once, and because there is some corroboration with preclinical data and other VEGFR inhibitors, fatigue has been assessed as an expected SAR of sitravatinib.

9.1.3 Nausea and Vomiting

The prevalence of nausea and vomiting in patients with advanced cancer is up to 70%, and these events result from several etiologies [21]. Nausea and vomiting are also listed among the most common AEs observed in patients being administered other kinase inhibitors of VEGFR. Given that nausea and vomiting have each been reported as SARs more than once, and corroboration with preclinical data and other VEGFR inhibitors exists, nausea and vomiting have been assessed as expected SARs of sitravatinib.

9.1.4 Palmar-Plantar Erythrodysesthesia Syndrome

Palmar plantar erythrodysesthesia syndrome (PPES) has been reported as a dose-limiting toxicity in the Phase 1 study of sitravatinib. Signs and symptoms of PPES include redness, swelling, pain, and less commonly blisters on the palms of the hands and/or the soles of the feet. Participants who develop PPES should be counseled on measures to mitigate the effects of PPES. Such measures include avoidance of exposure of hands and feet to hot water when washing dishes or bathing, or to other sources of heat, avoidance of activities that cause unnecessary force or friction (rubbing) on the hands or feet, avoiding contact with harsh chemicals such as cleaning products, use of tools or household items that result in pressure on the hands, such as garden tools, knives, and screwdrivers, and wearing of loose fitting, well-ventilated shoes and clothes. Treatment may include use of topical moisturizing agents, topical anesthetics, or topical anti-inflammatory medications such as corticosteroid creams. In more severe cases, dose interruption and reduction may be warranted.

9.1.5 Diarrhea

Diarrhea has been reported with sitravatinib treatment as with other small molecule RTK inhibitors, though the mechanism remains unclear. Participants should be counseled that diarrhea is a possible side effect and advised to take loperamide or a similar medication as needed if diarrhea develops. Diarrhea due to sitravatinib typically improves within several days if sitravatinib treatment is interrupted; any participants developing dehydration or clinically significant electrolyte abnormalities should interrupt treatment, but treatment may be restarted once diarrhea is controlled. For diarrhea prophylaxis, loperamide 4 mg daily can be started, followed by 2 mg after each loose stool (maximum: 16 mg/day).

9.1.6 Increased Transaminases

Sitravatinib dose modifications for increased transaminases are outlined in Table 6. Increased transaminases have been observed in patients treated with sitravatinib. Most cases were asymptomatic elevations in ALT or AST, while some were associated with liver metastases or cholestasis. No cases of drug-induced liver injury meeting Hy's Law have been identified. In the setting of sitravatinib monotherapy, grade 2 transaminase increases related to treatment should generally be managed with dose reduction in sitravatinib. For grade ≥ 3 increases, dose

interruption until return to baseline followed by dose reduction may be warranted. In cases of prolonged interruptions, sitravatinib should be discontinued.

Special consideration should be given to the potential for immune-mediated hepatitis in cases of combination treatment with checkpoint inhibitors. Where immune-mediated hepatitis is suspected, management should be consistent with standard treatment for immune-mediated hepatitis in consideration of the severity, and treatment with sitravatinib should also be interrupted.

Table 6: Dose Modifications for Increased Hepatic Transaminases

Toxicity Grade	Interruption	Reduction
Grade 1 (> ULN to 3.0 × ULN)	May be implemented based on investigator and participant discretion	
Grade 2 (> 3.0 to 5.0 × ULN)	Not required	Decrease by one dose level
Grade 3/4 (> 5.0 × ULN)	Hold until Grade ≤ 1 or return to baseline	If resolution occurs within 29 days, decrease by one dose level. If no resolution within 29 days, discontinue sitravatinib.

9.1.7 Increased Amylase and Lipase

Increased amylase and lipase have been observed in subjects treated with sitravatinib. Although the mechanism has not been fully elucidated, inhibition of VEGF may lead to acinar cell apoptosis resulting in the release of autodigestive enzymes (Sevin-2012). Accordingly, increases in amylase and lipase, and pancreatitis have been reported with other inhibitors of the VEGF pathway. Most sitravatinib-related treatment-emergent events of increased amylase and lipase were asymptomatic while some were associated with signs and/or symptoms of pancreatitis. Treatment with sitravatinib may continue without dose modification (e.g., interruption or reduction) in cases of asymptomatic amylase and/or lipase increases in the absence of other clinical evidence of pancreatitis (e.g., symptoms, electrolyte abnormalities, radiographic changes) at the investigator's discretion. Sitravatinib should be interrupted for any grade pancreatitis and the participant managed according to standard-of-care. After resolution of pancreatitis, sitravatinib resumption is at the discretion of the investigator; if pancreatitis is assessed as sitravatinib-related and treatment is resumed, a dose reduction is recommended.

9.1.8 Decrease in LVEF

Decreased left ventricular ejection fraction (LVEF) has been in observed in < 10% of patients treated with sitravatinib. In cases where LVEF < 50%, then the dose of sitravatinib should be interrupted and/or reduced. Permanent discontinuation should be considered for participants requiring acute hospitalization for treatment of congestive heart failure (CHF).

9.1.9 Hypothyroidism

Abnormalities in thyroid function have been described with small molecule RTK inhibitors; most commonly, hypothyroidism, sometimes preceded by a brief period of hyperthyroidism, have been reported. TSH should be monitored during treatment with sitravatinib. Participants

diagnosed with hypothyroidism should be treated with thyroid replacement and may continue treatment with sitravatinib. When sitravatinib is used in combination with checkpoint inhibitors, thyroid dysfunction, including thyroiditis and hypothyroidism, may be immune-mediated.

9.1.10 Proteinuria

Proteinuria has been observed with sitravatinib treatment and described with other inhibitors of the VEGFR pathway. Urinalysis for urine protein should be performed prior to treatment and as clinically warranted during treatment with sitravatinib. Participants who develop ≥ 2+ proteinuria should undergo 24-hour urine collection for assessment of urine protein; treatment with sitravatinib should be discontinued in the presence of ≥ 2g protein/24 hours and may restart when protein levels decrease to less than 2g/24 hours. Participants who develop nephrotic syndrome should be withdrawn from treatment with sitravatinib.

9.1.11 Thrombotic Events

Arterial and venous thrombotic events have been observed with sitravatinib and described with other inhibitors of the VEGFR pathway. The majority of thrombotic events observed with sitravatinib have been venous thrombotic events. The occurrence of thrombotic events with sitravatinib is being monitored for further characterization. Precautions should be taken in participants with recent, clinically significant thrombotic events, and treatment should be discontinued in subjects who develop clinically significant thromboembolic complications.

9.1.12 Hemorrhagic Events

The risk of hemorrhagic events with sitravatinib has not been fully characterized; however, such events have been reported with inhibitors of VEGFR. Patients with active hemoptysis or gastrointestinal bleeding should not take sitravatinib, and interruption of treatment is recommended for participants developing clinically significant bleeding.

9.1.13 Other Sitravatinib-Related Events

Other sitravatinib-related events include decreased appetite, dysphonia, fatigue, nausea, stomatitis, and vomiting. Management should be consistent with standard-of-care and sitravatinib dose modification as described in Tables 3 and 4.

9.2 Potential Drug Interactions

9.2.1 Cytochrome P-450 Substrates

In vitro experiments indicate that sitravatinib is a potential inducer of CYPs 2B6 and 3A4, as well as a potential inhibitor of CYPs 2C8, 2D6, and 3A4, though neither time dependent nor metabolism dependent inhibition has been observed. Medications that are sensitive substrates for CYPs 2C8, 2D6 or 3A4 with a narrow therapeutic index should be used with caution during treatment with sitravatinib.

In vitro experiments in microsomes and recombinant human P450 enzymes suggest that sitravatinib is metabolized by several cytochromes including CYPs 3A4, 2B6, and 2D6, with no single CYP enzyme contributing to > 25% of the total metabolism of sitravatinib. Therefore, the risk of drug-drug interactions with inhibitors or inducers of CYP enzymes is low. See Tables 7

and 8 for potential drug interactions and medications to be used with caution during treatment with sitravatinib.

Table 7: Clinical Inhibitors for P450-Mediated Metabolisms (to be used with caution/closely monitored during treatment with sitravatinib) *bold indicates medications that are commonly used*

Strong CYP3A4 Inhibitors	Boceprevir, **clarithromycin**, cobicistat, conivaptan, danoprevir/ritonavir, **diltiazem**, elvitegravir/ritonavir, **grapefruit juice**, idelalisib, indinavir/ritonavir, **itraconazole**, **ketoconazole**, lopinavir/ritonavir, **nefazodone**, nelfinavir,paritaprevir/ritonavir/ombitasvir plus dasabuvir, **posaconazole**, ritonavir, saquinavir/ritonavir, telaprevir, tipranavir/ritonavir, troleandomycin, **voriconazole**
Moderate CYP3A4 Inhibitors	**Aprepitant**, **cimetidine**, **ciprofloxacin**, **clotrimazole**, crizotinib, cyclosporine, dronedarone, **erythromycin**, **fluconazole**, fluvoxamine, imatinib, **tofisopam**, **verapamil**

Table 8: Sensitive Substrates with Narrow Therapeutic Index for the Indicated CYP Enzymes (to be used with caution/closely monitored during treatment with sitravatinib) *bold indicates medications that are commonly used*

Enzyme	
CYP2B6	Bupropion
CYP2C8	Repaglinide
CYP2D6	Atomoxetine,desipramine, **dextromethorphan**, eliglustat, nebivolol, **nortriptyline**, perphenazine, tolterodine, venlafaxine
CYP3A	Alfentanil, avanafil, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, eplerenone, everolimus, **felodipine**, ibrutinib, indinavir, lomitapide, **lovastatin**, lurasidone, maraviroc, **midazolam**, naloxegol, nisoldipine, quetiapine, saquinavir, sildenafil, **simvastatin**, sirolimus, tacrolimus, ticagrelor, tipranavir, tolvaptan, triazolam, vardenafil

9.2.2 Transporter Substrates and Inhibitors

Sitravatinib is a strong inhibitor of BCRP and P-gp transporters based on in vitro studies. Medications that are sensitive substrates or substrates with narrow therapeutic index for BCRP or P-gp transporters should be used with caution during treatment with sitravatinib (see Table 9).

Sitravatinib is a substrate of P-gp in vitro. Inhibitors of P-gp may increase sitravatinib exposure, while inducers of P-gp may decrease sitravatinib exposure. Caution should therefore be used when administering sitravatinib to participants taking medications that inhibit or induce P-gp (see Table 10).

Table 9: Sensitive Substrates and Substrates with Narrow Therapeutic Index for P-gp and BCRP Transporters (to be used with caution/closely monitored during treatment with sitravatinib)

Enzyme	
P-gp	Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan
BCRP	Methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan

Table 10: P-gp Inhibitors and Inducers (to be used with caution/closely monitored during treatment with sitravatinib)

P-gp Inhibitors	Clarithromycin, itraconazole, propafenone, quinidine, ranolazine, ritonavir, verapamil
P-gp Inducers	Rifampin

9.2.3 Medications that Prolong QTc

The risk of QTc prolongation in patients receiving treatment with sitravatinib has not been characterized. Use of medications known to prolong QTc and pose risk of Torsades de Pointes is to be avoided during treatment with sitravatinib (see Table 11).

Table 11: Elevated Risk of Torsades de Pointes with Concurrent Use During Sitravatinib Treatment (avoid during treatment with sitravatinib)

Anesthetics	Propofol, sevoflurane
Antiarrhythmics	Amiodarone, disopyramide, dofetilide, dronedarone, flecainide, hydroquinidine (dihydroquinidine)*, ibutilide, nifekalant*, procainamide, quinidine, sotalol
Antibiotics, antihistamines	Astemizole†, azithromycin, ciprofloxacin, clarithromycin, erythromycin, gatifloxacin†, grepafloxacin†, levofloxacin, moxifloxacin, roxithromycin*, sparfloxacin†, terfenadine†
Anticoagulants, calcium channel blockers, vasodilators	Anagrelide, bepridil, cilostazol, papaverine HCl (intra-coronary), terodiline*
Antifungals, antimalarials, antimicrobials	Chloroquine, fluconazole, halofantrine*, hydroxychloroquine, meglumine antimoniate*, pentamidine
Cancer treatment agents	Aclarubicin*, arsenic trioxide, oxaliplatin, vandetanib
GI	Cisapride†, domperidone*, ondansetron
Psychiatric	Chlorpromazine, chlorprothixene*, citalopram, donepezil, droperidol, escitalopram, haloperidol, levomepromazine (methotrimeprazine)*, levosulpiride*, mesoridazine†, pimozide, sulpiride*, sultopride*, thioridazine
Other	Cesium chloride, cocaine, ibogaine*, levomethadyl acetate†, methadone, probucol†, terlipressin*

* Only on non-US market † Removed from US market

9.3 Special Considerations

- For toxicities considered by the treating investigator unlikely to develop into serious or life–threatening events (e.g., alopecia, altered taste etc.), treatment may be continued at the same dose without reduction or interruption.
- The treating investigator may reduce a participant's dose for a toxicity of any grade/duration where s/he believes it to be in the best interest of the participant.
- Any consideration to modification of the above dose modification guidelines should be discussed with the Principal Investigator for approval or disapproval in advance.

10. SITRAVATINIB DRUG FORMULATION/STORAGE

Sitravatinib is an investigational agent and will be supplied free-of-charge by Mirati Therapeutics, Inc.

The malate capsule product consists of a blend of MGCD516 malate drug substance, microcrystalline cellulose, mannitol, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate. The blend is filled into hard gelatin capsules. The malate formulation is provided in dose strengths of 35 mg and 50 mg.

Sitravatinib capsules will be provided by Mirati as the malate drug product packaged in 30-count, high-density polyethylene, white opaque, round 60cc bottles. A tamper-resistant heat induction seal and a child-resistant closure are used for all dose strengths.

Bottles of sitravatinib are to be stored in refrigerated conditions (at 2-8°C, 36-46°F) at the pharmacy in accordance with the label. After dispensing to the participant, sitravatinib bottles are stored at ambient room temperature.

Each bottle is labelled with contents, product lot number, required storage conditions, and required regional specific information. Additional information regarding required storage conditions is provided in the study pharmacy manual.

The storage area should be secure with limited access. Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of small molecule therapeutic agents.

11. CORRELATIVE/SPECIAL STUDIES

11.1 Blood Samples

In order to address the exploratory objectives described in Sections 3.3.1 and 3.3.2, all participants will have two 10 mL Streck tubes of blood and two 10 mL Rarecyte tubes of blood collected at the following timepoints for ctDNA and CTC analysis respectively:

- Prior to beginning study treatment (may be collected at any time after the participant signs the informed consent, prior to the first dose of sitravatinib)
- Cycle 1, Day 14
- Cycle 2, Day 1
- Cycle 3, Day 1
- Day 1 of every odd-numbered cycle thereafter (e.g., C5D1, C7D1, etc.)
- End of Treatment

11.2 Tissue Samples

In order to address the exploratory objectives described in Sections 3.3.3 and 3.3.4, and to determine PTPN12 status, tissue samples will be collected from participants as outlined below.

Archival tissue from the primary tumor (if available) will be requested for all participants, but is not mandatory for enrollment.

Archival tissue from a metastatic or locally advanced site will be requested for all participants. If this is not available, a baseline biopsy of the metastatic or locally advanced site is required. Participants for whom archival tissue from a metastatic site is available will be offered an optional baseline biopsy (only if lesion is readily accessible, e.g., skin, regional superficial lymph nodes, peripheral liver lesions).

At least 3 core biopsy specimens should be collected, if feasible. If obtained, the first core will be fixed in formalin and used for PTPN12 IHC testing, the second core OCT-embedded and flash frozen on dry ice, and the third core placed in culture media and used for patient derived xenograft (PDX). If collection of additional cores is feasible, these should be OCT-embedded and flash frozen on dry ice. Participants with recurrent breast masses or chest wall/skin involvement where a core needle biopsy (or punch biopsy as a second preference) is feasible will be asked to undergo an additional research biopsy while on study treatment (between Cycle 1, Day 14 and Cycle 3, Day 14) and another upon progression of disease at the EOT visit. The on-treatment and EOT biopsies are optional, but highly encouraged for participants with accessible disease.

11.3 Translational Research Planned Analysis

11.3.1 Analysis of Blood Samples

11.3.1.1 CTC Analysis

We will track CTC number and expression of PTPN12 by immunofluorescence and compare, in an exploratory analysis, the relationships with PTPN12 tumor tissue expression and response to sitravatinib. After the depletion of red blood cell and enrichment of nucleated cells from 8mL of blood, CTCs and WBCs are spread onto microscope slides. Using automated fluorescence imaging, CTCs that are positive for EpCAM, cytokeratin, and

DAPI, but negative for the WBC marker CD45 are identified. The additional channels will be used for PTPN12 immunofluorescence. Positive and negative controls will be provided by appropriate cell lines. By monitoring PTPN12 expression in CTC we can explore the heterogeneity in PTPN12 expression and whether it is influenced by sitravatinib treatment.

11.3.1.2 ctDNA Analysis

Digital PCR affords the ability to determine ultrasensitive measurements of mutated and wild type copies of DNA over tens of thousands of individual droplets based on emission of HEX and FAM-labeled primer probes. An automated water-emulsion droplet generator (QX200DG, BioRad) creates tens of thousands of individual droplets that partition analyte molecules and detection probes into separate PCR reactions. A typical starting sample of 20 μL should yield up to 20,000 droplets. The QX200 can process and analyze up to 96 samples per run, yielding and counting approximately 1.5 million droplets per 96-well plate. Such microfluidics-based sample partitioning and statistical analyses of up to millions of droplets provide absolute quantification of target DNA molecules for probe-based detection at high sensitivity without the need for standard curves. Completed droplet reactions are streamed single file through a specialized reader for fluorescence analysis using a multi-pixel photon counter. Positive droplets exhibit increased fluorescence of target (mutant) probes compared to negative droplets (wild type), and the fraction of PCR-positive droplets are quantitated according to Poisson distribution. Thus, the fractional abundance of the mutant allele can be calculated by the ratio of the number of mutant-FAM probe copies per droplet over the total DNA concentration of the reaction.

For ddPCR we must know the mutations we want to detect *apriori*, as unlike next generation sequencing panels, the method is specific to confirming the presence or absence of a mutation at specific locus. Qualifying mutations for the longitudinal ctDNA analysis by ddPCR will be selected from the sequenced surgical tissue samples with mutations prioritized by likely clonal/driver status. For each mutant allele, a custom ddPCR probe set (BioRad) will be designed and used for serial ctDNA monitoring across blood collection timepoints in the study. Digital droplet construction will be performed on the BioRad AutoDG QX200 (automatic droplet generator) ddPCR system with assays utilizing TaqMan hydrolysis chemistry with custom and/or commercially available primer-probe sets (BioRad). The partitioned PCR droplet assays will be subjected to amplification using a C1000 Touch™ thermal cycler (BioRad) and fluorometrically assessed on the QX200 droplet reader. The fraction of positive droplets will be fitted to a Poisson distribution using available QuantaSoft Pro software (BioRad) to calculate the number of mutant and wild-type (WT) copies of DNA in the sample. We have previously confirmed that high sensitivity and specificity can be achieved on this platform using commercially available ctDNA reference standards prepared in synthetic plasma (Horizon Discovery). We will be utilizing this assay platform in collaboration with Dr. George Miles to monitor ctDNA abundance isolated from blood plasma at sampled timepoints outlined in the schema.

11.3.2 Analysis of Tissue Samples

11.3.2.1 PTPN12 IHC Assay

We will deploy the PTPN12 IHC on all formalin-fixed tissue accrued from the participants during the execution of the trial to identify changes in expression from primary to metastatic

disease, as a role of PTPN12 loss during metastatic progression has not been evaluated. If the PTPN12 status of the primary and metastatic samples are closely matched, analysis of the primary sample can be used for eligibility in future studies. For participants with accessible disease, pre-treatment, during treatment, and progression biopsies will be requested to profile the kinome in response to treatment using the drug bead technology. Upon completion of these studies we will understand whether primary tumor or CTC PTPN12 status, as opposed to a metastatic biopsy, can be used to determine eligibility in future studies.

11.3.2.2 Proteogenomic Analysis of Tumor Biopsies (DNA, RNA and Proteomics)

This protocol aims to evaluate the kinome and phosphoproteome of metastatic TNBC. The analysis pipeline includes quantitative tandem mass tag (TMT)-based proteomics and phosphoproteomics, kinase inhibitor profiling (KiP)-based kinomics, tumor/normal exome sequencing, and RNA sequencing [9]. For participants with accessible disease, pre-treatment, on-treatment, and progression biopsies will be requested for proteogenomic profiling. We aim to examine signaling perturbations in response to treatment as well as the influence of tumor PTPN12 status on the kinome. In the event of clinical trial success, we will build a kinome profile of responding versus non-responding tumors.

11.3.2.3 Generation and Analysis of Patient Derived Xenografts (PDX)

When possible, we will collect viable cells from tumor biopsies and engraft them into immunocompromised mice. When a PDX is successful, proteogenomic analysis will be conducted parallel to the tissue analysis outlined in Section 11.3.2.2 to validate the PDX as a facsimile for the tumor from which it was derived. The PDX will also be treated with sitravatinib and the results compared with the patient matched response. Later PDX studies will examine sitravatinib combinations including with a taxane.

11.3.2.4 Exploratory Immune Biomarkers

These are described in Table 1 (Section 4.2).

11.4 Specimen Banking

All collected biospecimens will be banked indefinitely at the Coordinating Center's Breast Center Tissue Bank, located at the following address:

Breast Center Tissue Bank
Baylor College of Medicine
One Baylor Plaza RM 330C
Houston, TX 77030

Study participants will be asked to indicate their preferences for the future use of tissue at the time informed consent is obtained.

12. MEASUREMENT OF EFFECT

For the purposes of this study, participants are to be re-evaluated for response per the study calendar. Response and progression will be evaluated using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors guideline, version 1.1 (RECIST 1.1) [22]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.1 Definitions

12.1.1 Evaluable for Toxicity

All participants will be evaluable for toxicity from the time of their first treatment with sitravatinib.

12.1.2 Evaluable for Objective Response

Only those participants who have measurable disease present at baseline, have received at least one cycle of study treatment, and have had their disease re-evaluated, will be considered evaluable for response. These participants will have their response classified according to the definitions outlined in Section 12.4. (Note: Participants who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable.)

12.1.3 Evaluable Non-Target Disease Response

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

12.1.4 Measurable Disease

A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥ 20 mm with chest x-ray, or as ≥ 10 mm with CT scan, CT component of a PET/CT, or MRI.

A superficial non-nodal lesion is measurable if its longest diameter is ≥ 10 mm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

A malignant lymph node is considered measurable if its short axis is ≥ 15 mm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

NOTE: Tumor lesions in a previously irradiated area are only considered measurable disease in the event that there is evidence of post-radiation progression.

12.1.5 Non-Measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes ≥ 10 to < 15 mm, are considered non-measurable disease. Bone

lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered non-measurable.

NOTE: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis < 10 mm are considered non-pathological (i.e., normal) and should not be recorded or followed.

12.2 Guidelines for Evaluation of Disease

12.2.1 Measurement Methods

The same assessment method/technique must be used to characterize each identified and reported lesion at baseline and during follow-up; all measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.

Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

12.2.2 Modalities for Measurable Disease

12.2.2.1 Conventional CT and MRI

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

Diagnostic quality CT is expected (with oral and IV contrast); any deviations from this must be approved by the Principal Investigator/designee in advance. (See note below regarding contrast allergy).

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

NOTE: If it is known prior to enrollment that a participant is unable to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) should be used to evaluate the participant

at baseline and follow-up should be guided by the anatomic location(s) of the disease. For participants who develop contraindications to contrast after the baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the anatomic location of the disease and should be optimized to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist and Principal Investigator/designee to determine if substitution of these other approaches is possible and, if not, the participant may be considered not evaluable from that point forward.

12.2.2.2 Chest X-ray

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

12.2.2.3 Clinical Exam

For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

12.2.2.4 Ultrasound

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

12.2.2.5 PET-CT

If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time with approval from the Principal Investigator/designee.

12.2.2.6 FDG-PET

FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease (PD) and particularly possible new disease. A positive FDG-PET scanned lesion is defined as one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered negative. New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, positive FDG-PET at follow-up: PD based on a new lesion.
- No FDG-PET at baseline, positive FDG-PET at follow-up: If the positive FDG-PET at

follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

12.2.3 Additional Considerations

- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response.
- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.
- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

12.3 Lesion Documentation

12.3.1 Target Lesions

12.3.1.1 Measurable Lesions

Up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

NOTE: If fewer than 5 target lesions and target lymph nodes are identified, there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.

12.3.1.2 Baseline Sum of Diameters (BSD)

A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

12.3.1.3 Post-Baseline Sum of the Diameters (PBSD)

A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measurement for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

12.3.1.4 Mimimum Sum of Diameters (MSD)

The minimum sum of the diameters (MSD) is the minimum of the BSD and the PBSD.

12.3.2 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions or non-target lymph nodes and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.4 Response Criteria

12.4.1 Overview

All target lesions, as well as non-target lesions must be measured at the evaluation time points specified in the study calendar. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

NOTE: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

12.4.2 Evaluation of Target Lesions

12.4.2.1 Complete Response (CR)

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

12.4.2.2 Partial Response (PR)

At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

12.4.2.3 Progressive Disease (PD)

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

NOTE: The appearance of one or more new lesions is also considered progression.

12.4.2.4 Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

12.4.3 Evaluation of Non-Target Lesions & Non-Target Lymph Nodes

12.4.3.1 Complete Response (CR)

Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

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

12.4.3.2 Non-CR/Non-PD

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

12.4.3.3 Progressive Disease (PD)

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

NOTE: To achieve unequivocal progression on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened." Where possible, similar rules to those described above for target lesions for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

12.4.4 Symptomatic Deterioration

Participants with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after

discontinuation of treatment due to symptomatic deterioration. A participant is classified as having PD due to symptomatic deterioration if any of the following occur that are not either related to study treatment or other medical conditions:

- Weight loss > 10% of body weight
- Worsening of tumor-related symptoms
- Decline in performance status of > 1 level on ECOG scale

12.4.5 Evaluation of Best Overall Response

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

For participants with measurable disease at baseline:

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	**CR**
CR	Non-CR/ Non-PD	No	**PR**
CR	Not evaluated	No	**PR**
PR	Non-PD or not all evaluated	No	**PR**
SD	Non-PD or not all evaluated	No	**SD**
Not all evaluated	Non-PD	No	**Non-evaluable**
PD	Any	Yes or No	**PD**
Any	PD*	Yes or No	**PD**
Any	Any	Yes	**PD**
*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.			

For participants with non-measurable/evaluable disease only at baseline:

Non-Target Lesions	New Lesions	Overall Response
CR	No	**CR**
Non-CR/Non-PD	No	**Non-CR/Non-PD**
UNK/Not All Evaluated	No	**Indeterminate**
Unequivocal progression	Yes or No	**PD**
Any	Yes	**PD**

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

12.4.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the time from the initiation of the study treatment until the date of objective disease progression or death (by any cause in the absence of

progression).

12.4.7 Response Review

There is no independent or central review of the radiology assessments planned for this trial. It is the responsibility of each participating site's Principal Investigator to ensure that tumor assessments are reported per the RECIST 1.1 criteria outlined above. The Principal Investigator (or designee) may choose to review select cases.

12.4.8 Confirmatory Measurement/Duration of Response

12.4.8.1 Confirmation of Response

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.

12.4.8.2 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.

12.4.8.3 Duration of Stable Disease

The duration of SD 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.

13. ADVERSE EVENT REPORTING REQUIREMENTS

13.1 General

Adverse event collection and reporting is a routine part of every clinical trial. This study will use the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events version (CTCAE *v5.0*) that is available at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Information on all adverse events, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported as described in the following sections.

Adverse events experienced by participants will be collected and reported from initiation of study medication, throughout the study, and within 30 days of the last dose of study medication. Participants who experience an ongoing adverse event related to a study procedure and/or study medication beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the participating investigator. Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and any other

applicable regulatory agency of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

13.2 Definitions

13.2.1 Adverse Event (AE)

An adverse event is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

13.2.1.1 Suspected Adverse Reaction

Suspected adverse reactions are the subset of all adverse events for which there is a "reasonable possibility" (i.e., there is evidence to suggest a causal relationship between the drug and the adverse event) that the drug caused the event.

13.2.2 Serious Adverse Event (SAE)

A serious adverse event is an undesirable sign, symptom, or medical condition which:

- is fatal;
- is life-threatening (immediate risk of death);
- requires or prolongs inpatient hospitalization for ≥ 24 hours;
- results in persistent or significant disability/incapacity to conduct normal life functions;
- constitutes a congenital anomaly or birth defect; or
- 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.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen, or that is required per protocol
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care
- Death due to disease progression unless attributable to the study treatment

Events listed above may be reported to a participating site's local IRB, if required per local regulations.

13.2.3 Expectedness

Expected: Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, AEs are considered "expected"

if they are included in the *Reference Safety Information* section of the most current version of the sitravatinib Investigator's Brochure.

Unexpected: An adverse event is considered unexpected when it is not included, or varies in nature, intensity or frequency, from information provided in the *Reference Safety Information* section of the most current version of the sitravatinib Investigator's Brochure.

13.2.4 Attribution

Attribution is the relationship between an adverse event and the study treatment. Attribution will be assigned as follows:

- Unrelated: The adverse event is clearly unrelated to the study treatment.
- Unlikely: The adverse event is unlikely to be related to the study treatment.
- Possibly: The adverse event is possibly related to the study treatment.
- Probably: The adverse event is probably related to the study treatment.
- Definite: The adverse event is clearly related to the study treatment.

13.3 Reporting Procedures

13.3.1 General

All adverse events will be recorded on study-specific case report forms (CRFs).

13.3.2 Serious Adverse Events

All serious adverse events, regardless of causality to study drug, will be reported to the Principal Investigator and/or the Study Coordinator. Information pertaining to the SAE should be compiled on the Form FDA 3500A – MedWatch Mandatory Reporting (available on the FDA website). The Principal Investigator or designee should review the information in this report, along with any supporting documentation, and make a determination of causality. The Principal Investigator or designee should also review any follow-up information as it becomes available to determine if the causality assessment has changed.

13.3.3 Suspected, Unexpected Serious Adverse Reactions (SUSARs)

The Principal Investigator or designee must report any suspected adverse reaction to study treatment that is both serious and unexpected to the FDA via an IND safety report no later than 15 calendar days after determining that the information qualifies for reporting. Any unexpected fatal, or life-threatening, suspected adverse reactions must be reported to the FDA no later than 7 calendar days after initial receipt of the information.

13.3.4 Institutional Review Board (IRB)

Adverse events requiring modifications to the protocol and/or informed consent will be reported to the IRB. These modifications will be provided to the IRB with the report of the adverse event.

13.3.5 Food and Drug Administration (FDA)

The Dan L. Duncan Cancer Center at Baylor College of Medicine (DLDCC-BCM) has been designated as the Coordinating Center to manage the Investigational New Drug Application

(IND) associated with this protocol. The Coordinating Center and/or CRO will cross-reference this submission to Mirati Therapeutics' parent IND at the time of submission. Additionally, the Coordinating Center will submit a copy of these documents to Mirati Therapeutics at the time of submission to FDA.

The Coordinating Center will be responsible for all communication with the FDA in accordance with 21 CFR Part 312, which includes but is not limited to the 7- and 15-Day Safety Reports, as well as an Annual Progress Report. Additionally, the Coordinating Center will submit a copy of these reports to Mirati Therapeutics at the time of submission to FDA.

13.3.6 Mirati Therapeutics, Inc.

Mirati Therapeutics' procedure for SUSAR exchange is outlined below. All exchange of processed data will be by Form FDA 3500A – MedWatch. The narratives must contain assessments of expectedness and causality for all SAEs. Non-SUSAR SAEs are not routinely exchanged.

13.3.6.1 From Coordinating Center to Mirati Therapeutics

The Coordinating Center will forward Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring on study with sitravatinib as follows:

- Reports of fatal or life threatening Serious Adverse Drug Reactions will be forwarded within three (3) calendar days of receipt date.
- Reports of Serious Adverse Drug Reactions (other than fatal or life threatening) will be forwarded within eight (8) calendar days of receipt date.

13.3.6.2 From Mirati Therapeutics to Coordinating Center

Mirati will forward SUSARs occurring with sitravatinib to the Coordinating Center as follows:

- Reports of fatal or life threatening Serious Adverse Drug Reactions will be sent within four (4) calendar days of receipt date.
- Reports of Serious Adverse Drug Reactions (other than fatal or life threatening) will be sent within ten (10) calendar days of receipt date.

Baylor College of Medicine Contact:
C. Kent Osborne, MD
Baylor College of Medicine
Email: kosborne@bcm.edu
Fax: (713) 798-8884
Phone (for fax issues): (713) 798-1641

Mirati Therapeutics Contact:
Mirati Therapeutics, Inc.
Email: wilsafety@ppdi.com
Fax: 1-888-488-9697
Phone (for fax issues): 1-800-201-8725

14. DATA AND SAFETY MONITORING

14.1 Data Management and Reporting

All participants who received any amount of study drug will be included in the safety analysis. Participants will be monitored at each clinic visit and at any other contact throughout the study for the occurrence of AEs and SAEs. The investigator and/or site staff will inquire about the occurrence of AEs/SAEs at every clinic visit or contact during the study. Adverse events will be graded according to the NCI Common Terminology Criteria v. 5.0 (CTCAEv5). All AEs/SAEs that occur during active treatment will be recorded in source documents and on CRFs, regardless

of grade or relationship to study treatment. Non-serious adverse events that occur during the 30-day follow-up period will only be recorded on the CRFs if the investigator believes there to be a possible relationship to study treatment. Serious adverse events occurring during the 30-day follow-up period should be recorded on the CRFs, regardless of suspected relationship to study treatment.

Safety analyses will include summaries of adverse event rates (both frequency and incidence tables), baseline laboratory parameters and changes from baseline, frequency of CTC toxicity grades for both laboratory and non-laboratory data. The investigators and others responsible for patient care at individual sites should institute any supplementary investigations of major adverse events based on their clinical judgment of the likely causative factors.

14.2 Meetings

We will utilize the Data and Safety Monitoring Plan of the Dan L. Duncan Cancer Center at Baylor College of Medicine (DLDCC-BCM). Additionally, the Principal Investigator will review all adverse events as they occur to evaluate causality and severity. This will ensure that any unanticipated risks or changes to the risk/benefit ratio are identified and reported in a timely manner.

The external Data and Safety Monitoring Board (DSMB) at DLDCC-BCM will review the study annually, at a minimum. The DSMB consists of five members not affiliated with BCM or the DLDCC, who have prior experience and expertise in the conduct of clinical trials. The DSMB will review and monitor study progress, toxicity, safety and other data from this study. Information that raises any questions about participant safety or protocol performance will be addressed by the Principal Investigator, statistician and study team. Should any major concerns arise, the DSMB will offer recommendations regarding whether or not to suspend the study.

Information to be provided to the DSMB includes, but is not limited to, the following: participant accrual, participant demographics, response data, and toxicity data. Additional information may be provided to the DSMB upon request. Additional information regarding DSMB policies and procedures is located in the DLDCC External DSMB Charter.

15. REGULATORY CONSIDERATIONS

15.1 Informed Consent

The investigator (or designee) will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each participant will be informed that participation in the study is voluntary, that s/he may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician(s) or institution. The informed consent will be given by means of a standard written statement, written in non-technical language, which will be IRB-approved. The participant should read and consider the statement before signing and dating it, and will be given a copy of the document. No participant will enter the study or have study-specific procedures done before his/her informed consent has been obtained.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written informed consent document (or a separate document to be given in conjunction with the consent document) will include a subject authorization to release medical information to the study sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including particpants' medical history.

15.2 Ethics and GCP

This study will be carried out in compliance with the protocol and Good Clinical Practice, as described in:

ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.

US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).

Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

15.3 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Principal Investigator is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow participants to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

16. STATISTICAL CONSIDERATIONS

16.1 Study Design

This phase 2 biomarker-stratified study employs a modified optimal Simon two stage design. The decision rule, based on an adaptation of the approach of Jones and Holgren[1], is detailed below.

The primary endpoint is PFS24, where the success is defined as being alive and progression-free at 24 weeks after initiation of study treatment.

16.2 Decision Rule(s)

The general flow and decision points are illustrated in Figure 4.

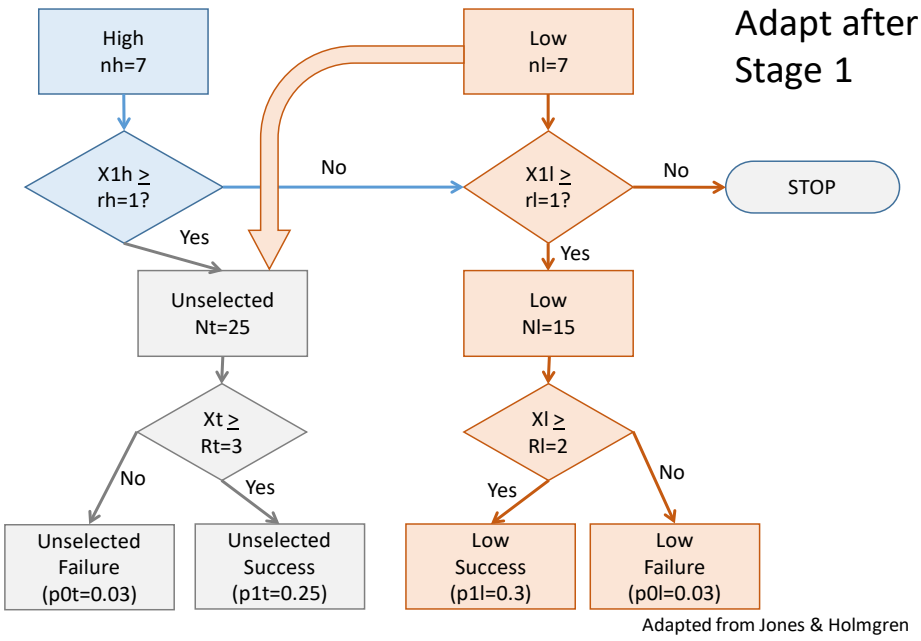

Figure 4. Adapted Phase 2 Design.

In Stage 1, the study will separately enroll seven PFS24 evaluable participants each in the PTPN12*high/normal* and PTPN12*low* cohorts. If there are no PFS24 events in the PTPN12*high/normal cohort*, enrollment to that stratum will close. If there is at least one PFS24 event observed in the PTPN12*high/normal* cohort, then, in Stage 2, the previously accrued PTPN12*low* and PTPN12*high/normal* cases will be combined into a single cohort, and the study will enroll additional cases, regardless of biomarker status, up to a total of 25 participants. At the end of the trial, three or more PFS24 events will be required to deem the therapy a success.

If there is no PFS24 event in the PTPN12*high/normal* cohort during Stage 1, the PTPN12*low* cohort will continue to accrue to 7 participants. If there are no PFS24 events in the PTPN12*low* cohort, enrollment to that stratum will close, and the trial will close. If there is at least one PFS24 event, then, in Stage 2, the study will accrue up to a total of 15 PFS24-evaluable PTPN12*low* participants. At the end of the trial, two or more PFS24 events will be required to deem the therapy a success, with PTPN12*low* status as a biomarker of benefit. Extensive simulations

indicate that operating characteristics of the proposed design perform as expected and are independent of the frequency of PTPN12*low* status.

16.3 Sample Size and Accrual Rate

Up to twenty-five PFS24-evaluable participants will be required. This study will have 90% power (alpha=0.075 one-tailed) to detect a PFS24 rate of 30% in the PTPN12*low* cohort compared to an unacceptable rate of 3%, and 85% power to detect 25% vs 3% in the unselected group. The study is expected to complete accrual within 2 years of study initiation.

16.4 Stratification Factors

Participants will be enrolled into two cohorts based on Protein Tyrosine Phosphatase, Non-Receptor Type 12 (PTPN12) status, which will be determined via analysis of tissue from a metastatic site: PTPN12*low* or PTPN12*high/normal*.

16.5 Endpoints and Analysis

16.5.1 Primary Endpoint and Analysis

Progression-free survival status at 24 weeks will be used in trial decision-making as described above. At the end of the trial, PFS24 events will be summarized descriptively with counts, rates and 95% confidence intervals, with appropriate adjustment for the group sequential nature of the study design [23].

16.5.2 Secondary Endpoints and Analysis

Time to progression (TTP), objective response rate (ORR), and clinical benefit rate (CBR) will be summarized descriptively using appropriate statistics such as counts, rates, and Kaplan-Meier estimates for time to events and 95% confidence intervals.

The assessment of safety will be based on the frequency of adverse events, grade, attribution, and on the number of laboratory values that fall outside of pre-determined ranges. In particular, the number of participants experiencing grade 3 or higher adverse events will be summarized. Data will be summarized descriptively with counts, rates and 95% confidence intervals, as appropriate.

16.5.3 Exploratory Endpoints and Analysis

CTCs, CTC PTPN12 expression and ctDNA will be assessed longitudinally and will be correlated with baseline PTPN12 expression, to determine whether baseline CTCs can be used to assess PTPN12 status, to determine whether CTCs and ctDNA are predictive of response and/or PFS24. As appropriate, general linear mixed models will be used to model CTC and/or ctDNA trajectories. Exploratorally, phosphoproteomics will be examined before and after treatment to identify differentially expressed phosphoproteins due to treatment and baseline levels or changes in the phosphoproteome that might be predictive of clinical benefit. Tumor kinome profiling will be examined to identify differential kinase activity. Similarly, immune biomarkers will be examined to identify baseline differences or differential changes that might indicate the effect of immunocomponents on response. Data will be summarized descriptively with means and/or medians and 95% confidence intervals. False discovery methods will be employed to avoid multiple comparison issues with these higher dimensional data.

16.6 Reporting and Exclusions

All PFS-evaluable participants will be included in analyses of the primary and secondary outcomes in their assigned group (modified-ITT population). All participants who receive any study treatment will be considered evaluable for the safety analysis (safety population).

All registered participants will be accounted for. Participants withdrawn or considered ineligible before starting study treatment will be replaced. Participants withdrawn prior to completing the first cycle of study treatment or determined to be ineligible, will be considered inevaluable for PFS24 and will be replaced.

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APPENDICES

APPENDIX A: ECOG Performance Status Scale

Score	Definition	Karnofsky Equivalent
0	Asymptomatic	100
1	Symptomatic, fully ambulatory	80 – 90
2	Symptomatic, in bed less than 50% of day	60 – 70
3	Symptomatic, in bed more than 50% of day, but not bedridden	40 – 50
4	Bedridden	20 – 30