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Brief Title: Sitravatinib Plus Pembrolizumab in Patients With Advanced Treatment-Naïve PD-L1+ Non-Squamous NSCLC

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Phase 2 Trial of Sitravatinib plus Pembrolizumab in Patients with Advanced Treatment-Naïve PD-L1+ Non-Squamous Non-Small Cell Lung Cancer

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PRINCIPAL INVESTIGATOR:

Sarah Goldberg, M.D., M.P.H.

Section of Medical Oncology Yale Cancer Center

333 Cedar St., FMP130

New Haven, CT 06520 Tel: (203) 785-7564

Fax: (203) 785-3788

Sarah.Goldberg@yale.edu

IND Number: 155305

IND Holder: Sarah Goldberg, M.D., M.P.H.

NCT Number: 04925986

Study Phase: 2

Confidentiality Statement:

I, the undersigned, have read and approve this protocol and agree on its contents. It is confirmed that the information and guidance given in this protocol complies with scientific principles, the guideline of Good Clinical Practice, the Declaration of Helsinki in the latest relevant version, and the applicable legal and regulatory requirements. I agree to conduct the study in compliance with all applicable regulations including International Ethical Guidelines for Biomedical Research Involving Human Patients (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (GCP) (International Council for Harmonisation [ICH] 1996), ICH E6 (R2) and concepts that have their origin in the Declaration of Helsinki (World Medical Association 1996, 2008 & 2013).

Printed Name of Principal Investigator: _____

Signature of Principal Investigator

Date

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Synopsis

Primary Objective

(1) The primary objective of this study is to evaluate the efficacy of sitravatinib in combination with pembrolizumab in the front-line treatment of patients with advanced non-squamous PD-L1 positive NSCLC by measuring Objective Response Rate (ORR).

Secondary Objectives

(1) To evaluate other measures of efficacy including Overall Survival (OS), Progression Free Survival (PFS), Duration of Response (DOR) and Clinical Benefit Rate (CBR) in the first-line setting for patients with advanced, non-squamous, PD-L1 positive NSCLC treated with the combination of sitravatinib and pembrolizumab.
(2) To evaluate the toxicity profile and tolerability of sitravatinib/pembrolizumab in advanced, treatment naïve, non-squamous, PD-L1 positive NSCLC.

Exploratory Objectives:

(1) To evaluate ORR, OS, PFS, DOR, and CBR in patients with advanced, non-squamous, treatment naïve, PD-L1 positive NSCLC who receive pembrolizumab run-in followed by pembrolizumab/sitravatinib combination therapy.
(2) To evaluate the CNS activity of sitravatinib/pembrolizumab in patients with advanced, treatment naïve, PD-L1 positive NSCLC by measuring Intracranial Objective Response Rate (iORR) and Intracranial Duration of Response(iDOR) in patients with baseline CNS disease, and Intercranial Progression-Free Survival (iPFS) in all patients.
(3) To study correlates of the adaptive and innate immune responses induced by sitravatinib and pembrolizumab treatment in both tumor tissue and peripheral blood.
(4) To explore the association between tumor immune contexture and clinical benefit to sitravatinib and pembrolizumab.

Study Duration

4 Years

Summary of Study Design

This is a multicohort phase 2 study to evaluate the efficacy of pembrolizumab combined with the investigational drug sitravatinib in the frontline treatment of advanced, non-squamous PD-L1 positive NSCLC. For clinical analysis, there will be two patient cohorts defined by PD-L1 status: Cohort 1 for patients with PD-L1 Tumor Proportion Score (TPS) 1-49% and Cohort 2 for patients with TPS≥50% using the FDA approved 22c3 PD-L1 IHC assay or a local assay performed in a CLIA facility. We will implement a Simon's two-stage design to evaluate the efficacy of sitravatinib in combination with pembrolizumab for each cohort separately.

There will be two groups within each cohort of this study: the "main study population" (Group A) in which patients will receive pembrolizumab plus sitravatinib beginning on Cycle 1 Day 1 (C1D1), and a "pembrolizumab run-in population" (Group B) in which patients will receive

pembrolizumab alone for 1 dose followed by pembrolizumab plus sitravatinib beginning C2D1.

The primary endpoint of the trial is the ORR for patients treated with pembrolizumab plus sitravatinib in the main study population. The purpose of the pembrolizumab run-in population is to obtain tissue and blood samples from these patients to be used as controls for correlative studies and to determine the preliminary efficacy of pembrolizumab alone followed by the combination.

Number of Study Sites

Up to 2 sites

Study Population

A total of 70 evaluable patients will be enrolled in the trial, 35 to cohort 1 and 35 to cohort 2. 30 patients from each cohort will be enrolled to Group A (main study population) and 5 patients from each cohort will be enrolled to Group B (pembrolizumab run-in population). Patients will be eligible if they have previously untreated, non-squamous, PD-L1 positive NSCLC with no known mutations/alterations in *EGFR, ROS1, ALK*, or *BRAF.*

Number of Participants

70

Primary Endpoints

(1) The primary endpoint for this study is ORR as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) in the main study population.

Secondary and Exploratory Endpoints

(1) Overall Survival (OS) in main study group
(2) Progression Free Survival (PFS) in main study group
(3) Duration of Response (DOR) in main study group
(4) Clinical Benefit Rate (CBR) in main study group
(5) Adverse events as per CTCAE v.5
(6) ORR, DOR, CBR, PFS, OS in the run-in population
(7) iORR, iDOR, and iPFS
(8) Percentage of activated myeloid cells, effector T cells, and AXL+/MERTK+ macrophages in the TME
(9) Immune cell population changes in the TME as defined by changes in population heterogeneity detected by single cell RNA sequencing
(10) Gene expression changes in peripheral blood mononuclear cells
(11) Correlation of clinical response to immune populations present in baseline samples and immune cell population changes induced by therapy

Abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BCRP	Breast Cancer Resistance Protein
CBR	Clinical Benefit Rate
CI	Confidence Interval
CIT	Checkpoint Inhibitor Therapy
C_{max}	Maximum Plasma Concentration
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography Scan
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	Trough Concentration
ctDNA	Circulating Tumor Deoxyribonucleic Acid
DKA	Diabetic Ketoacidosis
DLT	Dose Limiting Toxicity
DOR	Duration of Response
DSMC	Data and Safety Monitoring Committee
EKG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

EIU	Exposure In-Utero
FDA	Food and Drug Administration

GFR	Glomerular Filtration Rate
HDPE	High-Density Polyethylene
hERG	human Ether-a-go-go Related Gene
HGF	Hepatocyte Growth Factor
hr	Hour
HR	Hazard Ratio
IB	Investigator's Brochure
IC_{50}	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
iDOR	Intracranial Duration of Response
IgG4	Immunoglobulin G4
IND	Investigational New Drug
iORR	Intracranial Objective Response Rate
iPFS	Intracranial PFS
irAE	Immune-related Adverse Event
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine Device
kg	Kilogram

LVEF	Left Ventricular Ejection Fraction
mAb	Monoclonal Antibody
MDSC	Myeloid-Derived Suppressor Cell
mg	Milligram
mins	Minutes
mL	Milliliter
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid

NCI	National Cancer Institute
NE	Not Evaluable
NGS	Next Generation Sequencing
NK	Natural Killer
NPCB	No Prior Clinical Benefit
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cells
PCB	Prior Clinical Benefit
PD	Objective Progression of Disease
PD-1	Programmed Cell Death 1
PD-L1	Programmed Cell Death Ligand 1
PET	Positron Emission Tomography

PFS	Progression-Free Survival
P-gp	P-glycoprotein
PPE	Palmer Plantar Erythrodysesthesia
PPI	Proton Pump Inhibitor
PR	Partial Response
Q3W	Every 3 Weeks
QD	Once Daily
QTc	Corrected QT Interval
RANO-BM	Response Assessment in Neuro-Oncology-Brain Metastases
RECIST	Response Evaluation Criteria in Solid Tumors
RTKs	Receptor Tyrosine Kinases
SAE	Serious Adverse Event
scRNAseq	Single-cell RNA sequencing

SD	Stable Disease
T1DM	Type 1 Diabetes Mellitus
TAM	Tyro3, Axl and MERTK
TGI	Tumor Growth Inhibition
TKIs	Tyrosine Kinase Inhibitors
TMB	Tumor Mutation Burden
TME	Tumor Microenvironment
Tregs	T Regulatory Cells
ULN	Upper Limit of Normal
WHO	World Health Organization

WOCBP	Women of Child Bearing Potential
µg	Microgram
µM	Micromolar
USA	United States of America

Table of Contents

1 Introduction and Background

1.1 Introductory Statement

This document is a protocol for a human research study. The purpose of this protocol is to ensure that this study is to be conducted according to ICH GCP guidelines, and according to CFR 21 Part 312, other applicable government regulations and Institutional research policies and procedures

1.2 Disease and Current Therapeutics Background

1.2.1 Non-Small Cell Lung Cancer

Lung cancer remains the leading cause of cancer-related death worldwide, with approximately 2.1 million new cases diagnosed in 2018 and approximately 1.76 million deaths attributed to lung cancer(1). Non-small cell lung cancer (NSCLC) accounts for approximately 83% of lung cancer cases, of which approximately half are classified as adenocarcinoma of the lung(2). Increased understanding of cancer biology, and specifically the role of the immune system in tumor development and growth, has led to the development of new therapeutic strategies over the past 10 years. Immune-modulating drugs, in particular those targeting the “immune checkpoint” pathways, have emerged as paradigm shifting therapies in the treatment of many cancers, including NSCLC.

1.2.2 PD-1/PD-L1 Immune Checkpoint Pathway

The PD-1/PD-L1 interaction has been the main immune checkpoint pathway to be studied and used as a target for cancer therapeutics. The PD-1 receptor along with the ligands PD-L1 and PD-L2 constitute an important regulatory pathway for the immune system, inhibiting T-cell activation when engaged(3, 4). Under normal physiologic circumstances, PD-L1 functions to limit collateral damage in tissues where an immune response has been triggered. PD-1 is expressed on T-cells whereas PD-L1 and PD-L2 are expressed on other types of immune cells as well as some cancer cells. Upregulation of PD-1 ligands is utilized by tumors to help evade detection and elimination by the host immune system tumor response. PD-L1 expression in tumor, including in lung cancer, has been associated with poor survival motivating the development of PD-1 pathway inhibitors(5).

1.2.3 PD-L1/PD-1 Inhibitors in Treatment of NSCLC

Two PD-1/PD-L1 inhibitors have been shown in clinical trials to be effective as monotherapy treatment in the front-line setting for advanced NSCLC: pembrolizumab (PD-1 inhibitor) and atezolizumab (PD-L1 inhibitor)(6-8). Of these two, only pembrolizumab has been approved as a single agent in the front-line setting for all PD-L1 positive patients (PD-L1≥1%)(6).

1.2.4 Pembrolizumab

Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Details regarding pharmacokinetics and safety studies for pembrolizumab are described in current KEYTRUDA© product label.
Initial clinical trials for pembrolizumab in NSCLC patients demonstrated good tolerability and safety, as well as marked improvements in efficacy compared with standard of care chemotherapy(9, 10). Pembrolizumab was initially granted accelerated approval for use in metastatic NSCLC as second line treatment on the basis of the Phase I trial KEYNOTE-001; pembrolizumab demonstrated an acceptable safety and tolerability profile as well as significant anti-tumor activity(9). The Phase 2/3 study KEYNOTE-010 examined pembrolizumab versus standard second line chemotherapy in patients with pre-treated PD-L1 positive advanced or metastatic NSCLC (10). Patients were randomized to high or low dose pembrolizumab versus docetaxel, with significant improvements seen in objective response rate, duration of response and overall survival in the pembrolizumab group. In addition, pembrolizumab was better tolerated than docetaxel. Subsequently, a Phase 3 trial of first-line pembrolizumab versus standard chemotherapy in patients with PD-L1 high (TPS≥50%) advanced NSCLC demonstrated the superiority of pembrolizumab in the first line setting(7). Improvement was reported across multiple efficacy endpoints including overall survival, along with a favorable safety profile, leading to US approval for pembrolizumab in the first-line treatment setting in this patient population. Pembrolizumab has now also been approved as first-line monotherapy for patients with PD-L1≥1% on the basis of the Phase 3 KEYNOTE-042(6). More recently, the combination of pembrolizumab with a platinum-based doublet chemotherapy regimen demonstrated an OS advantage as compared to chemotherapy plus placebo in the first-line, advanced disease treatment setting(11).

1.3 Sitravatinib

1.3.1 Sitravatinib Mechanism of Action

Sitravatinib is a spectrum-selective receptor tyrosine kinase (RTK) inhibitor that acts on several closely related RTKs including the TAM family (Tyro3/Axl/MERTK), VEGFR2, KIT, and MET(12). These receptor tyrosine kinases are key regulators of multiple signaling pathways leading to cell growth, survival, and migration(13). RTKs are dysregulated in many cancers through overexpression, genetic alteration or co-expression with high affinity ligands (13). The family of RTKs inhibited by sitravatinib are genetically altered in a variety of cancers and act as oncogenic drivers, promoting cancer development and progression(14). In addition to the immunostimulatory effects of Axl and MET inhibition, sitravatinib may also condition the TME in favor of antitumor activity via immunomodulatory effects of VEGFR and KIT inhibition. Preclinical data with sitravatinib indicate that it can increase expression of PD-L1 on tumor cells in vitro and in vivo. Pilot studies in syngeneic mouse tumor models also suggest that sitravatinib increases the proliferation and fraction of systemic/spleen CD4+ and CD8+ T lymphocytes and reduces the number of systemic MDSCs. Reduction of intratumoral MDSCs as well as a shift in macrophage physiology was also observed clinically in patients with oral squamous cell carcinomas who were treated with sitravatinib (15).

1.3.2 Sitravatinib Pharmacology

Sitravatinib demonstrated potent, concentration-dependent inhibition of the kinase activity of MET, Axl, MERTK, VEGFR family, PDGFR family, KIT, FLT3, Trk family, RET, DDR2, and selected Eph family members in biochemical assays and inhibited phosphorylation and kinase dependent function in cell-based assays. Sitravatinib also inhibited oncogenic functions associated with target RTKs including MET-dependent cell viability and migration and endothelial tube formation and angiogenesis. Consistent with this anti-tumor and anti-angiogenic mechanism of action, sitravatinib demonstrated anti-tumor efficacy over a broad spectrum of human tumor xenograft models including robust cytoreductive anti-tumor activity in a subset of models exhibiting genetic alterations in RTK targets including MET, RET, FLT3 and others.

In a bidirectional permeability study with Caco-2 cell lines, sitravatinib was classified as a highly permeable compound and not a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Sitravatinib is an inhibitor of BCRP and P-gp transporters based on in vitro studies.

To assess CYP-mediated metabolism of sitravatinib, phenotyping of sitravatinib in human liver microsome CYPs and recombinant human CYP enzymes was performed. Results suggested that multiple enzymes, including CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP2E1, and CYP3A4, are involved in the metabolism of sitravatinib, with a low risk of any single CYP demonstrating a disproportionate contribution to sitravatinib metabolism.

The potential for sitravatinib to induce expression or activity of selected CYPs was investigated in primary cultures of cryopreserved human hepatocytes (PK-MGCD516-014) and in human liver microsomes (PK-MGCD516-013). For full details, please see the most current version of the Investigator's Brochure. The data overall suggest that sitravatinib is not expected to act as a CYP enzyme inducer at the concentration levels observed clinically. There was little or no evidence of direct inhibition of CYP1A2, CYP2A6, or CYP2E1 by sitravatinib. There was little or no evidence of time- or metabolism-dependent inhibition by sitravatinib of any of the CYP enzymes evaluated. Under the experimental conditions examined, sitravatinib demonstrated direct inhibition of CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5.

Based on the FDA Guidance for Industry on In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions (Jan 2020), the calculated ratio of intrinsic clearance values of a probe substrate for an enzymatic pathway in the absence and in the presence of the interacting drug (R1) for reversible inhibition for CYPs 2C8, 2C9, 2C19, 2D6, and 3A4 were equal to or greater than the 1.02 threshold, suggesting a potential for clinical drug interactions.

Preclinical studies suggest elimination of sitravatinib is mainly fecal, with very small (<1%) contribution of urinary excretion.

Using an ultra-centrifugation technique sitravatinib was 98.6% bound to human plasma proteins.

For additional information on sitravatinib pharmacology refer to the most current version of the Investigator's Brochure.

1.3.3 Sitravatinib Pharmacokinetics

Full details on sitravatinib pharmacokinetics are available in the most current version of the Investigator's Brochure.

After single dose administration of sitravatinib free base capsules, sitravatinib reaches peak concentration in a median time of approximately 3 to 9 hours. Exposure parameters (maximum concentration [C_{max}] and area under the curve [AUC]) were approximately dose proportional with single doses up to 200 mg. Median elimination half-life varies between approximately 43 and 58 hours after oral administration.

Mirati study 516-006 evaluated the relative bioavailability and PK of sitravatinib in plasma following single doses of sitravatinib free base and sitravatinib malate capsule formulations in healthy subjects in a 2-part, open-label, crossover study. Part 1 enrolled 16 healthy subjects and assessed the relative bioavailability and PK of a single oral dose of 80 mg sitravatinib free base capsule formulation and single oral dose of 80 mg sitravatinib malate capsule formulation. Bioavailability (as measured by C_{max}, $AUC_{0-\infty}$ and $AUC_{0-t)}$ was approximately 30% higher for the malate capsule formulation than the free base capsule formulation. Part 2 enrolled 26 healthy subjects and assessed the relative bioavailability and PK of a single dose of 120 mg sitravatinib free base capsule formulation and single oral dose of 100 mg sitravatinib malate capsule formulation. The geometric least squares (LS) means ratios (90% CI) of sitravatinib $AUC_{0-\infty}$, $AUC_{0-t,}$ and C_{max} for the 100 mg malate capsule formulation and the 120 mg free base formulation were 98.9% (91.8%, 106.6%), 98.8% (91.6%, 106.5%), and 102.4% (92.9%, 112.7%), respectively, demonstrating bioequivalence.

1.3.4 Sitravatinib Preclinical Studies

1.3.4.1 Sitravatinib

The anti-tumor efficacy of sitravatinib was evaluated in a variety of human tumor xenograft models (total of 17) representative of cancer indications in which dysregulation of target RTKs is implicated. Sitravatinib demonstrated significant anti-tumor efficacy (tumor regression or tumor growth inhibition vs. vehicle control) across all models evaluated at dose levels ranging from 1.25 to 20 mg/kg/day depending on the model. Anti-tumor efficacy was generally dose- dependent for models for which multiple dose levels were evaluated. Sitravatinib was generally well tolerated with minimal overt toxicity or body weight loss at dose levels up to 20 mg/kg/day for up to 18 days of administration. The 20 mg/kg/day dose

level was utilized as the maximum dose for comparative purposes across models utilized for efficacy studies. At this dose, anti-tumor efficacy ranged from partial growth inhibition to robust cytoreductive anti-tumor activity/tumor regression, with the minimum tumor growth inhibition observed being 77% (DU145 prostate and HCT-116 colon), which was statistically significant. Sitravatinib demonstrated near complete tumor growth inhibition (>90% inhibition) in the majority of models evaluated at the 20 mg/kg/day dose with multiple models exhibiting frank tumor regressions at this dose level.

Sitravatinib also demonstrated significant and robust anti-tumor efficacy at lower dose levels including the observation of tumor regression of the MKN45 and CTG-0838 models at 10 mg/kg/day and COLO205 model at 5 mg/kg/day indicating cytoreductive anti-tumor activity can be elicited at lower dose levels. Even at dose levels as low as 5 mg/kg/day sitravatinib demonstrated significant and robust TGI ranging from 47-101% in several models.

1.3.4.2 Sitravatinib plus Immunotherapy

Sitravatinib was evaluated in combination with a mouse surrogate anti PD-1 antibody in the CT26 syngeneic mouse tumor model. Treatment with sitravatinib or an anti-mouse PD-1 antibody resulted in limited growth delay effects whereas the combination led to dramatic and statistically significant reduction in tumor volume and sustained growth suppression compared to single agent and vehicle controls. Sitravatinib was evaluated in additional preclinical models in vitro and in vivo(16). Sitravatinib reduced immunosuppressive cell populations in vivo, including monocytic MDSCs and M2-polarized macrophages, increased intra-tumoral and circulating CD4+ and CD8+ populations, and augmented the effect of anti-PD-1 therapy. A subset of combination-treated mice had a complete remission and when these animals were re-implanted with tumor cell inoculum, no tumors formed, in contrast to tumor implantation in treatment naïve mice.

A similar approach was taken to evaluate the efficacy of sitravatinib alone or in combination with anti-PD-1 or anti-PD-L1 in the inhibition of MC38 colon cancer tumor growth (Rothlin-Ghosh lab, unpublished results). Sitravatinib (10mg/kg/day) potently suppressed tumor growth. While all control, vehicle treated-mice reached the end point (defined as tumors reaching a size of 1000mm^3) before day 40, 100% of mice treated with sitravatinib alone survived beyond 80 days and tumors were significantly reduced in size. Furthermore, sitravatinib (10mg/kg/day) was administered in combination with anti-PD-1 (5mg/kg/twice a week) or anti-PD-L1 (10mg/kg/twice a week) in the MC38 model. It should be noted that the doses chosen for anti-PD1 and anti-PD-L1 were below their IC50. Anti-PD-1 alone or anti-

PD-L1 alone, at these doses, did not show statistically significant differences from vehicle alone in tumor growth or survival. Sub-therapeutic doses were chosen to allow for the testing of any potential synergism upon combination with sitravatinib. When sitravatinib (10mg/kg/day) was administered in combination with anti-PD-1 (5mg/kg/twice a week) or anti-PD-L1 (10mg/kg/twice a week), tumor sizes were significantly smaller than when mice were treated with sitravatinib (10mg/kg/day) alone. Finally, depletion of $CD8^+$ T cells partially reversed the effect of sitravatinib (10mg/kg/day) on tumor growth. Sitravatinib treatment (10mg/kg/day) in $CD8^+$ T cell-depleted mice were less effective than immunocompetent mice (isotype treated), indicating that $CD8^+$ T cells, at least in part, mediate the beneficial effects of sitravatinib.

Collectively, these data illustrate broad anti-tumor activity of sitravatinib across a diverse set of human tumor xenograft models over an extensive dose range. In addition, these data suggest that concurrent treatment with sitravatinib may enhance the activity of anti-PD-1 therapy.

Additional details of preclinical sitravatinib studies can be found in the most current version of the Investigator's Brochure.

1.3.5 Clinical Experience with Sitravatinib

1.3.5.1 Sitravatinib Clinical Safety Experience

Sitravatinib has been administered to cancer patients in multiple clinical studies, including Phase 1 and 2 studies as a single-agent and in combination with other anticancer therapies in non-squamous non-small cell lung cancer (NSCLC), urothelial cancer (UC), renal cell carcinoma (RCC), and hepatocellular carcinoma (HCC), among other malignancies. In addition, sitravatinib in combination with nivolumab is being evaluated in a Phase 3 study in non-squamous NSCLC.

As of 26 Jun 2021, safety data are available for a total of 1106 subjects with advanced solid malignancies treated with sitravatinib, either as a single agent (n = 220), in combination with the PD-1 inhibitor nivolumab (n = 565), combination with ipilimumab/nivolumab (n=10), combination with pembrolizumab/EV (n=13) or in combination with tislelizumab (n = 300).

Among the 1106 subjects with solid malignancies who were treated with sitravatinib, 1012 (92%) experienced at least one sitravatinib-related AE. Among the 1106 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 was lipase increased in 5 subjects (0.5%). Sitravatinib-related Grade 5 AEs were reported in12 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.

For full details and most up to date information regarding safety data please see the most current version of the Investigator's Brochure.

1.3.5.2 Sitravatinib Clinical Efficacy in NSCLC Patients

Study MRTX-500 is a Phase 2 randomized trial which evaluated the efficacy and safety of the combination of sitravatinib and nivolumab versus docetaxel in patients who had progressed on or after checkpoint inhibitor treatment (CIT). Enrollment was stratified by prior outcome of treatment with a checkpoint inhibitor: those with prior clinical benefit (PCB) or no prior clinical benefit (NPCB) to prior CIT. Patients who were CIT-naïve were stratified according to their PD-L1 status: no/low PD-L1 expression or high PD-L1 expression. There was no limit to the number of prior therapies. Patients in the PCB stratum experienced clinical benefit (RECIST confirmed CR or PR or stable disease for at least 12 weeks) on their prior CIT. Data as of September 2019 included 79 patients enrolled into the PCB stratum of MRTX-500. The preliminary median overall survival for this stratum was 15.6 months. Fifty-four patients were evaluable for response; 8 patients had a confirmed response (2 CR, 6 PR). The median duration of response was 170 days (range: 64, NA). As of 26 Jun 2020, a total of 204 subjects have been enrolled, and 200 have received at least one dose of sitravatinib plus nivolumab.

A Phase 3 randomized trial was initiated in 2019 comparing the sitravatinib and nivolumab combination against docetaxel in checkpoint inhibitor-refractory NSCLC patients. This Phase 3 trial is currently enrolling and as of 26 Jun 2020, a total of 65 subjects have been randomized in the study, and 60 have received at least one dose of study treatment.

2 Study Rationale/Significance

2.1 Problem Statement

PD1/PD-L1 axis inhibitors have revolutionized the treatment of lung cancer by offering many patients significantly prolonged responses and improved overall survival. However, a significant subset of patients do not respond to first line treatment with immune checkpoint agents, either alone or in combination with chemotherapy. Additional approaches, such as combination with other drugs that target immune pathways, are needed to improve and prolong initial responses to checkpoint therapy.

2.2 Study Rationale

2.2.1 Rationale for Combination of Sitravatinib/Pembrolizumab

A logical step towards improving outcomes of immune therapy treatment is the use of combinations of agents that have both immune modulatory and anti-tumor properties and that target the molecular and cellular mechanisms seen in checkpoint inhibitor resistance.

Sitravatinib is a novel spectrum selective oral tyrosine kinase inhibitor, which targets the TAM family of RTKs as well as VEGFR2, KIT, RET and MET. Based on pre-clinical research at Yale and elsewhere, the TAM family of receptor tyrosine kinases (RTKs), including TYRO3, AXL and MERTK are one target that has emerged as a key modulator of the innate immune response(12). They are overexpressed in multiple types of cancer, including lung (overexpression tends to portend a worse prognosis(14)), and are also expressed on many cells of the innate immune system including macrophages, dendritic cells and NK cells (17). TAM RTKs are thought to serve as “innate immune checkpoints”, playing an important role in maintaining the immunosuppressive tumor microenvironment (TME) (12). This immune checkpoint function of TAM RTKs is achieved through several mechanisms, including suppression of dendritic cell function (18) and downstream regulation of cytokine release to favor an “anti-inflammatory” TME. The latter leads to a shift in macrophage phenotype (19, 20), further suppressing the release of pro-inflammatory cytokines (IL-12, IL-6, TNF) and enhancing the production of others (IL-10, IL-4, TGF-beta) to create a more pro-tumor environment (12). The inhibition of the TAM family RTKs would thus be expected to shift production towards a more pro-inflammatory cytokine milieu, which in turn supports response of cytotoxic T lymphocytes.

The addition of a TAM inhibitor would therefore be expected to augment the effects of PD-1 axis inhibitors by altering the TME in favor of anti-tumor activity, as well as promoting the anti-tumoral T-cell response which is unleashed through inhibition of the PD-1/PD-L1 pathway.

2.2.2 Rationale for Selected Study Population

The purpose of this study is to evaluate the combination of sitravatinib and pembrolizumab in the first-line treatment of NSCLC. Pembrolizumab is currently FDA-approved for first-line treatment of previously-untreated patients with stage IV NSCLC with PD-L1 expression ≥ 1% based on an improvement in overall survival compared to chemotherapy, however the response rate with pembrolizumab in this trial was only 27%. While the combination sitravatinib and a PD-L1 inhibitor has been studied in the second-line treatment of metastatic NSCLC, this regimen has not been evaluated in treatment naïve patients. Patients with NSCLC who are treatment naïve may have a higher response rate with the combination of sitravatinib and pembrolizumab compared to treatment with immunotherapy alone. In addition, correlative studies performed on treatment naive patients will allow for better understanding of sitravatinib's mechanism of action and help to characterize any molecular signatures associated with sitravatinib treatment and perhaps identify predictive biomarkers as well.

2.2.3 Rationale for Regimen Dosing/Schedule

Pharmacology and pharmacokinetics of sitravatinib has been discussed separately in Sections 1.3.2 and 1.3.3. Current recommended dosing of sitravatinib is 100mg daily of the sitravatinib malate capsule formulation based on results of Study 516-006, which showed equivalence of this dose to the previously used dose of 120mg sitravatinib free base capsule formulation.

100mg oral dose of sitravatinib malate capsule formulation will be administered as a continuous regimen expressed in 21-day cycles (based on the standard pembrolizumab schedule of q3 week administration). Pembrolizumab dosing will be a standard dose of 200mg IV every 3 weeks.

2.3 Potential Risks

Risks associated with this trial are those posed by use of the drugs sitravatinib and pembrolizumab, both alone and in combination. For details of pembrolizumab associated

risks, please see updated US Package Insert. Sitravatinib is a non-FDA approved novel therapy and details of potential risks associated with this drug can be found in the most current version of the Sitravatinib Investigator's Brochure. The potential exists for toxicity to be observed with increased severity or frequency during use of the combined agents. Data outlining the adverse events observed in combination studies with sitravatinib and PD-L1 inhibitors can be found in the most current version of the Investigator's Brochure. Close monitoring for safety and adverse events will be performed as described in Section 7.2.

There is additionally some risk associated with study-mandated procedures, including tissue biopsy.

2.4 Potential Benefits

Patients enrolled in this study may clinically benefit from the novel combination of sitravatinib and pembrolizumab. However, no individual patient can be guaranteed to derive benefit from participation in this trial.

Multiple correlative studies have been planned to help better understand the molecular and cellular actions of sitravatinib in vivo, and to evaluate for a potential molecular signature which may help predict response to this combination. Increased knowledge of cancer biology and mechanisms of treatment is a benefit to society at large.

3 Study Objectives and Hypotheses

3.1 Primary Objective and Hypothesis

(1) Primary Objective: To evaluate the efficacy of sitravatinib in combination with pembrolizumab in the front-line treatment of patients with advanced non-squamous PD-L1 positive NSCLC by measuring Objective Response Rate (ORR).

Hypothesis: Treatment with the novel combination of sitravatinib and pembrolizumab will improve ORR in this population.

3.2 Secondary Objectives and Hypotheses

(1) Objective: To evaluate other measures of efficacy including Overall Survival (OS), Progression Free Survival (PFS), Duration of Response (DOR) and Clinical Benefit Rate (CBR) of sitravatinib/pembrolizumab in the first-line setting for patients with PD-L1 positive non-squamous NSCLC.

Hypothesis: The combination of sitravatinib and pembrolizumab will improve OS, PFS, DOR, and CBR for patients with metastatic PD-L1 positive non-squamous NSCLC.

(2) Objective: To evaluate the toxicity profile and tolerability of sitravatinib/pembrolizumab combination in treatment-naïve patients with advanced PD-L1 positive non-squamous NSCLC.

Hypothesis: The combination of sitravatinib and pembrolizumab will be safe and tolerable in treatment-naïve patients with PD-L1 positive non-squamous metastatic NSCLC.

3.3 Exploratory Objectives and Hypotheses

(1) Objective: To evaluate ORR, OS, PFS, DOR, CBR in patients with treatment naïve advanced PD-L1 positive NSCLC who receive a 3 week pembrolizumab run-in followed by treatment with pembrolizumab/sitravatinib combination therapy.

Hypothesis: The combination of pembrolizumab/sitravatinib with a pembrolizumab run-in will improve clinical outcomes in patients with treatment naïve, metastatic PD-L1 positive non-squamous NSCLC.

(2) Objective: To evaluate CNS activity of the combination of sitravatinib and pembrolizumab by measuring intracranial ORR (iORR) and intracranial duration of response (iDOR) in patients with baseline CNS disease in the main study population, and intracranial progression-free survival (iPFS) in all patients.

Hypothesis: The combination of pembrolizumab/sitravatinib will result in improved iORR, iDOR, and iPFS.

(3) Objective: To study correlates of the adaptive and innate immune responses induced by sitravatinib and pembrolizumab treatment in both tumor tissue and peripheral blood.

Hypothesis: The combination of pembrolizumab with sitravatinib will increase the percentage of CD68+HLA-DR+CD163- myeloid cells as well as the percentage of effector CD3+GranzymeB+Ki67+ T cells in the tumor microenvironment (TME). The percentage change upon treatment with pembrolizumab + sitravatinib will be greater in patients receiving the combination than in patients treated with pembrolizumab alone.

The above-mentioned changes will be observed in samples with >50% AXL^+ and $MERTK^+$ $CD68^+$ myeloid cells before treatment and AXL and MERTK expression will inversely correlate with percentage of effector $CD8^+$ T cells and positively with $FOXP3^+$ T regulatory cells. Upon treatment, the percentage of effector $CD8^+$ T cells are expected to increase with a concomitant reduction in $FOXP3^+$ T regulatory cells.

There will be gene expression changes in myeloid and T cell populations following pembrolizumab + sitravatinib treatment as detected by single- cell RNA sequencing in CD45+ cells in the tumor microenvironment (TME). Similar gene expression changes are expected to occur in myeloid and T cell populations with pembrolizumab + sitravatinib treatment versus pembrolizumab alone. Single-cell RNA sequencing, being an unbiased genome-wide transcriptome analyses, may reveal novel population-level complexities and unique gene expression markers associated with sitravatinib + pembrolizumab treatment compared with baseline or pembrolizumab alone.

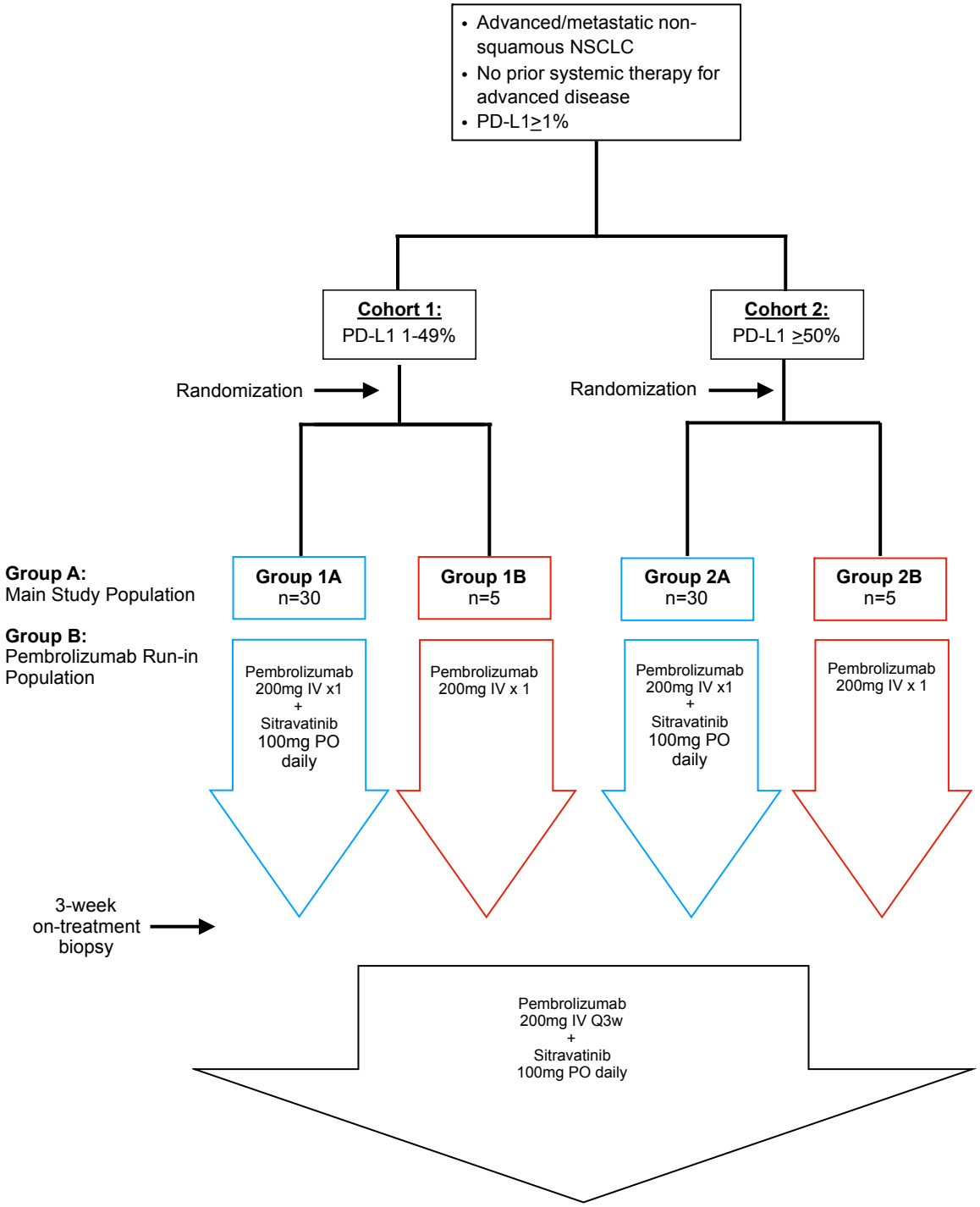
Corresponding mRNA changes are also expected in PBMCs in the peripheral blood as evaluated by bulk single cell and bulk RNA sequencing. These experiments may reveal surrogate peripheral blood predictive biomarkers of sitravatinib + pembrolizumab treatment.

(4) Objective: To explore the association between tumor immune contexture and clinical benefit to sitravatinib and pembrolizumab

Hypothesis: Changes observed in innate and adaptive immune responses with pembrolizumab/sitravatinib treatment will positively correlate with improved clinical outcomes.

4 Trial Design

4.1 Trial Schema



4.2 General Design Description

This is an open-label multicohort Phase 2 study to evaluate the efficacy and safety of pembrolizumab combined with the investigational drug sitravatinib in the first-line treatment of advanced, non-squamous, PD-L1 positive NSCLC. For clinical analysis, there will be two patient cohorts defined by PD-L1 status: Cohort 1 for patients with PD-L1 Tumor Proportion Score (TPS) 1-49% and Cohort 2 for patients with (TPS)≥50%, using the FDA approved 22c3 PD-L1 IHC assay or a local assay performed in a CLIA facility. A Simon's two-stage design will be used to evaluate the efficacy of sitravatinib in combination with pembrolizumab for each cohort separately. There will be two treatment groups within each cohort: the "main study population" (Group A) in which patients will receive pembrolizumab plus sitravatinib beginning on cycle 1 day 1 (C1D1), and a "pembrolizumab run-in population" (Group B) in which patients will receive pembrolizumab alone for one dose followed by treatment with pembrolizumab plus sitravatinib beginning C2D1.

Potentially eligible patients will undergo screening after informed consent. If they do not have archival tissue or PD-L1 status available, they will need to undergo pre-treatment biopsy. If patients require pre-treatment biopsy for other clinical reasons after enrollment, this tissue will also be collected for research purposes. Patients will then be stratified into cohorts by PD-L1 status (as above), before being randomized to either Group A (main study population) or Group B (pembrolizumab run-in population). The randomized portion of the study will be performed exclusively at Yale. Once 5 patients in each cohort have been randomized to Group B, all subsequent patients will be enrolled to Group A. Patients in Groups 1A and 2A will begin treatment with pembrolizumab IV 200mg every 3 weeks plus sitravatinib PO 100mg daily on C1D1 of the study. Patients in Groups 1B and 2B will begin pembrolizumab 200mg IV on study C1D1 and sitravatinib PO 100mg daily will be added on C2D1. All patients will undergo an on-treatment study biopsy within 7 days prior to C2D1 of the study. Research bloods will be drawn on a subset of patients prior to treatment and at intervals as specified in Study Calendars (Section 6.1).

Efficacy evaluations will be performed at 6 week intervals for the first 3 months, then 9 week intervals for the next 9 months and 12 week intervals thereafter. Efficacy evaluations will include CT scans of the chest/abdomen (and pelvis if indicated) and MRI brain if indicated (see Section 7.1.1) as well as survival assessments (see Section 7.1.2). Toxicity grading will occur as per CTCAE v5.0, with treatment interruptions or discontinuation of trial drugs as detailed in Sections 5.1.3 and 5.2.3. Treatment will continue for two years or until

progression of disease, unacceptable toxicity, patient refusal or death. Patients experiencing clinical benefit in the judgment of the Treating Investigator may continue study treatment beyond disease progression as detailed in Section 6.8. Post-treatment disease assessment will continue until objective disease progression or start of subsequent anti-cancer therapy, whichever is sooner.

4.3 Study Date Range and Duration

This study is expected to last for 48 months including 24 months of recruitment and 24 months of follow up.

4.4 Endpoints

4.4.1 Primary Endpoint

(1) Objective Response Rate (ORR): The primary endpoint for this study will be ORR as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) in the main study population.

4.4.2 Secondary Endpoints

(1) Overall Survival (OS) in the main study population (Section 9.2.3).

(2) Progression Free Survival (PFS) in the main study population (Section 9.2.3).

(3) Duration of Response (DOR) in the main study population (Section 9.2.4)

(4) Clinical Benefit Rate (CBR) in the main study population (Section 9.2.5)

(5) Adverse events in all groups. Toxicity will be evaluated as detailed in Section 7.2 at regular intervals according to the Study Calendars (Section 6.1). Severity will be graded as per CTCAE v.5.0.

4.4.3 Exploratory Endpoints

(1) ORR, PFS, OS, DOR in the pembrolizumab run-in population. These results will not be included in the analysis of the main study population, but will be used to generate a preliminary assessment of benefit with this strategy.

(2) Intracranial Objective Response (iORR) and intracranial Duration of Response (iDOR) in patients with baseline CNS disease (Sections 9.2.6 and 9.2.7).

(3) Intracranial Progression Free Survival (iPFS) in all patients (Section 9.2.8).

(4) Correlative Endpoints:

a. Percentage of activated myeloid cells, effector T cells, and AXL+/MERTK+ macrophages in the TME as assessed by multiplex qualitative immunofluorescence in pre- and post-treatment tissue samples in both the main study population and pembrolizumab run-in population.
b. Clinical response as correlated to immune populations present in baseline samples and immune cell population changes induced by therapy
c. Immune cell population changes in the TME as defined by changes in population heterogeneity detected by single cell RNA in pre- and post-treatment tissue samples in both the main study population and pembrolizumab run-in population
d. Gene expression changes in peripheral blood mononuclear cells in pre- and post-treatment tissue samples in both the main study population and pembrolizumab run-in population.
e. Percentage of $CD8^+$ T cells and $FOXP3^+$ T regulatory cells in pre- and post-treatment tissue samples in both the main study population and pembrolizumab run-in population.
f. The percentage of $CD8^+$ T cells and $FOXP3^+$ T regulatory cells correlated with the percentage of activated myeloid cells and AXL+/MERTK+ macrophages in the TME in pre- and post-treatment tissue samples in both the main study population and pembrolizumab run-in population.

4.4.4 Rationale for Endpoints

4.4.4.1 Rationale for Clinical Endpoints

The primary purpose of this trial is to evaluate the clinical efficacy of sitravatinib and pembrolizumab in the first line setting for patients with metastatic PD-L1 positive non-squamous NSCLC. There is no standard of care comparator arm in this study, however there are well established historical ORR for patients treated with pembrolizumab monotherapy. Our study is powered to detect a 25% increase in ORR for the combination of sitravatinib/pembrolizumab in Groups 1A and 2A (main study population) compared with historical ORR seen with pembrolizumab monotherapy. OS and PFS in Groups 1A and 2A

will also be determined as secondary endpoints. Safety and toxicity of this combination have been evaluated in the second line setting for NSCLC but have not been evaluated in the first-line setting. As such, adverse events will also a secondary endpoint in this trial.

Clinical outcomes in Groups 1B and 2B will not be included in analysis of the main study (given limited sample size) but will be assessed as an exploratory endpoint. Outcomes for these patients will be used to descriptively summarize clinical benefit with a pembrolizumab run-in followed by combination therapy, as well as to correlate outcomes with any observed immunologic and molecular changes found in tissue and blood.

4.4.4.2 Rationale for Exploratory Endpoints/Correlative Studies

Planned assessments of blood and tumor tissue including quantitative immunofluorescence and gene expression analysis will be performed with the aim of better understanding the underlying mechanisms of this drug combination. Analysis is also hoped to reveal predictive biomarkers which may help assess the patients that are most likely to achieve clinical benefit from this drug combination.

4.5 Study Population

4.5.1 Number of Participants

This study will plan to enroll a maximum of 35 evaluable patients to each cohort for a total of 70 study participants. 30 patients from each cohort will be enrolled to Group A and 5 patients from each cohort will be enrolled to Group B (see Trial Schema Section 4.1). In order to accrue 70 evaluable patients, we expect to screen 80 patients (~10% ineligibility rate). The randomized portion of the study will be performed exclusively at Yale, after which time we expect a roughly equal enrollment between the 2 sites.

4.5.2 Inclusion Criteria:

In order to be to be eligible to participate in this study, an individual must meet <u>all</u> of the following criteria:

1. Histologically or cytologically confirmed non-squamous NSCLC that is metastatic (Stage IV), recurrent, or unresectable locally advanced (Stage IIIB/IIIC) disease, not amenable to treatment with curative intent.

2. No prior systemic therapy for advanced disease. Prior chemotherapy for local or locally advanced disease is allowed if completed >6 months prior to trial enrollment. Prior immunotherapy is not allowed.
3. PD-L1 ≥ 1% using the 22c3 PD-L1 IHC assay or a local assay performed in a CLIA facility
4. Age ≥ 18 years.
5. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
6. Life expectancy of at least 3 months.
7. Measurable disease as per RECIST v1.1
8. Adequate bone marrow and organ function demonstrated by:
    a. Absolute neutrophil count ≥1,500/mm^3 (1.5×10^9/L).
    b. Hemoglobin ≥ 8.0 g/dL not dependent on transfusion support.
    c. Platelet count ≥ 75×10^9/L (≥ 75,000 per mm^3).
    d. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 1.5 × ULN without liver metastases; < 5.0 x ULN if documented liver metastases
    e. Serum total bilirubin ≤ ULN, or for patients with potential Gilbert's, direct bilirubin ≤ ULN
    f. Calculated creatinine clearance ≥ 40 mL/min, using the Cockcroft-Gault formula.
9. Women of child-bearing potential (WOCBP) or men whose partner is a WOCBP agrees to use contraception while participating in this study, and for a period of 6 months following termination of study treatment.
10. Completed informed consent process, including signing IRB approved informed consent form.
11. Willing to comply with clinical trial instructions and requirements.
12. Willing to undergo an on-treatment biopsy with an appropriate biopsy site identified prior to treatment initiation (see 6.5.1).

4.5.3 Exclusion Criteria:

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

1. Symptomatic or untreated brain metastases ≥ 2cm in diameter. Patients with brain lesions that are adequately treated with local therapy (i.e. radiation therapy) and neurologically stable without the need for corticosteroids for at least 2 weeks prior to enrollment are allowed. Patients with brain lesions that are asymptomatic, smaller than

2cm, in non-critical regions of the brain and not requiring corticosteroids for at least 2 weeks prior to enrollment may be eligible after review with the Sponsor Investigator.

2. Leptomeningeal disease
3. Known mutations/alterations in EGFR, ROS1, ALK, or BRAF
4. Any prior treatment with checkpoint inhibitor therapy or other immunotherapy agents
5. Any prior treatment with therapy having the same mechanism of action as sitravatinib (e.g., tyrosine kinase inhibitor with a similar target profile or bevacizumab/ramucirumab)
6. Active or prior documented autoimmune disease within the past 2 years (note: patients with type 1 diabetes, vitiligo, Graves' disease, hypothyroidism due to an autoimmune condition only requiring hormone replacement, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded).
7. Active or prior immunocompromising conditions, including use of immunosuppressive medication within 2 weeks of enrollment. This does not include topical, intranasal or inhaled steroids with minimal systemic absorption or systemic corticosteroids at physiologic doses not to exceed 10mg/day of prednisone or equivalent. Use of higher dose corticosteroids for short/defined course (ie prophylaxis in patients with contrast dye allergy) is also allowed if indicated.
8. Uncontrolled HIV. Patients with HIV may be eligible if they meet the following criteria:
    a. CD4+ T cell count>350 cell/uL
    b. No history of AIDS-defining opportunistic infection within the past 12 months
    c. Currently tolerating treatment with ART for at least 4 weeks prior to enrollment, with HIV viral load <400 copies/mL
    d. Patients on specific ART drugs with possibility for drug-drug interaction with sitravatinib may be excluded (see appendix 5).
9. Active hepatitis C (HCV) infection. Patients with a history of HCV may be eligible if they have completed curative antiviral treatment with undetectable HCV viral load and liver function tests are otherwise within acceptable limits (as described in Section 4.5.2). Patients with chronic Hepatitis B (HBV) infection are not excluded if liver function is within acceptable limits, but should be evaluated for reactivation risk and started on suppressive antiviral therapy prior to enrollment if appropriate.
10. History of stroke or transient ischemic attack within the previous 6 months.

11. History of life threatening venous thromboembolic event (such as hemodynamically significant pulmonary embolism) or any arterial thrombotic event within the previous 6 months. Patients with non-life threatening venous thromboembolic events are not excluded and should be managed with anti-coagulation as per standard institutional practice.
12. Any of the following cardiac abnormalities:
    a. Unstable angina pectoris within the past 6 months.
    b. Congestive heart failure ≥ NYHA Class 3 within the past 6 months.
    c. Prolonged QTc on electrocardiogram >500 milliseconds.
    d. Left ventricular ejection fraction (LVEF) < 40%.
13. Uncontrolled hypertension (>150mm Hg or >100mm Hg diastolic) on multiple observations despite standard of care treatment
14. Major surgery within 4 weeks of the date of randomization.
15. History of significant hemoptysis or hemorrhage within 4 weeks of the date of randomization.
16. Known or suspected presence of another malignancy that could be mistaken for the malignancy under study during disease assessments.
17. Has received a live vaccine within 30 days prior to the first dose of trial treatment.
18. Pregnancy. WOCBP must have a negative serum or urine pregnancy test documented within the screening period prior to the date of randomization.
19. Breast-feeding or planning to breast-feed during the study or within 30 days following the last dose of sitravatinib and within 5 months following the last dose of pembrolizumab.
20. Any serious illness, uncontrolled inter-current illness, psychiatric illness, active or uncontrolled infection, or other medical history, including laboratory results, which, in the Investigator's opinion, would be likely to interfere with the patient's participation in the study, or with the interpretation of the results.

4.5.4 Life Style Guidelines

Patients who are biologically capable of having children and sexually active must agree to use at least 2 acceptable methods of birth control, one of which must be highly effective for the duration of the treatment period and for at least 6 months after the last dose of study

treatment. The Investigator will counsel the patient on selection of contraception method and instruct the patient in its consistent and correct use.

Examples of acceptable birth control methods considered highly effective are the following:

1. Oral, inserted, injected or implanted hormonal methods of contraception, provided it has been used for an adequate period of time to ensure effectiveness.
2. Correctly placed copper containing intrauterine device (IUD).
3. Male sterilization with confirmed absence of sperm in the post-vasectomy ejaculate.
4. Bilateral tubal ligation or bilateral salpingectomy.
5. Sexual abstinence (in the context of this protocol, sexual abstinence is considered a highly effective method of birth control only if refraining completely from heterosexual intercourse during the entire period of risk (i.e., during study treatment, including during temporary breaks from treatment, and for at least 6 months after stopping study treatment)).

Acceptable birth control methods not considered highly effective include the following:

1. Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
2. Male or female condom with spermicide
3. Cap, diaphragm, or sponge with spermicide

The Investigator will instruct the patient to call immediately if the selected birth control method is discontinued or if pregnancy is known or suspected.

Note: Women are considered post-menopausal and/or not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 months ago. In case of any ambiguity, the reproductive status of the woman should be confirmed by hormone level assessment.

4.6 Method of Assignment/Randomization

Following review of all screening procedures, patient eligibility will be confirmed by appropriately qualified staff at the investigational site. Patients will be enrolled to 1 of the 2 cohorts based on PD-L1 status, TPS ≥ 50% and TPS 1-49%. Within each cohort, patients will initially be randomized 1:1 to either the Group A ("main study population") or Group B ("pembrolizumab run-in population"). Randomization in each cohort will continue until 5 patients have been enrolled to Group 1B and 5 patients have been enrolled to Group 2B. The randomized portion of the study will be performed exclusively at Yale. All subsequent patients will be assigned (not randomized) to Group A. This study will not be blinded.

5 Study Treatments

The investigational treatments to be used in this trial are the novel drug sitravatinib and FDA approved therapy pembrolizumab.

5.1 Sitravatinib

Sitravatinib is a spectrum-selective RTK inhibitor that acts on several closely related RTKs including the TAM family (Tyro3/Axl/MERTK), VEGFR2, KIT, and MET. This drug is currently experimental and is not FDA approved. It is administered as a daily oral medication.

5.1.1 Sitravatinib Formulation, Packing and Storage

The sitravatinib formulation used in this protocol is the malate salt capsule product which consists of a blend of sitravatinib malate salt drug substance, microcrystalline cellulose, mannitol, colloidal silicon dioxide, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate. The blend is filled into hard gelatin capsules.

Sitravatinib drug product is packaged in high-density polyethylene (HDPE), white opaque, round 60 cc bottles. A tamper-proof heat induction seal and a child-resistant closure are used. The provided bottles may be labeled for specific patient use and given to the patient. Sitravatinib medication labels comply with the legal requirements of the US.

Investigational clinical trial material must be stored in an area that is secure, with limited access and monitored for temperature using a calibrated thermostat or thermometer. 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. Sitravatinib capsules should be stored under the conditions stated on the container labels and the Pharmacy Study Manual.

Please Refer to the Pharmacy Study Manual for further details.

5.1.2 Sitravatinib Schedule and Administration

Sitravatinib capsules will be administered orally, once per day (QD), as a continuous regimen expressed in 21-day cycles. The starting dose of the sitravatinib malate capsule formulation is 100 mg QD. For patients in Groups 1A and 2A (main study population), sitravatinib dosing will begin on C1D1. For patients in Groups 1B and 2B (pembrolizumab run-in population) dosing of sitravatinib will begin on C2D1 of the study.

The following guidelines should be followed for sitravatinib administration:

- Dosing in the morning is preferred.
- Capsules should be taken on an empty stomach (at least 2-hour fast before each dose and no food for a minimum of 1 hour after each dose) until notified otherwise by the Sponsor.
- Capsules should be taken with at least 240 mL (approximately 1 cup) of water.
- Patients should swallow the capsules whole and not chew them.
- If vomiting occurs after dosing, sitravatinib doses should not be replaced.
- Missed doses should be taken within 12 hours of the scheduled time and the next dose should be taken at its scheduled time.

Additional details are provided in the Pharmacy Study Manual.

5.1.3 Sitravatinib Dose Modification or Discontinuation

Depending on safety observations, the sitravatinib dose during subsequent cycles of treatment may be reduced as per *Table 1*. Indications for dose modification and treatment delay are discussed in Section 5.3.1 (Management of Sitravatinib Adverse Events). Once the dose has been reduced, re-escalation is generally not recommended but may be considered on a case-by-case basis after discussion with the Sponsor Investigator. If the administration of sitravatinib is interrupted for reasons other than toxicity then treatment with the study drug may be resumed at the same dose.

Although sitravatinib has not been associated with irAEs, it may potentiate the effect of pembrolizumab and contribute to irAEs. Therefore, for any AE that requires interruption of pembrolizumab, sitravatinib should also be interrupted until the event improves to Grade ≤1. Please see section 5.3.1 for management of sitravatinib in the case of irAEs.

In the case of an AE that can clearly be attributed to sitravatinib and is not immune-mediated (ie hypertension), dose reduction with continuous treatment is preferred over repeated dose interruption. If treatment with sitravatinib is delayed for ≥ 14 days due to AEs, then resumption will be at a reduced dose. If treatment with sitravatinib is withheld for ≥ 28 consecutive days due to AEs, then sitravatinib will be permanently discontinued unless reviewed and approved by the Sponsor Investigator. In the case of interruption or discontinuation of sitravatinib, pembrolizumab may be continued at the discretion of the Treating Investigator if the AE is attributed to sitravatinib alone. If pembrolizumab is discontinued due to toxicity, the continuation of sitravatinib as monotherapy may be considered once the AE improves to Grade ≤1 and following discussion with the Sponsor-Investigator.

Table 1: Sitravatinib Sequential Dose Reductions for Individual Patients on Malate Capsule Formulation

100 mg once daily
70 mg once daily
50 mg once daily
35 mg once daily

5.1.4 Sitravatinib Dispensing and Accountability

Dispensing of sitravatinib will be performed as per the Pharmacy Study Manual. Receipt and dispensing of study drug must be recorded by an authorized person at the study site. Study drug may not be used for any purpose other than that stated in the Protocol.

Patients will be asked to record their daily dosing in a pill dairy (Appendix 6). and report any missed doses or lost doses at the next clinic visit. Patients should be told to bring study

treatment bottle(s) (empty or not) and completed dosing diaries with them to the clinic visit for a compliance check and capsule count.

At the end of the study, all unused sitravatinib drug supplies must be destroyed in accordance with local Standard Operating Procedure, or returned to the manufacturer.

5.2 Pembrolizumab

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) is approved in the United Stated as monotherapy for the treatment of patients with unresectable or metastatic NSCLC and PD-L1 expression ≥1%.

5.2.1 Pembrolizumab Formulation, Packing and Storage

Pembrolizumab will be provided commercially for patients as an FDA approved therapy for treatment naïve patients with PD-L1 positive NSCLC.

Refer to the current pembrolizumab approved product insert for further details on formulation, packing and storage information.

5.2.2 Pembrolizumab Schedule and Administration

All patients will receive pembrolizumab 200mg administered as a 30 minute IV infusion every 3 weeks starting on study Day 1. Treatment will be continued for 35 cycles or until progression, unacceptable toxicity, withdrawal of consent or study end, whichever occurs first. Patients with progression of disease by RECIST v1.1 may be allowed to continue trial therapy as per Section 6.8 at the discretion of Sponsor Investigator.

Further administration details as per current pembrolizumab product label.

5.2.3 Pembrolizumab Dose Modification or Discontinuation

Interruption or discontinuation of pembrolizumab may be required for some toxicities as summarized in *Table 2*. Treatment of suspected pembrolizumab related adverse events is discussed in Section 5.3.3. Dose reductions of pembrolizumab are not allowed. Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not

related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor Investigator. The reason for interruption should be documented in the patient's study record.

Table 2: Dose Modification Guidelines for Drug-Related Adverse Events for Pembrolizumab

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[1]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when patients are clinically and metabolically stable.
Hypophysitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Withhold until clinically stable or permanently discontinue depending on severity	Permanently discontinue depending on severity.
Hyperthyroidism	3-4	Withhold until clinically stable or permanently discontinue depending on severity	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
Hypothyroidism	2-4	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
All Other Drug-Related Toxicity[2]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

[1] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[2] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

5.3 Management of Adverse Events

A complete review of adverse events should be conducted at each clinic visit with laboratory assessment as per Study Calendars (Section 6.1).

5.3.1 Sitravatinib-Related Adverse Events

5.3.1.1 General Management of Sitravatinib Related Non-Hematologic Toxicities

General management of non-hematologic sitravatinib related toxicities are summarized in *Table 3*. Symptomatic Grade 2 sitravatinib-related non-hematological adverse events occurring any time on study, particularly early in treatment, are managed using dose reduction to the next lower dose level, per the reduction schedule outlined in *Table 1*, rather than continued dosing until interruption becomes necessary.

Non-hematological toxicities ≥ Grade 3 and considered to be related to sitravatinib treatment will be managed with sitravatinib interruption, with or without dose reduction, until resolution of toxicity to ≤ Grade 1 or to baseline value. If the toxicity is adequately managed by routine supportive care (such as electrolyte supplementation), 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 as outlined in *Table 1*. Recurrence of a toxicity may be managed similarly. If treatment is interrupted for ≥ 28 days, sitravatinib will be permanently discontinued unless reviewed and approved by the Sponsor Investigator.

5.3.1.2 General Management of Sitravatinib Related Hematological Toxicities

Hematological toxicities are not a frequent cause of treatment interruption or discontinuation of sitravatinib treatment. Observed ≥ Grade 3 hematological events that are considered to be causally related to sitravatinib should initially be managed using treatment interruption until resolution of toxicity to ≤ Grade 2. In addition, dose reduction of sitravatinib will be implemented in the following cases:

- Grade 3 or 4 febrile neutropenia;
- Grade 4 neutropenia persisting for ≥ 8 days; or
- Grade 4 thrombocytopenia of any duration or Grade 3 thrombocytopenia with bleeding.

Table 3: Dose Modifications for Sitravatinib Toxicity

Toxicity	Grade	Treatment Delay	Dose Modification
General non-hematologic toxicity[1]	1	Not required	None
	2	Not required	Asymptomatic: None required
			Symptomatic: None required. Early dose reduction to the next lower dose level is recommended over treatment interruption.
	3-4	Hold until ≤ grade 1 or return to baseline	Resume at reduced dose. Exceptions presented in footnotes[2]
Hematologic toxicities	1-2	Not required	None
	3	Hold until ≤ grade 2	Reduce dose for grade 3 febrile neutropenia or grade 3 thrombocytopenia with bleeding
	4	Hold until ≤ grade 2	Reduce for grade 4 febrile neutropenia, grade 4 neutropenia lasting ≥8 days or grade 4 thrombocytopenia
Hypertension	1-2	Not required	None required
	3	Not clinically significant[3]: Not required	Decrease dose if unresponsive to anti-hypertensive treatment
		Clinically significant[3]: Hold until ≤ grade 2 or return to baseline	Resume at decreased dose level
	4	Discontinue	Discontinue
Transaminitis	1	Not required	None required
	2	Not required	Decrease by one dose level
	3-4	Hold until ≤ grade 1 or return to baseline	If resolution occurs within 29 days, decrease by 1 dose level. If no resolution within 29 days, discontinue sitravatinib

[1] Management of selected sitravatinib toxicities as per Section 5.3.2

[2] Patients may resume at the same dose in the following cases:

a. Grade 3 or 4 electrolyte abnormality that is not clinically complicated and resolves spontaneously or with conventional medical treatment within 72 hours;

b. Grade 3 amylase or lipase elevation that is not associated with symptoms or other clinical (e.g., electrolyte abnormalities, radiographic changes) manifestations of pancreatitis.

[3] Clinical significance is 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

5.3.2 Management of Selected Sitravatinib Adverse Events

Hypertension

Hypertension, including Grade 4 events, has been reported with sitravatinib. Anti-hypertensive therapy should be considered for patients with Grade 3 hypertension without clinically significant increases in blood pressure (BP). In cases of Grade 3 hypertension with clinically significant increases in blood pressure (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), sitravatinib dosing will be temporarily suspended until blood pressure is controlled. Treatment with sitravatinib may then resume at the lower dose level (*Table 3*). If significant hypertension recurs, options include change in medical management of the patient, reduction of sitravatinib dose, or discontinuation of study treatment, at the discretion of the Treating Investigator. In the event of Grade 4 hypertension, sitravatinib will be permanently discontinued (*Table 3*)

Palmar-Plantar Erythrodysesthesia

Palmar plantar erythrodysesthesia (PPE) has been reported as a dose limiting toxicity in the Phase 1 study of sitravatinib. Measures that can be taken to manage PPE 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.

Diarrhea

Diarrhea should be evaluated to determine whether it may be immune-mediated colitis due to pembrolizumab, related to sitravatinib, or due to another cause. Diarrhea has been reported with sitravatinib treatment, though the mechanism remains unclear. Patients should be counseled that diarrhea is a possible side effect and advised to take loperamide or a similar medication as needed if diarrhea due to sitravatinib develops. Any patients

developing dehydration or clinically significant electrolyte abnormalities due to sitravatinib should interrupt sitravatinib treatment, but treatment may be restarted once diarrhea is controlled. The diarrhea observed with sitravatinib generally improves within several days of interrupting study medication so discontinuation with close observation may help establish causality. If any features of the clinical presentation, including timing of presentation, failure to improve with dose interruption, laboratory or radiologic tests suggests the presence of immune-related colitis, all study medications should be withheld and treatment with immunosuppressive therapy considered as per Section 5.3.3.2.

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 suspension of treatment is recommended for patients developing clinically significant bleeding.

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. Patients with a history of VTE should be anticoagulated as per local standard of care. Treatment should be discontinued in subjects who develop clinically significant thromboembolic complications.

Thyroid Dysfunction Other than Immune-Related

Hypothyroidism and increases in thyroid-stimulating hormone (TSH) have been reported in patients taking sitravatinib. Patients diagnosed with hypothyroidism should be treated with thyroid replacement therapy and may continue treatment with sitravatinib.

Decreased Left Ventricular Ejection Fraction

Decreased LVEF has been reported with sitravatinib. In addition, decreases of LVEF to <50% on-study were observed in patients undergoing scheduled echocardiograms (ECHO) or multigated acquisition (MUGA) scans. The dose of sitravatinib should be interrupted and/or reduced in patients with an ejection fraction that has dropped ≥20% below baseline and is <50%.. Discontinuation should be considered for patients requiring acute hospitalization for treatment of congestive heart failure (CHF).

Proteinuria

Proteinuria has been observed with sitravatinib and described with other inhibitors of the VEGFR pathway. Urinalysis for urine protein should be performed prior to each cycle following the start of sitravatinib and as clinically warranted during treatment with sitravatinib. Subjects 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 ≥2 grams of proteinuria/24 hours and may be restarted when protein levels decrease to less than 2 grams/24 hours. Subjects who develop nephrotic syndrome should be withdrawn from treatment with sitravatinib.

Increased Transaminases

The management of increases in AST and ALT should be guided by the clinical judgment of the Treating Investigator, including an assessment of the most likely causative etiology, with special consideration given to the potential for immune-related hepatitis. Increased transaminases should be evaluated to determine whether confounding factors exist, such as viral infection, metastatic lesions or biliary obstruction. Increased transaminases have been observed in subjects 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.

For cases where transaminase increases are not likely to be immune-related, treatment management decisions should be made using the Treating Investigator's discretion in consideration of clinical factors. Recommended treatment modifications for sitravatinib are provided in *Table 3* . However, if any features of the clinical presentation, including timing of presentation, failure to improve with dose interruption, laboratory or radiologic tests suggests the presence of immune-related hepatitis, all study medications will be withheld and treatment with immunosuppressive therapy considered as detailed in management of pembrolizumab related adverse events (Section 5.3.3)

Increased Amylase and Lipase

Increased amylase and lipase have been observed in subjects treated with sitravatinib and 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 (eg, interruption or reduction) in cases of asymptomatic

amylase and/or lipase increases in the absence of other clinical evidence of pancreatitis (eg, symptoms, electrolyte abnormalities, radiographic changes) at the Treating Investigator's discretion. Sitravatinib should be interrupted for any grade pancreatitis and the subject managed according to standard-of-care. After resolution of pancreatitis, sitravatinib resumption is at the discretion of the Treating Investigator; if pancreatitis is assessed as sitravatinib treatment-related and treatment is resumed, a dose reduction is recommended.

Immune-Related Adverse Events (irAEs)

Single agent sitravatinib has not been associated with irAEs. However, the potential exists for irAEs associated with sitravatinib to contribute to irAEs associated with pembrolizumab treatment. In the event of a Grade 2 irAE during study treatment, administration of sitravatinib and pembrolizumab will be interrupted until the event stabilizes to Grade ≤1 (see Section 5.3.3 on pembrolizumab associated adverse event treatment). At the time of resumption of sitravatinib dosing, a dose reduction may be implemented at the discretion of the Treating Investigator.

Management of Grade 3 and 4 irAEs should be performed as in section on pembrolizumab related adverse events management (Section 5.3.3). Recurrent Grade 3, or any Grade 4, irAEs should generally be managed with permanent discontinuation of pembrolizumab, and temporary or permanent interruption of sitravatinib. Sitravatinib may be resumed at the same or lower dose at the discretion of the Treating Investigator once the event stabilizes to Grade ≤ 1.

5.3.3 Pembrolizumab-Related Adverse Events

5.3.3.1 General Management of Pembrolizumab-Related Adverse Events

Pembrolizumab related AE management is as per institutional standard of care, with the following recommended guidelines. Pembrolizumab must be withheld for certain drug-related toxicities and severe or life-threatening AEs as per *Table 2*. Subjects should receive appropriate supportive care measures as deemed necessary by the Treating Investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. These are guidelines and local standard of

care/institutional standards may be followed at the discretion of the Treating Investigator. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be irAEs. For guidelines regarding restarting pembrolizumab, please see *Table 2*.

5.3.3.2 Management of Selected Pembrolizumab-Related Adverse Events

Pneumonitis:

For Grade 2 events pembrolizumab should be held and treatment with corticosteroids initiated. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. For Grade 3-4 events, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed. Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

Diarrhea/Colitis:

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. GI consultation should be considered for Grade 2 or higher diarrhea/colitis. For Grade 2 diarrhea/colitis that persists greater than 3 days despite supportive treatment and anti-diarrheals, pembrolizumab should be held and oral steroids should be administered. For Grade 3 or 4 diarrhea/colitis, pembrolizumab should be held and IV or oral corticosteroids should be administered. For grade 3-4 diarrhea that persists > 4 days despite oral steroids, treat with intravenous steroids followed by high dose oral steroids. If not improving despite IV steroid administration, may also consider additional anti-inflammatory treatments. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

New Onset Type 1 diabetes mellitus (including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA):

For T1DM or Grade 3-4 Hyperglycemia associated with metabolic acidosis or ketonuria, initiation of insulin is recommended. Pembrolizumab may be held while glucose control is

obtained. Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

Hypophysitis:

For Grade 2 events, hold pembrolizumab, treat with corticosteroids and provide hormonal supplementation as appropriate. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. For Grade 3-4 events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

Hyperthyroidism or Hypothyroidism:

Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. For grade 2-4 hypothyroidism, thyroid hormone replacement therapy is indicated per standard of care. Pembrolizumab may be held if patients are severely symptomatic or show signs of myxedema For Grade 2 hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy. For Grade 3-4 hyperthyroidism, hold pembrolizumab and consider treatment with corticosteroids in addition to treatment with non-selective beta-blockers. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

Hepatitis:

For Grade 2 events, hold pembrolizumab and monitor liver function tests more frequently. Consider treatment with IV or oral corticosteroids if elevation persists for 3-5 days or if there are accompanying clinical symptoms. For Grade 3-4 events, hold pembrolizumab and treat with intravenous corticosteroids for 24 to 48 hours followed by high dose oral steroids. When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

Renal Failure or Nephritis:

For Grade 2 events, hold pembrolizumab and administer IV or oral corticosteroids. Consider nephrology consultation. For Grade 3-4 events, treat with IV corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Management of Infusion Reactions:

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. See *Table 6* below for treatment guidelines for patients who experience a transfusion reaction.

Table 6: Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion);	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	• NSAIDS • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	

5.4 Concomitant Therapies

5.4.1 Concomitant Medications

Prior medications (including chronically administered medication) used in the 28 days prior to signing consent will be reviewed and recorded. Patients may continue to use any ongoing medications not prohibited by the inclusion/exclusion criteria or treatment plan. Comprehensive list of medications to be used with caution or avoided are listed for sitravatinib in Appendix 5.

Anti-diarrheals: In general, patients should be counseled that diarrhea is a possible side effect of the study treatments and advised to take loperamide or a similar medication as needed if diarrhea develops.

Anti-Emetics: Patients may be premedicated for nausea and vomiting.

Medications with QTc Prolonging Activity: The risk of QTc prolongation in patients receiving sitravatinib has not been characterized. Use of medications known to prolong QTc and pose risk of Torsades de Pointes (listed in Appendix 5) should be used with caution.

P-gp and BCRP transporters with Sitravatinib: Sitravatinib is a strong inhibitor of P-gp and BCRP transporters. Concomitant medications that are sensitive substrates or substrates with narrow therapeutic index for these transporters (listed in the Appendix 5) should be used with caution during sitravatinib treatment.

Cytochrome p450 Substrates with Sitravatinib**:** In vitro experiments in microsomes and recombinant human P450 enzymes suggest that sitravatinib is metabolized by several cytochromes, including CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP2E1, and CYP3A4, with a low risk of any one CYP demonstrating a disproportionate contribution to its metabolism. Caution should therefore be used when administering sitravatinib to subjects taking medications that are strong inhibitors or inducers of the cytochrome P450 system (Appendix 5).

Herbal Medications/Preparations**:** Herbal medications and preparations should be avoided throughout the study. Herbal medications include but are not limited to the following: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe (yohimbine), saw palmetto, and ginseng.

Immunosuppressive Medications: Use of immunosuppressive mediations should be limited to the extent possible to allow testing of the immune-stimulatory mechanisms proposed in this clinical trial. Immunosuppressive medications should be used as needed to manage irAEs and the extent required to manage comorbidities and symptoms of disease.

Anticancer treatments: Use of approved or investigational anticancer treatment is not permitted during the study treatment period, including chemotherapy, bevacizumab/ramucirumab, biological response modifiers, hormone therapy or immunotherapy. No other investigational drug may be used during treatment on this protocol. Concurrent participation in another therapeutic clinical trials is not allowed. Certain ongoing hormonal therapies taken to prevent recurrence of a malignancy not under study (e.g., tamoxifen/aromatase inhibitor for breast cancer) may be permitted after discussion with and agreement of the Sponsor Investigator.

5.4.2 Other Concomitant Treatments

5.4.2.1 Surgery

The use of surgery to manage cancer lesions during study treatment is discouraged. The impact of sitravatinib on wound healing has not yet been characterized. In the event that major surgery is needed during study treatment, the patient should, if possible, interrupt dosing with sitravatinib 2 weeks in advance of the surgery and resume dosing 2 weeks after the surgery.

5.4.2.2 Radiation

Any foreseeable need for palliative radiotherapy should be addressed before study entry if possible and clinically appropriate (e.g., bone lesions at risk for spontaneous fractures or painful lesions). However, these treatments may be used in cases where it is medically necessary or in select cases of oligoprogression at the Sponsor Investigators discretion (see Section 6.8). If radiotherapy is required, sitravatinib should be held the day prior to radiation and resume the day after.

5.4.2.3 Transfusions

Patients may receive transfusions as necessary.

5.4.2.4 Other Anticancer or Experimental Therapy

Use of approved or investigational anticancer treatment will not be permitted during the study treatment period as discussed in Section 5.4.1. No other investigational drug may be used during treatment on this protocol. Concurrent participation in another therapeutic clinical trial is not allowed.

6 Study Procedures

6.1 Study Calendars

6.1.1 Study Calendar for Group A

	Screening Visit[1]	On Study Visits[3]					Follow-Up[2]
		C1D1[3]	C1D8	C2D1	C3D1 and subsequent	End of Treatment[4]	
Informed Consent[5]	x						
Biopsy	X[6]			X[7]		If clinically indictated[8]	
Complete medical history, disease history	x						
Tissue analysis (PDL-1 staining, mutation testing)	x						
Vital signs, weight	x	x	x	x	x	x	
Height	x						
Toxicity Assessment/ AE Monitoring	x	x	x	x	x	x	X[9]
ECOG performance status	x	x	x	x	x	x	
Physical Exam[10]	x	x	x	x	x	x	
ECHO[11]	x				Required cycle 3 only, then as clinically indicated[12]	x	
Urinalysis	x			x	x	x	
Pregnancy Test[13]	x	As clinically indicated					
CBC, CMP	x	x	x	x	x	x	
TSH with reflex free T4	x				Cycle 3 and then every other cycle	x	
Triplicate 12- lead EKGs	x		x	x	As clinically indicated		
MRI Brain (or CT head with contrast if MRI is contraindicated)[11]	x	As per protocol[14]					
CT C/A/P[11]	x	q6 weeks x 3 months, q9 weeks x 9 months, q12 weeks thereafter					X[15]
Survival Status		x	x	x	x	x	x
Pembrolizumab Administration		x		x	x		
Sitra Dispensing and Reconciliation		x		x	x		
Blood work for correlative studies		x		x	Cycle 3 only, not subsequent	x	

[1]All screening procedures must be completed within 28 days of start of trial

[2] Survival status and subsequent therapies will be collected during long term follow-up every 3 months (±14 days) from the End of Treatment Visit until death or lost to follow-up. Long-term follow-up may be performed by telephone contact or email.

[3] Study treatment is administered in 21 day cycles; all study visits have a window of +/- 3 days

[4] To occur 28-35 days after last dose of study treatment

[5] Must be completed prior to any initiation of any study specific assessments
[6] Archival tissue from within 3 months of screening may be substituted for pre-treatment biopsy if available
[7] To be performed within 7 days prior to C2D1
[8] If biopsy is required for clinical purposes, research tissues samples may also be collected and stored at that time for future analysis
[9] Subjects with an AE of Grade > 1 will be followed for at least 28 days after the last dose of study drug or until the resolution of the AE to Grade 0-1 or progression to chronic condition, or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 28 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded
[10] Full physical exam should be performed at screening, C1D1 and End of Treatment visit. At other visits, symptom directed exam is permissible
[11] Window for echocardiogram and radiologic assessments is -7 days;screening imaging and ECHO should be completed no more than 28 days prior to starting trial drug; first on study imaging to occur 6 weeks (+/-7 days) after C1D1
[12] Following mandatory ECHO with C3, further ECHOs only need to be performed if there are clinical concerns for cardiac disease (eg signs or symptoms concerning for heart failure, pericarditis, tamponade, pulmonary hypertension)
[13]Pregnancy Test: If the patient is a woman of childbearing potential, negative serum or urine pregnancy test performed by the local laboratory at screening will be required. The informed consent process must include discussion of the risks associated with pregnancy and adequate contraception methods. Additional pregnancy testing may be necessary if required by local practices or regulations, or if potential pregnancy is suspected.
[14]MRI brain (or CT head with contrast if MRI is contraindicated) should be performed on schedule with other radiologic disease evaluations if there is known CNS disease. If no known CNS metastases, MRI brain/CT head with contrast should be performed as clinically indicated
[15] If study treatment is discontinued prior to disease progression, disease assessments should continue as per study protocol until the time of disease progression or start of new therapy

6.1.2 Study Calendar for Group B

	Screening Visit[1]	On Study Visits[3]					Follow-Up[2]
		C1D1	C2D1	C2D8	C3D1 and subsequent	End of Treatment[4]	
Informed Consent[5]	x						
Biopsy	X[6]		X[7]			If clinically indictated[8]	
Complete medical history, disease history	x						
Tissue analysis (PDL-1 staining, mutation testing)	x						
Vital signs, weight	x	x	x	x	x	x	
Height	x						
Toxicity Assessment/ AE Monitoring	x	x	x	x	x	x	X[9]
ECOG performance status	x	x	x	x	x	x	
Physical Exam[10]	x	x	x	x	x	x	
ECHO[11]	x				Required cycle 3 only, then as clinically indicated[12]	x	
Urinalysis	x				x	x	
Pregnancy Test[13]	x	As clinically indicated					
CBC, CMP	x	x	x	x	x	x	
TSH with reflex T4	x				Cycle 3 then every other cycle	x	
Triplicate 12- lead EKGs	x			x	Required cycle 3 only, then as clinically indicated		
MRI Brain (or CT head with contrast if MRI is contraindicated)[11]	x	As per protocol[14]					
CT C/A/P[11]	x	q6 weeks x 3 months, q9 weeks x 9 months, q12 weeks thereafter					X[15]
Survival Status		x	x	x	x	x	x
Pembrolizumab Administration		x	x		x		
Sitra Dispensing and Reconciliation			x		x		
Blood work for correlative studies		x	x		Cycle 3 only, not subsequent	x	

[1]All screening procedures must be completed within 28 days of start of trial

[2] Survival status and subsequent therapies will be collected during long term follow-up every 3 months (±14 days) from the End of Treatment Visit until death or lost to follow-up. Long-term follow-up may be performed by telephone contact or email.

[3] Study treatment is administered in 21 day cycles ;all study visits have a window of +/- 3 days

[4] To occur 28-35 days after last dose of study treatment

[5] Must be completed prior to any initiation of any study specific assessments

[6] Archival tissue from within 3 months of screening may be substituted for pre-treatment biopsy if available

[7] To be performed within 7 days prior to C2D1

[8] If biopsy is required for clinical purposes, research tissues samples may also be collected and stored at that time for future analysis

[9] Subjects with an AE of Grade > 1 will be followed for at least 28 days after the last dose of study drug or until the resolution of the AE to Grade 0-1 or progression to chronic condition, or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 28 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded

[10] Full physical exam should be performed at screening, C1D1 and End of Treatment visit. At other visits, symptom directed exam is permissible

[11] Window for echocardiogram and radiologic assessments is -7 days; screening imaging and ECHO should be completed no more than 28 days prior to starting trial drug; first on study imaging to occur 6 weeks (+/-7 days) after C1D1

[12] Following mandatory ECHO with C3, further ECHOs only need to be performed if there are clinical concerns for cardiac disease (eg signs or symptoms concerning for heart failure, pericarditis, tamponade, pulmonary hypertension)

[13]Pregnancy Test: If the patient is a woman of childbearing potential, negative serum or urine pregnancy test performed by the local laboratory at screening will be required. The informed consent process must include discussion of the risks associated with pregnancy and adequate contraception methods. Additional pregnancy testing may be necessary if required by local practices or regulations, or if potential pregnancy is suspected.

[14] MRI brain (or CT head with contrast if MRI is contraindicated) should be performed on schedule with other radiologic disease evaluations if there is known CNS disease. If no known CNS metastases, MRI brain/CT head with contrast should be performed as clinically indicated

[15] If study treatment is discontinued prior to disease progression, disease assessments should continue as per study protocol until the time of disease progression or start of new therapy

6.2 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial. Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion. A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

The informed consent will adhere to IRB requirements, applicable laws and regulations and Sponsor requirements.

6.3 Screening

- Voluntary, written, dated, and signed informed consent must be obtained before any study specific procedures are performed. Patients who completed the informed consent process but were not randomized into the study will be considered as screen failures. Limited information will be recorded in the CRF for these patients.
- All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.
- A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that is considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.
- The investigator or qualified designee will obtain prior and current details regarding disease status.
- The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject in the 28 days prior to signing consent. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.
- The investigator or qualified designee will record medication, if any, to be taken by the subject during the trial.
- Screening evaluations and studies (as outlined in study schedule) are to be conducted within 28 days prior to start of systemic therapy.

6.4 Enrollment

Once patient has signed informed consent and screening, and investigator or qualified designee has confirmed that patient has met eligibility criteria, patient will be enrolled in the study. Patient will be assigned to a cohort based on PD-L1 status, and then may undergo randomization as described in Section 4.6. Study treatment should begin within 7 days of randomization.

6.5 Research Blood and Tissue Collection

6.5.1 Biopsy Collection for Correlative Studies

Baseline tissue samples are required prior to initiation of study treatment. Archival tissue may be used if available and collected within 3 months of signing consent (see lab manual for detailed tissue requirements). If no archival tissue is available, pre-treatment biopsy will be required with tissue collected for research purposes. This can be the same biopsy collected for PD-L1 testing if required. All patients are required to undergo on-treatment biopsy within 7 days prior to C2D1. Patients may be exempted from the pre-treatment or on-treatment biopsy by the Sponsor Investigator if there is a contraindication to biopsy at that time. Tissue may also be collected from patients at the time of progression if biopsy is indicated for clinical reasons. This tissue will be stored for potential future analysis to explore mechanisms of resistance. Any additional samples obtained from clinically indicated biopsies while the patient is treated on study will be stored for possible future analysis.

For full details on tissue collection and analysis, please refer to the Laboratory Manual.

6.5.2 Research Blood Sample Collection for Correlative Studies

Research blood samples will be collected as per the Study Calendars (Section 6.1). For full details on research blood collection and analysis, please refer to the Laboratory Manual.

6.6 On Study Visits

On study visits will be conducted as per the Study Calendars (Section 6.1) every 21 days (+/- 3 days) on the day of pembrolizumab infusion and issuance of the sitravatinib cycle. Mid-cycle safety visit will take place on Cycle 1 Day 8 (+/- 3 days) for patients in Group A and on C2D8 (+/-3 days) for patients in Group B, with procedures as indicated for standard study visit as outlined below.

6.6.1 Laboratory Testing

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided in Section 7.2.3 and in the Study Calendars (Section 6.1).

6.6.2 Toxicity Assessment/Adverse Event Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs at each study visit as per Study Calendars (Section 6.1), and more frequently if clinically indicated. Adverse events will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0. Toxicities will be characterized in terms of seriousness, causality, toxicity grading, and action taken with regard to trial treatment. Please refer to Section 8 for detailed information regarding the assessment, recording and reporting of AEs.

6.6.3 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to administration of pembrolizumab and at treatment discontinuation, as specified in the Study Calendars (Section 6.1). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

6.6.4 Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded at that time. A full physical exam should be performed during screening, on C1D1 and at the End of Treatment visit. At all other visits, a symptom directed physical exam is permissible according to the Treating Investigator's discretion.

6.6.5 ECOG performance status

The investigator or qualified designee will assess ECOG performance status at screening, prior to the administration of each dose of pembrolizumab and at discontinuation of trial treatment, as specified in Study Calendars (Section 6.1)

6.6.6 Tumor Imaging/Disease Assessment

Tumor imaging and assessment of disease will be performed every 6 weeks (from C1D1) for the first 3 months of treatment, every 9 weeks for 9 months and every 12 weeks thereafter as per Study Calendars (Section 6.1). Please see Section 7.1 for further details on imaging assessments.

6.7 End of Treatment Visit

End of Treatment Visit should occur 28-35 days after last dose of study treatment. Evaluations at that time should be performed as per the Study Calendars (Section 6.1). Assessments completed in the previous 4 weeks do not need to be repeated with the exception of assessment of AEs and hematology and chemistry lab testing. Subjects with an AE of Grade > 1 will be followed for at least 28 days after the last dose of study drug, resolution of the AE or progression to chronic condition, or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. See Section 8 for further details of AE monitoring and reporting.

6.8 Treatment Beyond Progression

If radiologic assessment shows progressive disease (PD), tumor assessment should be repeated >4 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression. If repeat imaging shows a reduction in tumor burden compared to the initial scan demonstrating PD, treatment may be continued as per treatment calendars. If repeat imaging confirms progressive disease, subject will be discontinued from study therapy unless the Treating Investigator believes that the patient is deriving clinical benefit. Patients may continue treatment with study drugs beyond PD if they are determined by the Treating Investigator to be deriving clinical benefit from treatment and meet the following criteria: no signs or symptoms of clinically significant disease progression; continued adequate performance status; absence of rapid disease progression with threat to vital organs or critical anatomical sites; no significant, unacceptable or irreversible toxicities related to study treatment. The decision to continue treatment beyond initial progression should be discussed with the study Sponsor Investigator. Separate written consent must be obtained for treatment beyond radiologic disease progression.

Additionally, in cases where the majority of the disease is stable or responding, progressing lesions may be treated with local therapy (i.e. resection or radiotherapy) at the discretion of the Sponsor Investigator and the patient may be continued on trial following local therapy.

6.9 Study Follow up

6.9.1 Initial Follow Up

Patients discontinuing treatment for reasons other than objective disease progression (e.g., due to an adverse event or delivery of maximal number of cycles per standard-of-care) will be moved into the follow-up phase, and should be monitored by radiographic evaluation at the intervals established for disease assessment in the Study Calendars (Section 6.1) until objective disease progression or start of subsequent anti-cancer therapy, whichever is sooner. Survival status and start of subsequent therapy will be collected and recorded. Survival status and start of subsequent therapies will be recorded for all patients.

6.9.2 Long Term Follow Up

Survival status and subsequent therapies will be collected during long term follow-up every 3 months (+/-14 days) until death or loss to follow-up. Follow-up may be performed by telephone contact or email. Treatments received following participation in the study will be collected in the CRF.

6.10 Removal of Subjects/Patient Discontinuation/Withdrawal

Patients may discontinue from study treatment or from study follow-up at any time at their own request, or they may be discontinued at any time at the discretion of the Treating Investigator or Sponsor Investigator for safety, behavioral reasons, or the inability of the patient to comply with the protocol required schedule of study visits or procedures at a given study site. Criteria that may be used to discontinue patients from receipt of study medication will include, but will not be limited to:

- Objective disease progression according to RECIST 1.1 as determined by the Investigator (patients who may derive clinical benefit may continue on treatment at the discretion of the Sponsor Investigator in accordance with the above section 6.8);
- Global deterioration of health status requiring discontinuation;
- Adverse event;
- Significant protocol violation;
- Lost to follow-up;
- Refusal for further treatment;
- Study termination by Sponsor Investigator;
- Pregnancy;

- Death.

Reasons for discontinuation from study follow-up may include:

- Study terminated by Sponsor Investigator;
- Lost to follow-up;
- Refusal for further follow-up for survival;
- Death

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. At least 2 attempts should be made to contact the patient, and each attempt should be recorded in the source documents. In any circumstance, every effort should be made to document patient outcome if possible. The Investigator should inquire about the reason for withdrawal, request that the patient returns for a final visit, and if applicable, follow-up with the patient regarding any unresolved AEs.

If the patient withdraws from the study treatment and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The Sponsor Investigator may retain and continue to use any data collected before such refusal for further follow-up.

7 Study Assessments

7.1 Efficacy Assessments

7.1.1 Radiographic Disease Assessment

All patients enrolled in the study are to undergo disease evaluations as outlined in the Study Calendars (Section 6.1). If symptoms develop or clinical deterioration occurs, patients may be imaged prior to the pre-specified time points for imaging. Patients discontinuing treatment prior to objective disease progression will be followed by radiographic evaluation until disease progression is documented or until the start of subsequent anti-cancer therapy, whichever is sooner.

Screening/baseline tumor assessments should include CT (with contrast, unless contraindicated) of the chest and abdomen (plus pelvis if indicated) and MRI of the brain

with and without gadolinium (preferred) or head CT with contrast if MRI is contraindicated. The allowable windows for screening/baseline assessments is 28 days prior to randomization.

Disease assessments performed on-study will include CT of the chest/abdomen (plus pelvis if indicated) and assessment of all known and suspected sites of disease. MRI brain should be performed on schedule with other radiologic disease evaluations if there is known CNS disease. If no known CNS metastases, MRI brain should be performed as clinically indicated. Assessments will be performed as per study calendars: every 6 weeks (starting from C1D1) for 3 months, every 9 weeks for 9 months and every 12 weeks thereafter. The allowable windows for on-study assessments is +/- 7 days. Assessments will be performed until objective disease progression is documented by the Investigator, or subsequent anti-cancer therapy is begun.

The Investigator's assessment of disease response and progression per RECIST 1.1 (for extracranial disease) and RANO-BM criteria (for intracranial disease) will be the basis for patient management and statistical analyses of radiology-based study endpoints. RECIST v1.1 and RANO-BM criteria are summarized in Appendices 3 and 4.

7.1.2 Survival Assessments

Overall survival and Progression Free Survival are secondary efficacy endpoints for this study. Survival status and information concerning subsequent therapies will be collected during initial and long-term follow-up as discussed in Section 6.9. For more details on OS and PFS assessment and analysis see Section 9.2.3. In the event a patient discontinues treatment due to loss to follow-up or withdraws consent for use of data from medical records, surveillance of public sources of death information (e.g., published obituaries) should be undertaken and reported date of death recorded in the CRF.

7.1.3 CNS Disease Assessment

Intracranial Objective Response Rate (iORR), Intracranial Duration of Response (iDOR) and Intracranial Progression Free Survival (iPFS) are all exploratory endpoints of this study. MRI or CT head with contrast (as above) will be assessed at baseline for evidence of CNS disease and ongoing CNS imaging evaluation will be performed thereafter at intervals as per the Study Calendars (Section 6.1). CNS tumor response assessment will be performed

according to RANO-brain-metastasis criteria, summarized in Appendix 4. Clinical status and steroid requirement will be assessed and documented at each study visit as per Study Calendars (Section 6.1).

7.2 Safety Assessments

7.2.1 Medical History

Medical history, including clinically significant past and present medical conditions, will be recorded at screening visit. Lung cancer history will be recorded separately at that time. Signs and symptoms of the patient's cancer diagnosis and/or comorbidities present prior to the first dose of study treatment should be noted and recorded separately. Interval history of symptoms should be collected at each visit. Any worsening or newly identified signs or symptoms after C1D1 will be recorded in the AE log.

7.2.2 Physical Exam and Vital Signs

Exam and vital signs should be performed as per Section 6.6. Clinically significant findings noted during screening and prior to first dose of study treatment will be documented separately, while those noted after C1D1 will be collected in the AE log.

7.2.3 Laboratory Safety Assessments

Safety labs will be collected for each cycle prior to pembrolizumab infusion and sitravatinib release. Labs to be collected are summarized in *Table 7.*

Table 7: Laboratory Safety Parameters

Hematology Panel	**Blood Chemistry Panel**
Hemoglobin/Hematocrit	Aspartate aminotransferase
Platelet count	Alanine aminotransferase
White blood cell count	Alkaline phosphatase
Neutrophil count	Total bilirubin (if Total bilirubin is ≥2×ULN and no evidence of Gilbert's syndrome, then fractionate into direct and indirect bilirubin)
Lymphocyte count	
Urinalysis	Sodium
Blood	Potassium
Protein	Chloride
	Bicarbonate or carbon dioxide (CO2)
Thyroid Function Test	Blood urea nitrogen (BUN) or urea
Thyroid-stimulating hormone with reflex free T4	Creatinine
	Albumin
	Total Calcium

7.2.4 Electrocardiograms

Triplicate 12 lead EKGs to be performed as outlined in the Study Calendars (Section 6.1) for baseline/screening, and on C1D8 and C2D1 for the main study group (Group A) and C2D8 and C3D1 for the pembrolizumab run-in group (Group B). Thereafter EKGs will be performed as clinically indicated.

7.2.5 Echocardiogram

Echocardiogram will be performed at baseline/screening, within 7 days prior to C3D1, and at end of treatment. ECHO can be performed thereafter as clinically indicated at the Treating Investigator's discretion if there are signs or symptoms of cardiotoxicity.

8 Adverse Event Reporting

8.1 Evaluating Adverse Events

8.1.1 Definitions

An Adverse Event (AE) is any reaction, side effect or other undesirable medical event that occurs during participation in a clinical trial, regardless of treatment group or suspected causal relationship to study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of study drugs, is also an adverse event. Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

An abnormal laboratory test result should be recorded as an AE in the CRF only if it is associated with one or more of the following: clinical symptoms; additional testing, treatment or intervention; change in study dosing; discontinuation from study treatment; or if it is considered by the Sponsor or Treating Investigator to be an AE.

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the Treating Investigator.

Assessment of AEs will include type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE, Version 5.0]), timing, seriousness, and relatedness to study treatment.

8.1.2 Recording AEs

All observed or volunteered AEs will be recorded in source documents and reported in the CRF along with severity, relatedness and expectedness as defined below (Sections 8.1.3, 8.1.4, 8.1.5). The best available medical terminology should be used to describe AEs in

source documents and CRFs. Terms describing the diagnosis are preferred over individual signs and symptoms of the diagnosis. If determination of the diagnosis is delayed, record signs and symptoms and add the diagnosis as an additional AE when available; follow all recorded AEs to resolution. The actual date of onset should be recorded in all cases. Ongoing AEs that change in attribution or severity should have the date of change entered as the “end date” and a new AE record should be opened with the changed details.

8.1.3 Severity Assessment

AEs occurring during this study will be graded in accordance with the NCI CTCAE Version 5.0. Documentation of AE grading in the source documents and CRF should be consistent with provided definitions.

8.1.4 Causality

For each AE, the Treating Investigator will determine and document whether there exists a reasonable possibility that the study treatment caused or contributed to the AE. Potential attribution of an adverse event associated with trial therapy will be provided for all study drugs, sitravatinib and/or pembrolizumab. The Investigator’s assessment should be recorded in the source document. The CRF will provide the options for attribution to each study treatment as “related” or “not related.” If the Investigator's causality assessment is "unknown but not related to investigational product," this should be recorded in the CRF as “not related.” If the Investigator does not know whether or not the study treatment is causally related to the event, reporting for study purposes will be as “related” to study treatment.

8.1.5 Expectedness

The Treating Investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information listed in the reference safety information. Reference safety information is the US Package Insert for pembrolizumab and the most current version of the Investigator’s Brochure for Sitravatinib.

8.2 Serious Adverse Events

A Serious Adverse Event (SAE) is any event that meets any of the following criteria:

- Results in death
- Is life-threatening (immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/permanent damage (substantial disruption of the ability to conduct normal life functions)
- Results in congenital anomaly/birth defect
- Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are: Intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in inpatient hospitalization; development of drug dependency or drug abuse

8.3 Reporting of AEs and SAEs

8.3.1 Reporting Period

Please refer to the Manual of Procedures (MOPs) for SAE reporting procedures.

The reporting period for non-serious AEs begins from the day of the first dose of study treatment and continues until at least 28 days after last administration of study treatment, or until resolution of AEs to Grade 0-1. If a patient begins a subsequent anticancer therapy the AE reporting period ends at the time the new treatment is started. Signs and symptoms of the patient's cancer diagnosis and/or comorbidities present prior to the first dose of study treatment should be noted and recorded separately (not as an AE).

The active reporting period for SAEs begins from the time that the patient provides informed consent (i.e., prior to undergoing any study-specific procedure or assessment) and continues until at least 28 days after the last administration of study treatment. All SAEs ongoing at the end of treatment should be followed until they have resolved or stabilized to a chronic condition, whichever is later. If a patient begins a subsequent anticancer therapy, the reporting period for new SAEs ends at the time the new treatment is started. Serious adverse events occurring after the active reporting period has ended should be reported to Mirati if the Treating Investigator becomes aware of them and if the Sponsor Investigator

assesses at least a reasonable possibility of being related to study treatment. These SAEs should be followed until resolved or stabilized to a chronic condition.

8.3.2 Reporting Requirements

Please refer to the Manual of Procedures (MOPs) for SAE reporting procedures.

All AEs (including SAEs) must be documented in source documents and reported in the CRF. Please note that the CRF and SAE report forms may collect information in somewhat different formats. Where the requested data overlap in different formats, the information should be consistent between the two forms.

All SAEs will be reported to the Sponsor Investigator within 24 hours of becoming aware of the event. Local investigators will complete the provided SAE form and send to the assigned Project Manager and Sponsor Investigator via email. The Sponsor Investigator will review the event and determine final attribution to study treatment. The Sponsor Investigator is responsible for expedited reporting to the FDA, when required, including meeting all timelines. Each site is responsible for following local procedures for submitting SAEs to the IRB of record.

8.3.3 SAE reporting to Mirati Therapeutics Inc.

For patients who sign the study informed consent form (ICF), SAE collection starts at time of main study informed consent whether the patient is a screen failure or not. The Sponsor, by way of the assigned Project Manager, is also required to notify Mirati Therapeutics, using the contact details supplied in Section 8.3.4. within 24 hours/1 business day of learning of its occurrence. Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, the Sponsor, by way of the assigned Project Manager, will send a notification to Mirati Therapeutics, as it sees appropriate, who may need to issue an Investigator Notification (IN), to inform all Investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities (except FDA as Sponsor is responsible for reporting) and relevant ethics committees.

Mirati Therapeutics Contact:

Mirati Therapeutics

Email: wilsafety@ppdi.com

Fax: +1-888-488-9697

Phone (for fax issues): +1-800-201-8725

Investigative site must also indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications and if the SAE is related to disease progression, as determined by the principal investigator.

All SAEs have to be reported to Mirati Therapeutics, whether or not considered causally related to the investigational product. All SAEs will be documented. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

8.3.4 Reporting of SUSARs to Yale Cancer Center

Mirati Therapeutics will forward SUSARs occurring with Sitravatinib to the Yale Cancer Center in the following timelines:

- Reports of fatal or life threatening Serious Adverse Drug Reactions will be sent within five (5) calendar days of Receipt Date.
- Reports of Serious Adverse Drug Reactions (other than fatal or life threatening) will be sent within twelve (12) calendar days of Receipt Date.

8.3.5 Reporting to the FDA

This study will be conducted under an IND (Investigational New Drug application) that will be held by Dr. Goldberg. The Sponsor Investigator, by way of the assigned Project Manager and the IND/IDE Management Office, will report in an expedited manner all SAEs meeting the criteria of “serious”, “unexpected” and “related to study treatment”. Written safety reports will use a MedWatch Form 3500A. A “fillable pdf” version with instructions is available at: http://www.fda.gov/medwatch/safety/FDA-3500A_Fillable_08-16-2006.pdf

There are two types of expedited safety reports to the FDA:

1. **7-Calendar-Day FDA Telephone or Fax Report:** The sponsor-investigator will directly notify the FDA, within 7 calendar days after his initial receipt of the information, of any adverse event that is ALL of the following:

Death or immediately life-threatening
Unexpected
Associated with the use of study drug

Notification to the FDA will be made directly to the new drug review division in the Center for Drug Evaluation and Research or in the product review division for the Center for Biologics Evaluation and Research, whichever was responsible for the review of the IND. [21CFR312.32(c)] A written report of the event is to follow within 8 calendar days from the submission of the initial report.

2. **15-Calendar-Day FDA Written Report:** The sponsor-investigator will directly notify the FDA within 15 calendar days of any adverse event that is ALL of the following:

Serious (due to non-fatal and non-life threatening criteria
Unexpected
Associated with the use of study drug

Note: Serious Adverse Events which do not meet the criteria for expedited reporting will be reported to the FDA in the IND Annual Report.

8.4 Reporting of Pregnancy and Lactation

Exposure during pregnancy (i.e., exposure in-utero [EIU]) may occur in a female study participant, or the female partner of a male study participant if:

- A female becomes or is found to be pregnant during treatment or within 6 months after discontinuing treatment or having been directly exposed to the investigational product;
- A male is exposed to the investigational product within 6 months of conception or during the pregnancy of his partner.

If EIU occurs, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor Investigator and Mirati without delay and within 24 hours to the Sponsor Investigator if the outcome is a serious adverse event (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor Investigator and Mirati. If the outcome of the pregnancy meets the criteria for an SAE (i.e., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), an SAE report should be submitted to Sponsor Investigator and Mirati.

8.5 Safety Reporting and Monitoring (DSMP)

8.5.1 Data and Safety Monitoring Committee

The Yale Cancer Center (YCC) Data and Safety Monitoring Committee (DSMC) will provide the primary oversight of data and safety monitoring. The Yale DSMC will review and monitor compliance, toxicity and deviations from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Sponsor Investigator.

The DSMC will review this protocol bi-annually, at a minimum. Information to be provided to the committee includes: a study narrative by the PI, a summary DSMC report (which includes participant accrual, response, trial status history, SAEs, adverse events, deviations and survival); audit results, and monitoring reports, as applicable. Other information (e.g., scans, laboratory values, etc.) will be provided upon request. Upon completing the review, the DSMC will approve whether the study should continue as planned, require modification/ amendment, or be placed on administrative hold with accrual temporarily suspended.

Trials being monitored by the YCC DSMC will remain under the YCC DSMC purview until a DSMC review has occurred that includes the research activity of the last subject who completed the intervention, or until the DSMC feels there are no patient safety concerns that require further monitoring. The DSMC will determine the length of continued DSMC review.

The DSMC has authority to intervene in the conduct of these studies as necessary to ensure the safety of the participants and to maintain the highest quality in the clinical research performed at YCC. The DSMC has the authority to require additional monitoring and/ or more frequent reporting on study progress and serious adverse events.

8.5.2 Study Site Monitoring

Study site monitoring is necessary to assure adequate protection of the rights of human subjects and the safety of all subjects involved in clinical investigations and the quality and integrity of the resulting data submitted.

The Sponsor-Investigator-designated monitor(s) conducts monitoring visits to ensure that clinical investigators and study team members are compliant with the protocol, ICH good clinical practice, federal, state and local regulations and institutional policies and procedures, that data are of high quality and integrity, and that the facilities and staffing are adequate for continued study participation. This will be performed by conducting monitoring visits including a site initiation visit, regularly scheduled interim monitoring visits and/or remote interim monitoring visits while subjects are on study, and a site close-out visit at Choose an item.. Following each site visit, a visit report will be generated containing information on site activities and a summary of pertinent points and action items. The report will be provided with a follow-up letter. Site-specific data status reports will be distributed to the site regularly

to outline planned, missing or incomplete case report forms and any outstanding data queries.

During monitoring visits, the following may be reviewed:

- Protection of the rights, safety and welfare of subjects through review of informed consentinformed consent process and documentation, adverse events (AEs) and serious adverse events (SAEs) and safety procedures
- Subject eligibility
- Source verification
- Protocol compliance
- Deviations and Non-compliance
- Investigator Site File
- GCP compliance
- If applicable, include: Investigational Drug/ Device Storage and Accountability (including quantity and disposal procedures)
- If applicable, include: Laboratory Facilities
- If applicable, include: Equipment maintenance and calibration
- Additional study supplies inventory and assessment
- Study progress and/or follow-up on issues with Site Principal Investigator (PI) and relevant members of the study team

The Sponsor-Investigator and YCCI will define the required study monitoring activities in a Study Monitoring Plan.

9 STATISTICS

9.1 Statistical Methods

9.1.1 Statistical Design

This is a Phase 2 trial of the novel therapeutic sitravatinib in combination with pembrolizumab for the first-line treatment of patients with PD-L1 positive non-squamous metastatic NSCLC. The primary endpoint of this study is ORR as defined by RECIST 1.1, for patients treated with this combination. This study will enroll patients into two cohorts defined by PD-L1 status: PD-L1 TPS$\geq$50% and TPS 1-49%. We will implement a Simon's Two-Stage Design to evaluate the efficacy of sitravatinib in combination with pembrolizumab for each cohort separately.

Each cohort will contain 35 patients, for a total of 70 patients (see discussion of sample size calculation below, section 9.1.3). Within each cohort, 30 patients will comprise the "main

study population" or Group A (see Study Schema 4.1), who will receive sitravatinib and pembrolizumab in combination starting on C1D1 of the study. It is hypothesized that this combination will result in at least 25% improvement in ORR when compared with historical control ORR of 39% for TPS≥50% and 17% in TPS 1-49%(6). Secondary endpoints include OS, PFS, Duration of Response (DOR) and Clinical Benefit Rate (CBR) in this population.

Initially patients will be randomized until five patients from each cohort have been assigned to Group B (to receive a 3-week run-in with pembrolizumab alone followed by the addition of sitravatinib on C2D1). The patients from this "pembrolizumab run-in" group, or Group B (see Study Schema 4.1), will not be included in the main statistical analysis of the primary endpoint. ORR, OS, PFS, DOR and CBR in Group B will be analyzed separately and will be secondary endpoints for this study.

9.1.2 General Analysis Plan

In general, summary statistics will be presented as percentages in the case of categorical variables and as means with standard deviations in the case of continuous variables. When applicable, t-tests or Wilcoxon rank-sum tests will be used to make comparisons between responders and non-responders, depending on the distribution of data. Paired t-tests or Wilcoxon signed-rank tests will be used to compare continuously distributed markers measured at different time points. Chi-square tests or Fisher's exact tests will be used to make comparisons between patient subgroups of interest for categorical variables. Summaries of safety data will be tabulated. Additional summaries or listings of adverse events for AEs of special interest may also be provided if appropriate. All analyses will be done separately for Cohorts A and B.

9.1.3 Sample Size Considerations

In Group A, for the cohort with TPS≥50%, we intend to enroll a maximum of 30 evaluable patients using Simon's minimax design. The sample size calculation is based on the desire to discriminate a promising ORR of 64% from a disappointing ORR of 39%(6). At stage 1, 17 subjects will be entered on the study. If ≤ 7 responses are seen, the study will be terminated. At stage 2, 13 additional subjects will be entered. At the end of stage 2, if 16 or more subjects experience a response, the combination will be considered worthy of further study. *This design yields a type I error rate of 0.07 and power of 90% when the true response rate is 64%.*

In Group A, for the cohort with TPS 1-49%, we intend to enroll a maximum of 30 evaluable patients using the admissible two-stage design. The sample size calculation is based on the desire to discriminate a promising ORR of 42% from a disappointing ORR rate of 17%.(6) At stage 1, 16 subjects will be entered on the study. If ≤ 3 responses are seen, the study will be terminated. At stage 2, 14 additional subjects will be entered. At the end of stage 2, if 9 or more subjects experience a response, the combination will be considered worthy of further study. *This design yields a type I error rate of 0.05 and power of 91% when the true response rate is 42%.*

9.2 Efficacy Endpoints Definition and Analyses

9.2.1 Analysis Population

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) will be included in the main analysis of the response rate and the other efficacy analyses. Conclusions will be based on all eligible patients. Sub analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these sub analyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.

Safety analysis will be performed on all patients who receive at least one dose of study treatment.

9.2.2 Objective Response Rate (ORR)

Objective Response Rate (ORR) per RECIST in Group A (main study population) is the primary endpoint of this study and is defined as the percent of patients with confirmed Complete Response (CR) or Partial Response (PR). ORR in Group B is an exploratory endpoint. ORR, along with the 95% exact confidence interval, will be estimated using the Clopper–Pearson method.

9.2.3 Overall Survival and Progression Free Survival Analysis

Overall Survival (OS) and Progression Free Survival (PFS) in the main study populations (ie groups 1A and 2A) are secondary endpoints for this study. OS and PFS in groups 1B and 2B are exploratory endpoints.

OS is defined as the time from date of treatment start to death due to any cause. PFS is defined as the time from first dose to first progressive disease (PD) or death due to any cause in the absence of documented PD. Survival status will be collected during initial and long-term follow-up as outlined in the Study Calendars (Section 6.1). If a patient discontinues treatment due to loss to follow-up or withdraws consent for use of data from medical records, surveillance of public sources of death information (e.g., published obituaries) should be undertaken and reported date of death recorded in the CRF. Patients with no event will be censored at the last available tumor assessment for PFS and at the last timepoint known alive for OS.

Kaplan-Meier estimates (product-limit estimates) will be presented for the analysis of PFS and OS together with a summary of associated statistics (median survival time, landmark survival rate estimates and estimates for every 6 months thereafter if applicable) including the corresponding two-sided 95% confidence intervals. The confidence intervals for the median will be calculated according to Brookmeyer and Crowley (1982) and confidence intervals for the survival function estimates at above defined time points will be derived using the log-log transformation according to Kalbfleisch and Prentice (1980). The estimate of the standard error will be computed using Greenwood's formula.

9.2.4 Duration of Response

Duration of Response (DOR) for patients in Group A is a secondary endpoints for this study; DOR for Group B is an exploratory endpoint. DOR is defined as the time that measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented or to death due to any cause in the absence of documented PD.

The Kaplan-Meier method will be used for the subgroup of patients with a confirmed objective response in order to obtain the estimate of median DOR. Censoring for the DOR

endpoint will be assigned on the date of the last tumor assessment if no assessment of tumor progression is recorded and the patient does not die and prior to the start of subsequent anti-cancer therapy. Descriptive statistics will be provided for the DOR in responding patients (i.e., median duration of response and 95% CIs) by cohort, including the associated Kaplan-Meier curves.

9.2.5 Clinical Benefit Rate

Clinical Benefit Rate (CBR) in Group A is a secondary endpoints for this study, while CBR in Group B is an exploratory endpoint. CBR is defined as the percent of patients documented to have a confirmed Complete Response (CR), confirmed Partial Response (PR), or Stable Disease (SD) documented on at least 1 on-study assessment and including at least 5 weeks on study. An approach similar to that described for analysis of ORR (Section 9.2.1) will be used to assess CBR.

9.2.6 Intracranial Objective Response Rate

Intracranial Objective Response Rate (iORR) in patients with baseline CNS metastases is an exploratory endpoint of this study. iORR will be determined by the proportion of patients with a brain metastasis response in clinically evaluable lesions using RANO-brain metastasis criteria. RANO-brain metastases criteria is summarized briefly in Appendix 4.

9.2.7 Intracranial Duration of Response

Intracranial duration of response in patients with baseline CNS metastases is an exploratory endpoint of this study. iDOR is defined as the time from first complete intracranial response or partial intracranial response (whichever is documented first) to date of intracranial disease progression (not considering extracranial disease progression). An approach similar to that described above for DOR will be used to assess iDOR (Section 9.2.4).

9.2.8 Intracranial Progression Free Survival

Intracranial Progression Free Survival (iPFS) in all patients regardless of the presence of baseline CNS metastases is an exploratory endpoint of this study. iPFS is defined as the time from first dose to the date of first intracranial progressive disease (as per RANO-brain metastasis criteria). An approach similar to that described for the analysis of PFS (Section 9.2.3) will be used.

9.3 Safety Analysis

Evaluation of the safety and toxicity profile of the combination of sitravatinib and pembrolizumab in the first-line treatment of patients with non-squamous metastatic NSCLC is a secondary objective in this study. Secondary endpoint is adverse events as per CTCAE v.5. The Safety population is defined as all patients who received any dose of study treatment (i.e., sitravatinib and/or pembrolizumab) and will be used for all safety analyses.

9.4 Correlative Analyses Plan

- Wilcoxon's rank-sum test will be used to compare the % of $T_{effector}$, % of myeloid activation, % of CD 8^+ T cells and % of $FOXP3^+$ T cells between AXL hi versus lo ($\geq$ 50% and <50%, respectively) and MERTK high versus low groups.
- Comparisons between pre- and post-treatment will be evaluated by Wilcoxon signed rank test.
- To compare differences (% change) between sitravatinib + pembrolizumab versus pembrolizumab alone, Wilcoxon's rank-sum test will be used.
- To compare differences in sitravatinib + pembrolizumab treatment across cohorts with distinct PD-L1 status Wilcoxon's rank-sum test will be used.
- Baseline or changes in immune cell populations will be compared between responders and non-responders using Wilcoxon rank sum test.
- Single-cell RNA sequencing and bulk RNA sequencing are exploratory pilot assessments.

9.5 Handling of Missing Data

For all variables, only the observed data from patients will be used in the statistical analyses; there is no plan to estimate missing data. Patients without a valid clinical response assessment will be assigned a best overall response of not evaluable (NE). Data from patients who are lost to follow-up or have missing observations before reaching an endpoint in any of the time-to-event analyses will be treated as censored at the last available tumor assessment (or last time known alive).

10 Trial Administration

10.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization

This study will be conducted in accordance with International Ethical Guidelines for Biomedical Research Involving Human Patients (Council for International Organizations of

Medical Sciences 2002), Guidelines for Good Clinical Practice (GCP) (International Council for Harmonisation [ICH] 1996), ICH E6 (R2) and concepts that have their origin in the Declaration of Helsinki (World Medical Association 1996, 2008 & 2013).

Specifically, this study is based on adequately performed laboratory and animal experimentation as well as ongoing clinical data; the study will be conducted under a protocol reviewed and approved by an IRB; the study will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the patients will be respected; the physicians conducting the study do not find the hazards to outweigh the potential benefits; and each patient will give his or her written informed consent before any protocol-driven tests or evaluations are performed.

10.2 Institutional Review Board (IRB) Review

This protocol will be submitted to the IRB for review and approval. Prior to the shipment of clinical supplies or initiation of the study, the clinical trial protocol along with the informed consent form (ICF), Investigator's Brochure, and any other written information or instructions for the patient must be submitted to the IRB for written approval. The Investigator is responsible for notifying the IRB of any amendments to the protocol or ICF, SAEs occurring in patients treated at the study site in accordance with local IRB practice, and all expedited safety reports.

Any change to the protocol will require an approved IRB amendment before implementation. Other study events (e.g. data breaches, protocol deviations) will be submitted per local IRB's policies.

10.3 Subject Confidentiality

Subject confidentiality is held in strict trust by the research team. Only authorized HIPAA and GCP trained study team members will be allowed to extract research data from medical records.

All information generated in this study is considered confidential, is subject to applicable privacy rules and regulations, and must not be disclosed to any person or entity not directly

involved with the study without the patient's prior written consent or in accordance with applicable law or regulations.

The identifying patient information collected for and during the clinical trial will be kept confidential. However, study information may be published in formal reports and medical papers and may include de-identified medical information of the patient. In either way, the patient name will not be used in publicly available documents.

10.4 Data Collection

The clinical trial data consisting of all required observations, AEs, and laboratory data are entered into a computerized database in a timely manner. The accuracy and completeness of the database, timely submission of SAEs and compliance with the protocol, is reviewed during site monitoring visits described in Section 8.5.2. Safety data will be reviewed in accordance with the DSMP (Section 8.5.1). Regular meetings are held to discuss ongoing patient treatment and adverse events.

10.5 Study Records

A CRF must be completed for each patient for whom informed consent for the study is obtained. The CRFs must be maintained by properly trained and delegated site representatives. The Sponsor Investigator has responsibility for ensuring the authenticity, accuracy, completeness and timeliness of all data collected in the CRF.

Source documents include hospital or clinical patient charts, pertinent historical medical records, laboratory test reports, ECG tracings, pathology reports, radiographs, etc. All source documents must be legible. Data reported in CRFs and evidence of patient's informed consent must be documented in source documents. All documents collected as part of this clinical trial are considered study records, to include: regulatory documents, protocols, consent forms, and subject medical records.

10.6 Data or Specimen Storage/Security

Data will be collected in an electronic data capture system. This is maintained on a secure server. Access to the system is password protected. All study data and specimens will be stored for future use and analysis.

10.7 Retention of Records

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations.

10.8 Study Modification

A protocol change intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRB is notified within 5 days. Any urgent safety measures taken by the Investigator to protect the study patients against any immediately life-threatening hazard must be reported immediately to the Sponsor Investigator.

10.9 Study Discontinuation

If the study is prematurely terminated or suspended, the Sponsor Investigator will promptly inform study participants, the Institutional Review Board and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

10.10 Study Completion

Study completion is defined as the time at which all patients enrolled in the study have completed the last study visit and data from those visits have been reviewed by the Investigator or designee.

10.11 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the appropriate conflict of interest review committee has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest. All investigators will follow the applicable conflict of interest policies.

10.12 Funding Source

This study is being funded by Mirati Therapeutics.

10.13 Publication Plan

Results will be reported by the Sponsor Investigator in abstract form at medical conferences and manuscripts will be published in medical journals.

11 Correlative Studies

11.1 Introduction/Summary

Correlative studies will be conducted on tumor tissue as well as serial blood samples. Brief summary of planned analyses included below in *Table 8*.

Tissue/Biopsy Analysis
Multiplex Quantitative Immunofluorescence T-Cell • Subsets/activation: CD3, Ki67, granzyme B and cytokeratin • Macrophage Panel: CD68, CD11b, HLADR, CD163 • MERTK Pathway: MERTK, AXL, CD68, cytokeratin • T cell panel: CD8, FOXP3, CD4 and cytokeratin Single-cell RNA sequencing of CD45+ sorted cells

Blood Sample Analysis:
Isolation of PBMCs (peripheral blood mononuclear cells) • Bulk and single-cell RNA sequencing

Table 8:

Planned Correlative Studies

11.2 Sample Collection

11.2.1 Tissue Collection

Baseline tissue sample, either archival (within 3 months) or by fresh biopsy is required unless medically contraindicated. 3 week on-treatment biopsy is also required unless medically contraindicated. If biopsy is performed for clinical reasons at the time of progression or at other times during the study, these samples will also be collected and stored for future research purposes. For details on tissue collection and storage please see Laboratory Manual.

11.2.2 Blood Collection

Serial research bloods will be collected from 35 patients, including all patients in the pembrolizumab-run in population. Samples will be collected prior to treatment on C1D1, C2D1, C3D1 and at End of Treatment/Progression. Samples will be collected and initially processed as described in the Laboratory Manual before being transferred to the lab of Dr. Carla Rothlin and Dr. Sourav Ghosh (Yale University) for further analysis and storage. Note that research blood is only required for patients treated at a site that has the ability to transport blood to Drs. Rothlin and Ghosh's laboratory within 2 hours. For full details on blood collection and storage please see Laboratory Manual.

11.3 Tumor Tissue Analysis

11.3.1 Tissue Samples

For tissue analysis, the primary focus will be the comparison of baseline and on-treatment biopsies of patients receiving the pembrolizumab/sitravatinib combination versus patients receiving pembrolizumab alone (during the run-in period). Baseline and 3-week on treatment biopsy samples will be processed initially for 15 patients in each cohort: all patients from Groups 1B and 2B (pembrolizumab run-in population) and 10 patients each from Group 1A and 2A (main study population), with storage of any additional tissue for future analysis. All additional tumor samples that are collected will be stored for potential future analysis.

11.3.2 Multiplex Quantitative Immunofluorescence

Analysis of the tumor microenvironment will be done using multiplexed quantitative immunofluorescence (QIF) to spatially map the MERTK pathway (MERTK, Axl and Tyro3), major T-cell subsets (CD4, CD8 and FOXP3) and tumor-associated macrophages (CD11b, CD68, HLA-DR or CD163). QIF will be performed on tumor tissue from baseline and 3 week on-treatment tissue samples from 30 patients as outlined above. A minimum of 4 panels are planned as listed below:

- Panel 1: Dapi-CK-CD3-GranzymeB-Ki67
- Panel 2: Dapi-CD68-Cd11b-CD163-HLA-DR A
- Panel 3: Dapi-CK-CD68-MERTK-AXL
- Panel 4: Dapi-CK-CD8-CD4-FOXP3

Percentage of activated myeloid cells, effector T cells and AXL+ and MERTK+ macrophages in the TME will be measured and compared in pre- and post-treatment samples for patients treated with sitravatinib/pembrolizumab combination versus pembrolizumab alone. The expression of AXL and/or MERTK in $CD68^+$ cells will be correlated with the percentage of $CD8^+$ T cells, $FOXP3^+$ T regulatory cells, effector T cells and activated myeloid cells across multiple stained sections.

Additional panels may be added. For full details please see Laboratory Manual.

11.3.3 Isolation of CD45+ cells and Single-cell RNA Sequencing

CD45+ cells will be isolated from baseline and 3-week on selected treatment tumor samples as per section 11.3.1. Single-cell RNA sequencing will then be performed to detect gene expression changes in myeloid and T-cell populations induced by pembrolizumab + sitravatinib combination treatment. As an unbiased genome-wide transcriptome analyses, single-cell RNA sequencing may reveal novel population-level complexities and unique gene expression markers associated with sitravatinib + pembrolizumab treatment versus pembrolizumab treatment alone. For additional details please see Laboratory Manual.

11.4 Peripheral Blood Analysis

Research blood will be collected and analyzed on a subset of patients at multiple time points as described above. Peripheral blood mononuclear cells (PBMCs) will be isolated and used for bulk RNA sequencing to evaluate gene expression changes in PBMCs over all serial time points with sitravatinib/pembrolizumab treatment versus pembrolizumab alone. For full details please see Laboratory Manual.

11.5 Other Analyses

Any blood and tissue collected during this trial that is not used for the above analyses will be stored for potential future studies. Additional analyses may include, but are not limited to, whole exome DNA sequencing, additional multiplex IHC panels, T-cell receptor (TCR) sequencing, cytokine analysis from blood, and circulating tumor DNA (ctDNA).

12 Appendices

12.1 Appendix 1: NCI Common Terminology Criteria for Adverse Events (CTCAE)

Please use the following link to the NCI CTCAE website:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

12.2 Appendix 2: Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about > 50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair > 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

12.3 Appendix 3 Abbreviated Presentation of RECIST Version 1.1 Guidelines [21]

Categorizing Lesions at Baseline

Measurable Lesions

- Accurately measured in at least one dimension.
- When assessed by CT or MRI, longest diameter at least 10 mm or greater (slice thickness 5-8 mm), measured in the axial plane. If the slice thickness is greater than 5 mm (including any inter-slice gap), the longest diameter must be at least twice the slice thickness.
- Malignant lymph nodes with a short axis (defined as the largest measurement perpendicular to the longest diameter of the lesion) 15 mm or greater when assessed by CT or MRI.

The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other lesions.

Non-Measurable Disease

- Lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) or truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, and abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.
- Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previously irradiated lesions (or those subjected to other local treatment) are non-measurable unless they have progressed since completion of treatment.

Normal Lesions

- Non-malignant simple cysts should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above.
- Lymph nodes with short axis <10 mm are considered normal and should not be followed as disease.

Tumor Assessments

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. All required scans must be done within the window of time specified in the Schedule of Assessments prior to randomization. If the baseline assessment is inadequate, subsequent statuses generally should be not evaluable.

The determination of whether lesions are measurable is performed only at baseline. “Measurable” at baseline means eligible for selection as target lesions, and thus for quantitative assessment throughout the trial. Once selected as a target lesion, a lesion remains target throughout the trial.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to look for partial response at later assessments.

- If 2 target lesions coalesce the longest diameter measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.
- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.
- When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Non-Target Lesions

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather qualitative evaluations of status will be recorded. Multiple non-target lesions in one organ may be recorded as a single item on the CRF (e.g., ‘multiple liver metastases’).

Objective Response Status at Each Evaluation

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast. If not, subsequent objective statuses may be not evaluable.

Target Disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis < 10 mm). All target lesions must be assessed.
- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.
- Stable Disease (SD): Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.
- Progressive Disease (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy) with a minimum absolute increase of 5 mm.
- Not evaluable:
  - one or more target lesions have not been assessed,
  - or assessment methods used were inconsistent with those used at baseline and impaired assessment,
  - or one or more target lesions cannot be measured accurately (e.g., poorly visible unless due to being too small to measure),
  - or one or more target lesions were excised or irradiated and have not reappeared or increased.

Non-Target Disease

- CR: Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be ‘normal’ in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.

- PD: Unequivocal progression of preexisting lesions. Generally, the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

- Not evaluable: One or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

12.4 Appendix 4 Abbreviated Presentation of RANO-Brain Metastases Criteria[22]

Categorizing Lesions at Baseline

Measurable Lesions:

- Bidimensionally contrast enhancing lesions with clearly defined margins by CT or MRI scan
- Two perpendicular diameters of at least 10mm, visible on two or more axial slices that are 5mm apart with 0-mm skip
- If MRI is performed with thicker slices, size of a measurable lesion at baseline should be two times the slice thickness

Non-Measurable Lesions

- Unidirectional Lesions
- Lesions without sharp delineation(e.g. lesions around a cyst or surgical cavity)
- Lesions with a size less than 2 times slice thickness
- Dural metastases or leptomeningeal disease

Target Lesions:

- At least 2 lesions and up to 5 lesions in patients with multiple lesions
- Should be selected on the basis of size and as those that can be measured reproducibly
- Lesions with prior local treatment can be considered measurable if progression has occurred since the time of local treatment
- A sum of diameters for all target lesions will be calculated and reported as the baseline sum of longest diameters

Non-Target Lesions

- All lesions not designated as target lesions should be recorded as non-target lesions
- Measurements are not required and these lesions should be classified as present, absent, or unequivocal progression, and followed up

Response Assessment of Target and Non-Target Lesions:

Target Lesions:

- Complete Response (CR): Disappearance of all CNS target lesions sustained for at least 4 weeks; with no new lesions, no use of corticosteroids, and patient is stable or improved clinically.
- Partial response (PR): At least a 30% decrease in the sum longest diameter of CNS target lesions, taking as reference the baseline sum longest diameter sustained for at least 4 weeks; no new lesions; stable to decreased corticosteroid dose; stable or improved clinically.
- Progressive disease: At least a 20% increase in the sum longest diameter of CNS target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, at least one lesion must increase by an absolute value of 5 mm or more to be considered progression.
- Stable disease: Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter while on study.

Non-Target Lesions

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

- Complete response: Requires all of the following: disappearance of all enhancing CNS non-target lesions, no new CNS lesions.
- Non-complete response or non-progressive disease: Persistence of one or more non-target CNS lesion or lesions.
- Progressive disease: Any of the following: unequivocal progression of existing enhancing non-target CNS lesions, new lesion(s) (except while on immunotherapy-based treatment), or unequivocal progression of existing tumor-related non-enhancing (T2/FLAIR) CNS lesions. In the case of immunotherapy-based treatment, new lesions alone may not constitute progressive disease.

12.5 Appendix 5: Medications or Substances to be Avoided or Used with Caution During Treatment with Sitravatinib

Drugs with a Known Risk of Torsades de Pointes*

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Aclarubicin (Only on Non US Market)	Aclacin, Aclacinomycine, Aclacinon, Aclaplastin, Jaclacin	Anti-cancer	Cancer
Amiodarone	Cordarone, Pacerone, Nexterone	Antiarrhythmic	Arrhythmia
Anagrelide	Agrylin, Xagrid	Phosphodiesterase 3 inhibitor	Thrombocythemia
Arsenic trioxide	Trisenox	Anti-cancer	Cancer (leukemia)
Astemizole (Removed from US Market)	Hismanal	Antihistamine	Allergic rhinitis
Azithromycin	Zithromax, Zmax	Antibiotic	Bacterial infection
Bepridil	Vascor	Antianginal	Angina Pectoris (heart pain)
Cesium Chloride	Energy Catalyst	Toxin	Alternative therapy cancer
Chloroquine	Aralen	Antimalarial	Malaria
Chlorpromazine	Thorazine, Largactil, Megaphen	Antipsychotic / Antiemetic	Nausea, Schizophrenia, many others
Chlorprothixene (Only on Non US Market)	Truxal	Antipsychotic	Schizophrenia
Cilostazol	Pletal	Phosphodiesterase 3 inhibitor	Intermittent claudication
Ciprofloxacin	Cipro, Cipro-XR, Neofloxin	Antibiotic	Bacterial infection
Cisapride (Removed from US Market)	Propulsid	GI stimulant	Increase GI motility
Citalopram	Celexa, Cipramil	Antidepressant, SSRI	Depression
Clarithromycin	Biaxin, Prevpac	Antibiotic	Bacterial infection
Cocaine	Cocaine	Local anesthetic	Anesthesia (topical)
Disopyramide	Norpace	Antiarrhythmic	Arrhythmia
Dofetilide	Tikosyn	Antiarrhythmic	Arrhythmia
Domperidone (Only on Non US Market)	Motilium, Motillium, Motinorm Costi, Nomit	Antiemetic	Nausea, vomiting

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Donepezil	Aricept	Cholinesterase inhibitor	Dementia (Alzheimer's Disease)
Dronedarone	Multaq	Antiarrhythmic	Arrhythmia
Droperidol	Inapsine, Droleptan, Dridol, Xomolix	Antipsychotic / Antiemetic	Anesthesia (adjunct), nausea
Erythromycin	E.E.S., Robimycin, EMycin, Erymax, Ery- Tab, Eryc Ranbaxy, Erypar, Eryped, Erythrocin Stearate Filmtab, Erythrocot, E-Base, Erythroped, Ilosone, MY-E, Pediamycin, Abboticin, Abboticin-ES, Erycin, PCE Dispertab, Stiemycine, Acnasol, Tiloryth	Antibiotic	Bacterial infection, increase GI motility
Escitalopram	Cipralex, Lexapro, Nexito, Anxiset-E, Exodus, Esto, Seroplex, Elicea, Lexamil, Lexam, Entact, Losita, Reposil, Animaxen, Esitalo, Lexamil	Antidepressant, SSRI	Depression (major), anxiety disorders
Flecainide	Tambocor, Almarytm, Apocard, Ecrinal, Flécaine	Antiarrhythmic	Arrhythmia
Fluconazole	Diflucan, Trican	Antifungal	Fungal infection
Gatifloxacin (Removed from US Market)	Tequin	Antibiotic	Bacterial infection
Grepafloxacin (Removed from US Market)	Raxar	Antibiotic	Bacterial infection
Halofantrine (Only on Non US Market)	Halfan	Antimalarial	Malaria
Haloperidol	Haldol, Aloperidin, Bioperidolo, Brotopon, Dozic, Duraperidol, Einalon S, Eukystol, Halosten, Keselan, Linton, Peluces, Serenace, Serenase, Sigaperidol	Antipsychotic	Schizophrenia, agitation
Hydroquinidine (Dihydroquinidine) (Only on Non US Market)	Serecor	Antiarrhythmic	Arrhythmia
Hydroxychloroquine	Plaquenil, Quineprox	Antimalarial, Anti-inflammatory	Malaria, SLE, rheumatoid arthritis
Ibogaine (Only on Non US Market)		Psychedelic	Narcotic addiction, unproven
Ibutilide	Corvert	Antiarrhythmic	Arrhythmia
Levofloxacin	Levaquin, Tavanic	Antibiotic	Bacterial infection
Levomepromazine (Methotrimeprazine) (Only on Non US Market)	Nosinan, Nozinan, Levoprome	Antipsychotic	Schizophrenia
Levomethadyl acetate (Removed from US Market)	Orlaam	Opioid agonist	Narcotic dependence
Levosulpiride (Only on Non US Market)	Lesuride, Levazeo, Enliva	Antipsychotic	Schizophrenia
Mesoridazine (Removed from US Market)	Serentil	Antipsychotic	Schizophrenia
Methadone	Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadon	Opioid agonist	Narcotic dependence, pain
Moxifloxacin	Avelox, Avalox, Avelon	Antibiotic	Bacterial infection
Nifekalant (Only on Non US Market)	Shinbit	Antiarrhythmic	Arrhythmia

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Ondansetron	Zofran, Anset, Ondemet, Zuplenz, Emetron, Ondavell, Emeset, Ondisolv, Setronax	Antiemetic	Nausea, vomiting
Oxaliplatin	Eloxatin	Anti-cancer	Cancer
Papaverine HCl (Intra-coronary)		Vasodilator, Coronary	Diagnostic adjunct
Pentamidine	Pentam	Antifungal	Fungal infection (Pneumocystis pneumonia)
Pimozide	Orap	Antipsychotic	Tourette's Disorder
Probucol (Removed from US Market)	Lorelco	Antilipemic	Hypercholesterolemia
Procainamide	Pronestyl, Procan	Antiarrhythmic	Arrhythmia
Propofol	Diprivan, Propoven	Anesthetic, general	Anesthesia
Quinidine	Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora	Antiarrhythmic	Arrhythmia
Roxithromycin (Only on Non US Market)	Rulide, Xthrocin, Roxl-150, Roxo, Surlid, Rulide, Biaxsig, Roxar, Roximycinv, Roxomycin, Rulid, Tirabicin, Coroxin	Antibiotic	Bacterial infection
Sevoflurane	Ultane, Sojourn	Anesthetic, general	Anesthesia
Sotalol	Betapace, Sotalex, Sotacor	Antiarrhythmic	Arrhythmia
Sparfloxacin (Removed from US Market)	Zagam	Antibiotic	Bacterial infection
Sulpiride (Only on Non US Market)	Dogmatil, Dolmatil, Eglonyl, Espiride, Modal, Sulpor	Antipsychotic, atypical	Schizophrenia
Sultopride (Only on Non US Market)	Barnetil, Barnotil, Topral	Antipsychotic, atypical	Schizophrenia
Terfenadine (Removed from US Market)	Seldane	Antihistamine	Allergic rhinitis
Terlipressin (Only on Non US Market)	Teripress, Glypressin, Terlipin, Remestyp, Tresil, Teriss	Vasoconstrictor	Septic shock
Terodiline (Only on Non US Market)	Micturin, Mictrol	Muscle relaxant	Bladder spasm
Thioridazine	Mellaril, Novoridazine, Thioril	Antipsychotic	Schizophrenia
Vandetanib	Caprelsa	Anti-cancer	Cancer (thyroid)

* Woosley RL, Heise CW, Gallo T, Tate J, Woosley D and Romero KA, www.CredibleMeds.org, QTdrugs List, [Accession Date: 10 April 2020], AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755; for the most current information, access the website: www.CredibleMeds.org.

Drugs with Conditional Risk of Torsades de Pointes*

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Abiraterone	Zytiga, Abiratas, Abretone, Abirapro	Anti-androgen	Cancer (Prostate)
Amantadine	Symmetrel, Symadine	Antiviral	Viral infection (Influenza), Parkinson's disease
Amisulpride	Barhemsys, Solian, Supitac, Soltus, Amitrex, Amazeo	Antiemetic, Antipsychotic	Nausea and vomiting, postoperative

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Amitriptyline	Elavil (Discontinued 6/13), Tryptomer, Tryptizol, Laroxyl, Saroten, Sarotex Lentizol, Endep	Antidepressant, Tricyclic	Depression
Amphotericin B	Fungilin, Fungizone, Abelcet, AmBisome, Fungisome, Amphocil, Amphotec	Antifungal	Fungal infection
Amsacrine (Acridinyl anisidide)(Only on Non US Market)	Amsidine	Antineoplastic Agent	Cancer (Acute Lymphoblastic Leukemia)
Atazanavir	Reyataz, Evotaz	Antiviral	Viral infection (HIV/AIDS)
Bendroflumethiazide (Bendrofluazide)	Aprinox, Corzide	Diuretic, thiazide	Hypertension, diuresis
Chloral hydrate	Aquachloral, Novo-Chlorhydrate, Somnos, Noctec, Somnote	Sedative	Sedation, insomnia
Cimetidine	Tagamet	Antacid	Gastric hyperacidity, GERD
Clomipramine	Anafranil	Antidepressant, Tricyclic	Depression
Diphenhydramine	Benadryl, Nytol, Unisom, Sominex, Dimedrol, Daedalon, Banophen	Antihistamine	Allergic rhinitis, insomnia
Doxepin	Sinequan, Silenor, Aponal, Adapine, Doxal, Deptran, Sinquan	Antidepressant, Tricyclic	Depression
Eperisone (Only on Non US Market)	Myonal, Epry	Antispasmodic	Spasticity
Esomeprazole	Nexium, Nexum, Inexium	Proton Pump Inhibitor	Gastric hyperacidity, GERD
Famotidine	Pepcid, Fluxid, Quamatel	H2-receptor antagonist	Gastric hyperacidity, GERD
Fluoxetine	Prozac, Sarafem, Fontex	Antidepressant, SSRI	Depression
Fluvoxamine	Faverin, Fevarin, Floxyfral, Dumyrox, Luvox	Selective Serotonin Reuptake Inhibitor	Depression, Obsessive Compulsive Disorder
Furosemide (frusemide)	Lasix, Fusid, Frumex, Lasilix	Diuretic	Hypertension, diuresis
Galantamine	Reminyl, Nivalin, Razadyne-ER, Lycoremine	Cholinesterase inhibitor	Dementia (Alzheimer's Disease)
Garenoxacin (Only on Non US Market)	Geninax	Antibiotic	Bacterial infection
Hydrochlorothiazide	Apo-Hydro, Aquazide H, BP Zide, Dichlotride, Hydrodiuril, HydroSaluric, Microzide, Esidrex, Oretic	Diuretic	Hypertension, diuresis
Hydroxyzine	Atarax, Vistaril, Aterax, Alamon, Durrax, Equipose, Masmoran, Orgatrax, Paxistil Quiess, Tran-Q, Tranquizine	Antihistamine	Allergic reaction, anxiety disorders
Indapamide	Lozol, Natrilix, Insig	Diuretic	Hypertension, diuresis
Itraconazole	Sporanox, Onmel	Antifungal	Fungal infection
Ivabradine	Procoralan, Coralan, Corlentor, Coraxan, Ivabid, Bradia	Antianginal	Angina Pectoris (heart pain)
Ketoconazole	Nizoral, Sebizole, Ketomed, Keton	Antifungal	Fungal infection
Lansoprazole	Prevacid, Ogast	Proton Pump Inhibitor	Gastric hyperacidity, GERD
Loperamide	Imodium	Opioid agonist	Diarrhea
Metoclopramide	Reglan, Afipran, Maxolon, Cerucal, Clopamon, Clopra, Maxeran, Maxolon,	Antiemetic	Nausea, vomiting

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
	Metozolv, Plasil, Pramin, Primperan, Perinorm		
Metolazone	Zytanix, Zaroxolyn, Mykrox	Diuretic	Hypertension, diuresis
Metronidazole	Flagyl	Antibiotic	Trichomoniasis, amebiasis, bacterial infection
Nelfinavir	Viracept	Antiviral	Viral infection (HIV/AIDS)
Olanzapine	Zyprexa, Zydis, Relprevv	Antipsychotic, atypical	Schizophrenia, bipolar disorder
Omeprazole	Losec, Prilosec, Zegerid, Mopral	Proton Pump Inhibitor	Gastric hyperacidity, GERD
Pantoprazole	Protonix, Inipomp, Eupantol	Proton Pump Inhibitor	Gastric hyperacidity, GERD
Paroxetine	Paxil, Aropax, Pexeva, Seroxat, Sereupin, Seroxat, Deroxat	Antidepressant, SSRI	Depression
Piperacillin/Tazobactam	Tazosyn, Zosyn	Antibiotic	Bacterial infection
Posaconazole	Noxafil, Posamol	Antifungal	Fungal infection
Propafenone	Rythmol SR, Rytmonorm	Sodium channel blocker	Arrhythmia
Quetiapine	Seroquel	Antipsychotic, atypical	Schizophrenia
Quinine sulfate	Qualaquin, Hexaquine	Antimalarial	Malaria, leg cramps
Ranolazine	Ranexa, Ranozex	Antianginal	Angina Pectoris (heart pain)
Risperidone	Risperdal	Antipsychotic, atypical	Schizophrenia
Sertraline	Zoloft, Lustral	Antidepressant, SSRI	Depression
Solifenacin	Vesicare	Muscle relaxant	Bladder spasm
Telaprevir	Incivo, Incivek	Antiviral	Viral infection (hepatitis C)
Torsemide (Torasemide)	Demadex, Diuver, Examide	Diuretic	Hypertension, diuresis
Trazodone	Desyrel, Oleptro, Beneficat, Deprax, Desirel, Molipaxin, Thombran, Trazorel, Trialodine, Trittico, Mesyrel	Antidepressant, SARI	Depression, insomnia
Voriconazole	VFend	Antifungal	Fungal infection
Ziprasidone	Geodon, Zeldox	Antipsychotic, atypical	Schizophrenia

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Sensitive Substrates and Substrates with Narrow Therapeutic Index for P-gp and BCRP transporters

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

Sensitive Substrates and Substrates with Narrow Therapeutic Index for the indicated CYP3A4 Enzymes

Enzyme	
CYP3A4	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, tolvaptan, triazolam, vardenafil

12.6 Appendix 6 – Pill Diary

Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

STUDY MEDICATION CALENDAR
(Research Nurse to fill out all this top information)

Patient's Name/ ID#: **Total #Pills Dispensed/Cycle_____**
HIC# **Total #Pills Returned/Cycle_____**
Cycle# **Total # Pills Taken/Cycle_____**
RN signature/Date_____

Day of the week	Day of the week	Day of the week	Day of the week	Day of the week	Day of the week	Day of the week
Day of Cycle 1 ____# of Pills Taken ___:___ AM ___:___ PM	Day of Cycle 2 ____# of Pills Taken ___:___AM ___:___PM	Day of Cycle 3 ____# of Pills Taken ___:___AM ___:___PM	Day of Cycle 4 ____# of Pills Taken ___:___AM ___:___PM	Day of Cycle 5 ____# of Pills Taken ___:___ AM ___:___ PM	Day of Cycle 6 ____# of Pills Taken ___:___ AM ___:___ PM	Day of Cycle 7 ____# of Pills Taken ___:___ AM ___:___ PM
Day of Cycle 8 ____# of Pills Taken ___:___ AM ___:___ PM	Day of Cycle 9 ____# of Pills Taken ___:___ AM ___:___ PM	Day of Cycle 10 ____# of Pills Taken ___:___ AM ___:___ PM	Day of Cycle 11 ____# of Pills Taken ___:___ AM ___:___ PM	Day of Cycle 12 ____# of Pills Taken ___:___AM ___:___PM	Day of Cycle 13 ____# of Pills Taken ___:___ AM ___:___PM	Day of Cycle 14 _ ___# of Pills Taken ___:___ AM __:___ PM
Day of Cycle 15 ____# of Pills Taken ___:___ AM ___:___ PM	Day of Cycle 16 ____# of Pills Taken ___:___ AM ___:___ PM	Day of Cycle 17 ____# of Pills Taken ___:___ AM ___:___ PM	Day of Cycle 18 ____# of Pills Taken ___:___ AM ___:___ PM	Day of Cycle 19 ____# of Pills Taken ___:___ AM ___:___ PM	Day of Cycle 20 ____# of Pills Taken ___:___ AM ___:___ PM	Day of Cycle 21 ____# of Pills Taken ___:___ AM ___:___ PM
Day of Cycle 22 ____# of Pills Taken ___:___ AM ___:___ PM	Day of Cycle 23 ____# of Pills Taken ___:___ AM ___:___PM	Day of Cycle 24 ____# of Pills Taken ___:___ AM ___:___ PM	Day of Cycle 25 ___# of Pills Taken ___:___AM ___:___PM	Day of Cycle 26 ____# of Pills Taken ___:___ AM ___:___PM	Day of Cycle 27 ____# of Pills Taken ___:___ AM __:___ PM	Day of Cycle 28 ____# of Pills Taken ___:___ AM ___:___PM
Day of Cycle 29 ___# of Pills Taken ___:___ AM ___:___ PM	Day of Cycle 30 ___# of Pills Taken ___:___ AM ___:___ PM	Day of Cycle 31 ___# of Pills Taken ___:___ AM ___:___ PM	**Please be sure to bring this calendar and all your remaining pills and pill bottles with you for your return appointment at the end of each cycle, and return them to the person who gave them to you. Please sign that you have returned all the pills and/or pill bottles.** **Patient signature_____Date_____**			

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