Protocol Number: MRTX-500

Official Title: A Parallel Phase 2 Study of Glesatinib, Sitravatinib or Mocetinostat in Combination With Nivolumab in Advanced or Metastatic Non-Small Cell Lung Cancer

NCT Number: NCT02954991

Document Date: 11-February-2020

MIRATI
THERAPEUTICS

CLINICAL RESEARCH PROTOCOL

DRUG:	Glesatinib, Provisional USAN Name (MGCD265) Sitravatinib, Provisional USAN Name (MGCD516) Mocetinostat (MGCD0103) Nivolumab (OPDIVO®)
STUDY NUMBER(S):	MRTX-500
PROTOCOL TITLE:	A Parallel Phase 2 Study of Glesatinib, Sitravatinib or Mocetinostat in Combination With Nivolumab in Advanced or Metastatic Non-Small Cell Lung Cancer
IND NUMBER:	130023
SPONSOR:	Mirati Therapeutics, Inc. 9393 Towne Centre Drive, Suite 200 San Diego, California, 92121, USA
ORIGINAL PROTOCOL DATE:	05 May 2016
VERSION NUMBER:	V6.0 (Amendment #5)
VERSION DATE:	11 February 2020

DOCUMENT HISTORY

Document	Version Date	Summary of Changes
Original Protocol, Version 1.0	05 May 2016	NA
Amendment #1, Version 2.0	31 May 2016	At the request of US Food and Drug Administration during IND review: • Revised definition of Dose Limiting Toxicity to include any grade 4 non-hematologic toxicity and any toxicity requiring treatment suspension for more than 2 weeks. • Added inclusion criterion that patients with tumors positive for *EGFR* mutation or *ALK* fusion must have received treatment with an applicable tyrosine kinase inhibitor.
Amendment #2, Version 3.0	06 June 2017	Study Summary: • Added study arm allowing for enrollment of patients who have experienced disease progression after prior first line chemotherapy (checkpoint inhibitor therapy [CIT] naïve). Patients will be stratified by PD-L1 expression. • Revised statistical considerations to Predictive Probability Design allowing for flexibility in the number of evaluable patients for making study decisions. Schedule of Assessments (Table 1): • Added clarification for CIT Naïve cohorts for PD-L1 testing prior to enrollment. • Clarified footnote 12 to require collection of RR interval to calculate QTcF. • Removed requirement for ECHO at Cycle 2 for patients in the mocetinostat and sitravatinib arms. • Clarified footnote 13 for the timing of on-study disease evaluations to be calculated based on the calendar from the first day of dosing. Section 1 Introduction: • Updated clinical data section for consistency with the most current version of the Investigator's Brochure for glesatinib, sitravatinib and mocetinostat and the nivolumab package insert. Section 1.9 Study Rationale: • Added rationale for including patients who are checkpoint inhibitor therapy naïve. Section 3 Study Design: • Added study arm allowing for enrollment of patients who have experienced disease progression after prior first line chemotherapy (checkpoint

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		inhibitor therapy [CIT] naïve). Patients will be stratified by PD-L1 expression. • Revised statistical considerations to Predictive Probability Design allowing for flexibility in the number of evaluable patients for making study decisions. • Added definition of evaluable population. • Nivolumab will be administered as per the approved labeling of 240 mg every 2 weeks (per Protocol Administrative letter dated 26Sep16). Section 4.1 Inclusion criteria: • Inclusion criteria #2: updated to include patients who have not received prior treatment with a checkpoint inhibitor in the CIT naïve arm. • Removed criteria #2b and included these patients in exclusion criteria #2. • Added inclusion criteria #3 regarding PD-L1 assay for CIT naïve patients. Section 4.2 Exclusion criteria: • Revised exclusion #1 to note that patients are eligible if brain metastases are adequately treated and patients are neurologically stable (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to enrollment without the use of corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent). • Added exclusion #1a: Patients with carcinomatous meningitis. • Added exclusion #2: Patients who test positive for *EGFR, ROS1, ALK* mutations or *ALK* fusions or any other mutations for which there are tyrosine kinase inhibitors available or under development. • Revised exclusion #7 to include patients with a history of chronic hepatitis C that is no longer present. Section 5 Study Treatments: • Added reference to the Pharmacy Manual for details on dose strengths, bottle size and number of units per bottle supplied. Section 5.4 Concomitant medications and Appendix 3: • Added sitravatinib arm patients to those who should avoid medications that may prolong QT interval. Section 7.3.5 Sample collection for PD-L1 expression:

Document	Version Date	Summary of Changes
		• Added language regarding tissue sample collection for PD-L1 expression through the central laboratory for the CIT naïve cohort. Section 9.1.2 Statistics: • Revised statistical considerations to Predictive Probability Design allowing for flexibility in the number of evaluable patients for making study decisions. • Added statistics regarding CIT naïve patients. Section 9.3.2 Statistics: • Added definition of Phase 2 clinical activity evaluable population. Addressed clerical errors and made minor clarifications.
Amendment #3, Version 4.0	15 June 2018	• Added update on status of glesatinib, sitravatinib and mocetinostat cohorts. • Updated anticipated number of patients in study. • Added update on preliminary results of sitravatinib plus nivolumab segment of study in Section 1.5.3.2.2. • Added two sitravatinib PK sub-studies: o Appendix 5 – PK of three sitravatinib capsule formulations o Appendix 6 – PK of sitravatinib administered with food • Adjusted sitravatinib CIT-experienced cohort expansion plan following discussion with the US FDA: combined CIT-experienced cohorts (prior clinical benefit and no prior clinical benefit) for the purpose of enrollment expansion, with the limit of 125 patients in the combined population. • Eliminated potential consideration of expansion of enrollment into sitravatinib CIT-naïve cohorts beyond Stage 2. • Clarified schedule for triplicate ECGs. • Clarified exclusion criterion concerning patients with tumors having driver mutations. • Updated details concerning sitravatinib free-base capsule content and storage. • Added guidance for sitravatinib or nivolumab dose management: o Sitravatinib recommended Phase 2 starting dose: 120 mg QD.

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		○ Following sitravatinib dose reduction and control of adverse event, re-challenge at a higher sitravatinib dose is permitted at the discretion of the Investigator. ○ In the event of sitravatinib-related AE, dose reduction with continuous treatment is preferred over repeated dose interruption. ○ If sitravatinib or nivolumab treatment is interrupted, administration of the other study drug may continue at the discretion of the Investigator. • Updated nivolumab information and guidance to OPDIVO US Prescribing Information dated April 2018. Provided web site with current manufacturer updates for consultation during conduct of the study. ○ Updated recommended dose of nivolumab to either 240 mg Q2W or 480 mg Q4W, infused over approximately 30 minutes, per Product Information changes and at the discretion of the Investigator. ○ Updated reprint of nivolumab AE management guidelines per OPDIVO US Product Information dated April 2018. • Added that disease assessments will be performed until objective disease progression is documented or subsequent anti-cancer therapy is begun. • Addressed clerical errors and made minor clarifications.
Amendment #4, Version 5.0	16 August 2018	Following FDA review of Amendment #3, Amendment # 4 is implemented to provide additional details in the update on clinical experience in the sitravatinib segment of the study and to clarify the purpose of enrollment beyond Stage 2. The two amendments together describe changes to the protocol for Study MRTX-500. A document showing a composite of the changes is available from the Sponsor. • Updated preliminary safety and clinical activity results of ongoing studies of sitravatinib monotherapy and the sitravatinib plus nivolumab segment of the current study in Section 1.5.3.2. • Clarified that the purpose of enrollment beyond Stage 2 is to further evaluate safety and efficacy in the treatment setting (previous description of the purpose was to narrow the 95% CI around the ORR point estimate). • Clarified timing of early triplicate ECGs for patients participating in the PK sub-studies that includes a lead-in period.

Document	Version Date	Summary of Changes
		• Exempted patients enrolled in PK sub-studies from participation in flow cytometry and protein/cytokine biomarker studies to reduce blood sample collection. • Increased the potential size of patient cohorts in the sitravatinib formulation sub-study from 8-10 patients to as many as 12 patients per cohort.
Amendment #5, Version 6.0	11 February 2020	The rationale for this protocol amendment is to incorporate study information that were provided via various protocol administrative letters during 2018, 2019 and 2020 specifically in the following sections: • 24Oct2018 Administrative Letter to the Protocol providing a modified process for PK sub-study as outlined within Appendix 5 based on the Food and Drug Administration's review and feedback for the study protocol amendment #4 • 28Jan2019 Administrative Letter to the Protocol clarifying Inclusion Criterion #2 and Exclusion criterion #3 for the patients participating in the PK sub-studies as outlined within Appendix 5 and Appendix 6 • 18Mar2019 Clarification / modifications regarding Pharmacokinetic (PK) collection timepoints for the PK sub-studies described within Appendix 5 and Appendix 6 • 10Apr2019 letter clarifying the protocol exclusion criterion #2 for patients participating for the PK sub-study • 16May2019 Administrative Letter providing modified recommendations to section 5.1.4.2.5: Management of Investigational Study Treatment in Event of Non-Hematological Toxicities • 28Aug2019 Update to the sitravatinib Drug Formulation Pharmacokinetic (PK) sub-study as described within Appendix 5 • 18Oct2019 Administrative Letter to the Protocol providing a revised meal requirement for patients participating in the sub-study to evaluate PK of sitravatinib administered with food (Appendix 6) based on Food and Drug Administration's feedback. • 09Jan2020 Administrative Letter to the Protocol to provide the starting dose of sitravatinib for Cohort-3 of the Pharmacokinetic drug formulation sub-study with sitravatinib malate capsules (roller compaction formulation) and the food effect sub-study cohort with sitravatinib malate capsules

Document	Version Date	Summary of Changes
		• Provide more clarity with unacceptable toxicity on prior checkpoint inhibitor treatment (CIT-experienced patients only) within Exclusion Criterion #4 • Provide clarification with active or prior immunocompromising conditions within Exclusion Criterion #6 • Updates provided to sitravatinib formulation, packaging and storage within section 5.1.2.1 • Table 9: Sitravatinib Dose Reductions were updated based on sitravatinib dose formulations utilized in the study • Table 15: Investigational Study Treatment Dose Modifications – Non-Hematological Drug-Related Toxicities was updated to provide clarity • Global change: volume of water during sitravatinib administration was updated to keep it consistent across all sitravatinib dosings • Global editorial changes and fix formatting errors

STUDY SUMMARY

Title: A Parallel Phase 2 Study of Glesatinib, Sitravatinib or Mocetinostat in Combination With Nivolumab in Advanced or Metastatic Non-Small Cell Lung Cancer

Rationale: Combining an immunotherapeutic PD-1/PD-L1 checkpoint inhibitor with an agent that has both immune modulatory and antitumor properties could enhance the antitumor efficacy observed with either agent alone.

The use of tyrosine kinase inhibitors (TKIs) to treat cancer is well established based on robust clinical efficacy achieved with well-tolerated inhibitors directed toward oncogenic tyrosine kinases. In addition, selected TKIs have been shown to modulate the immunogenic status of tumors, improve tumor perfusion by reducing intratumoral pressure and modulate subsets of immune cells, increasing the frequency and function of effector immune elements, while decreasing the number and function of immune suppressor cells. Taken together, these effects on the tumor microenvironment (TME) may lead to improved efficacy when TKIs are combined with checkpoint inhibitors. The TAM (Tyro3, Axl and MERTK) receptor tyrosine kinases (RTKs) are expressed by select innate immune cell subpopulations including macrophages and dendritic cells. The TAM receptors cooperate to create and maintain an immunosuppressive TME. MERTK suppresses the M1 macrophage pro-inflammatory cytokine response involving IL-12, IL-6 and TNF and enhances M2 macrophage anti-inflammatory cytokine production involving IL-10, IL-4, TGFβ and hepatocyte growth factor (HGF). Given that anti-tumor host defense is usually mediated by cytotoxic T lymphocytes whose activation and stimulation is supported by Th1 type cytokines, the inhibition of Axl and MERTK are predicted to enhance an anti-tumor immune response. Furthermore, both Axl and MERTK are expressed by natural killer (NK) cells and negatively regulate NK cell activity in the TME as part of a feedback regulatory mechanism resulting in decreased NK cell anti-tumor activity and enhanced tumor progression and metastasis. Given the immunosuppressive function of TAM RTKs in the TME, inhibition of Axl and MERTK may complement PD-1/PD-L1 checkpoint inhibition to unleash the host anti-cancer immune response.

The MET (Mesenchymal-Epithelial Transition) RTK is implicated in modification of tumor immune responses based on its role in mediating an immunosuppressive TME as well as its role in regulating antigen presenting cell (APC) function. MET is expressed by

immature CD14-positive monocytes and can induce an immunosuppressive phenotype when its ligand, hepatocyte growth factor (HGF), is secreted by tumor stroma and mesenchymal stem cells (MSCs). Depletion of CD14-positive monocytes or neutralization of HGF secretion by MSCs reverses the suppression of T effector proliferation and triggers a shift back toward a Th1 activated T cell phenotype. MSCs are also implicated in expansion of immunosuppressive myeloid-derived suppressor cells (MDSCs), which are also dependent on the secretion of HGF. APCs (i.e., dendritic cells) also express MET and the activation of MET by HGF results in suppression of APC function including both antigen presenting capacity and antigen-dependent T cell responses. Therefore, inhibition of MET may enhance the antitumor response by restoring APC function and reducing or eliminating MDSCs within the TME.

Glesatinib is an orally administered multi-targeted TKI that primarily targets the Axl and MET receptors. Additional RTK targets potentially include the MERTK, DDR2, and PDGFRα and β receptors. The TKI profile of glesatinib suggests the potential for synergistic anti-tumor effect when administered in combination with a checkpoint inhibitor.

Inhibition of the VEGF receptor family and KIT may further enhance antitumor immunoreactivity by depletion of immunosuppressive cellular subset from the TME including regulatory T cells and MDSCs. T regulatory cells express VEGFR2 and the inhibition of VEGFR2 utilizing a specific VEGFR2 antibody antagonist or VEGFA neutralizing antibody (but not a VEGFR1 antagonist) inhibited Treg proliferation in vitro and in tumor-bearing mice and patient peripheral blood. MDSCs notably express both KIT and VEGFR1 and the inhibition of these RTKs using pharmacologic or genetic approaches resulted in the inhibition of MDSC viability in vitro and depletion of this cell population in mouse tumor models.

Sitravatinib is an orally-available, potent small molecule inhibitor of a closely related spectrum of RTKs including MET, Axl, MERTK, VEGFR family, PDGFR family, KIT, FLT3, Trk family, RET, DDR2, and selected Eph family members. In addition to the immunostimulatory effects of Axl and MET inhibition, sitravatinib may further condition the TME in favor of antitumor activity by its immunomodulatory effects mediated through VEGFR and KIT inhibition.

Histone deacetylases (HDACs) have been implicated in the epigenetic regulation of innate and adaptive immunity. Increasing evidence supports the proposal that spectrum-selective inhibitors of class I HDACs can reverse immune evasion and elicit antitumor host response through immunostimulatory mechanisms. The immunomodulatory properties of class I HDAC inhibitors are reported to be mediated through multiple mechanisms including: 1) induction of programmed cell death ligand 1 (PD-L1) expression on the tumor cell surface, 2) induction of tumor associated antigens (TAAs) and MHC Class I and Class II molecules on tumor cells, 3) induction of immunogenic cell death via activation and cross-presentation of tumor antigens by antigen presenting cells (APCs), 4) enhanced function of T effector cells, and 5) decreased function of immunosuppressive cell subsets including Tregs and MDSCs. In addition, HDAC inhibitors are associated with anticancer effects through inhibiting cell cycle progression and inducing apoptosis in tumor cells.

Mocetinostat is an orally administered spectrum-selective Class I/IV HDAC inhibitor specifically targeting HDACs 1, 2, 3 and 11. Given these pleiotropic immune activating effects of class I HDAC inhibitors, combination therapy of mocetinostat with checkpoint inhibition may result in increased efficacy compared to immunotherapy alone.

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response.

This study will evaluate the clinical activity of nivolumab in combination with 3 separate investigational agents, glesatinib, sitravatinib or mocetinostat. The study will begin with a lead-in dose escalation evaluation in small cohorts of patients administered one of the investigational study treatments in combination with nivolumab. Following identification of the dose level to be used in the Phase 2 evaluation for each investigational study treatment, full enrollment will proceed.

Target Population: Patients with advanced or metastatic non-squamous NSCLC, who have experienced disease progression on or after prior treatment with a checkpoint inhibitor therapy (CIT) (CIT- experienced) or patients who have experienced disease progression after prior first line platinum-based doublet chemotherapy (CIT- naive).

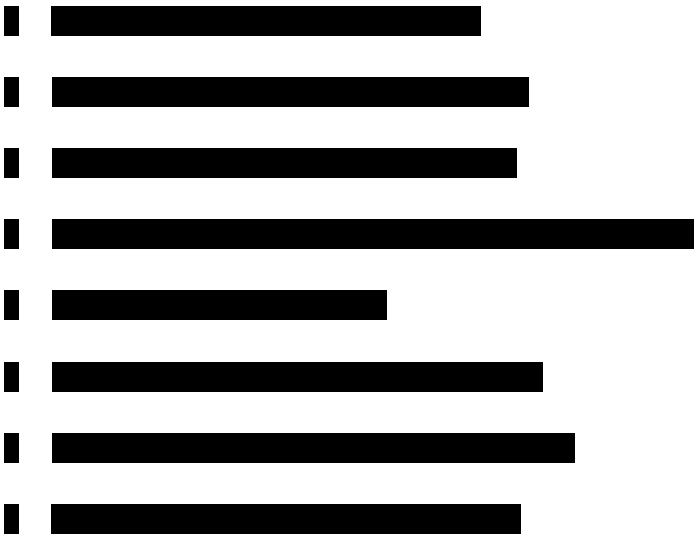
Number in Trial:	As many as 280 patients.
Primary Objective:	To evaluate the clinical activity of nivolumab in 3 combination regimens with the investigational agents glesatinib, sitravatinib, or mocetinostat, in patients with non-squamous NSCLC.
Secondary Objectives:	• To evaluate the safety and tolerability of the combination regimens in the selected population. • To evaluate secondary efficacy endpoints of the combination regimens in the selected population. • To evaluate the pharmacokinetics (PK) of the investigational agents administered in combination with nivolumab. • To evaluate the PK of three sitravatinib capsule formulations. • To evaluate the PK of sitravatinib administered with food.
Exploratory Objectives:	[redacted]
Primary Endpoints:	Objective Response Rate (ORR) as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).

Secondary Endpoints:	• Safety characterized by type, incidence, severity, timing, seriousness and relationship to study treatment of adverse events and laboratory abnormalities.
	• Secondary efficacy endpoints:
	  o Duration of Response (DR);
	  o Clinical Benefit Rate (CBR);
	  o Progression-Free Survival (PFS);

- 1-Year Survival Rate; and
- Overall Survival (OS).

- Blood plasma concentrations of the investigational agents.

Exploratory Endpoints:



Study Segment Update

June 2018

Glesatinib: Enrollment into glesatinib cohorts was discontinued in November 2017 as the result of Sponsor portfolio reprioritization. The decision was not based on patient safety in Study MRTX-500. Five patients were treated with nivolumab plus glesatinib in this study.

Sitravatinib: Enrollment is ongoing in all sitravatinib cohorts. A brief summary of preliminary results available to date is presented in Section 1.5.3.2.2.

Mocetinostat: Enrollment into mocetinostat cohorts is not planned at this time. Results from a parallel Phase 1/2 clinical trial of mocetinostat in combination with durvalumab, a PD-L1 inhibitor, are pending. Plans for further investigation of mocetinostat in combination with checkpoint inhibitor therapies are pending.

Study Design: Study MRTX-500 is an open-label, parallel Phase 2 evaluation of nivolumab in combination with 3 investigational agents, glesatinib, sitravatinib or mocetinostat, in patients with locally advanced, unresectable or metastatic non-squamous NSCLC. Patients who have experienced progression of disease on or after treatment with a checkpoint inhibitor (CIT-experienced) as well as those who have experienced disease progression after treatment with platinum-based doublet chemotherapy (CIT- naïve) will be enrolled. The primary

objective is to evaluate the clinical activity of the combination study treatments using ORR in accordance with RECIST 1.1. Secondary objectives include evaluation of safety, secondary efficacy endpoints, and PK for the investigational agents. The Schedule of Assessments to be performed in the study is presented in Table 1. Pharmacokinetic and blood biomarker sample collection and triplicate ECG assessment time points are presented in Table 2, Table 3, and Table 4. Specifics of two sitravatinib sub-studies are presented in appendices, including the PK evaluation of three sitravatinib capsule formulations (Appendix 5) and the PK of sitravatinib administered with food (Appendix 6).

The treatment arms included in this study are the following:

1. Glesatinib plus nivolumab.

2. Sitravatinib plus nivolumab.

3. Mocetinostat plus nivolumab.

To control bias in assignment of individual patients to treatment arms and to mitigate the risk of medication errors with the 3 investigational study treatments administered in specific regimens, study sites will be aligned with one specified treatment combination. Site alignment may change as patient cohorts are filled or patient recruitment factors shift at sites.

The study will begin with a lead-in dose escalation evaluation of two dose levels of each investigational agent in combination with nivolumab in small cohorts of CIT-experienced patients. The dose escalation plan is described below under Study Treatments and in more detail in Section 3.1.

Following completion of the lead-in dose escalation evaluation, enrollment into the Phase 2 will proceed.

For CIT-experienced patients, each investigational study treatment arm (i.e., glesatinib, sitravatinib and mocetinostat) will be stratified by prior outcome of treatment with a checkpoint inhibitor:

a. Clinical benefit (i.e., RECIST defined partial, complete response or stable disease for at least 12 weeks [-2 week window permitted for radiograph scheduling]) followed by radiographic progression of disease.

b. No prior clinical benefit (i.e., radiographic progression of disease ≤ 12 weeks after initiation of treatment [+2 week window permitted for radiograph scheduling]).

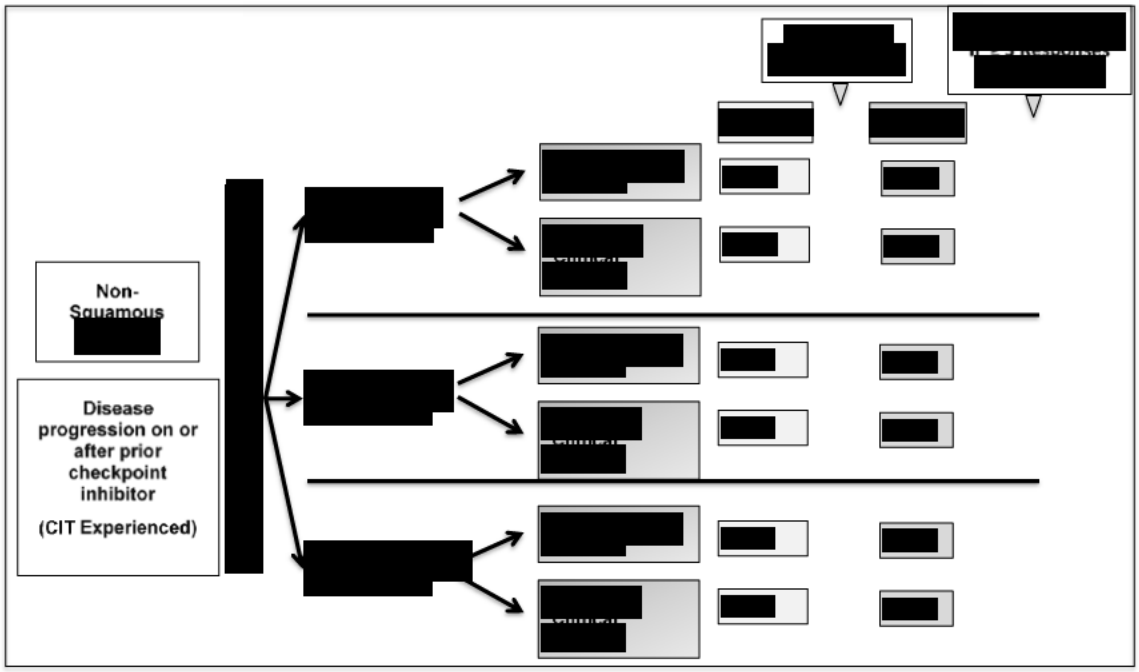
For patients without prior checkpoint inhibitor therapy (CIT-naïve), each investigational study treatment arm (i.e., glesatinib, sitravatinib, and mocetinostat) will be stratified according to PD-L1 status:

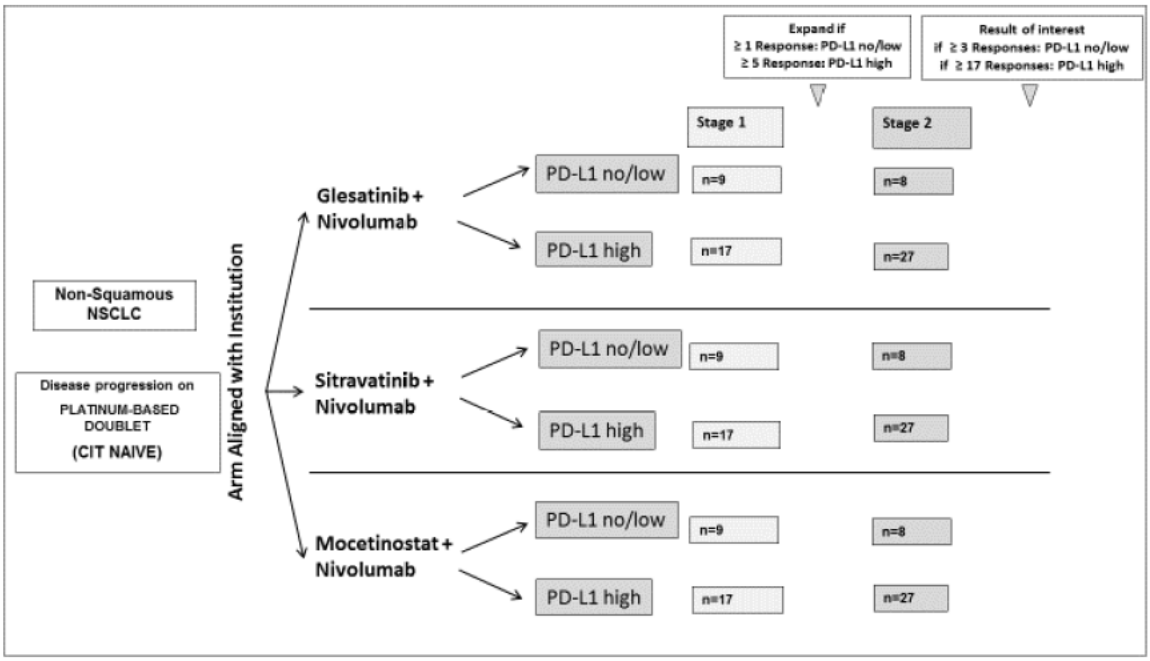
a. Having tumor with no/low PD-L1 expression.

b. Having tumor with high PD-L1 expression.

Tumor PD-L1 expression will be determined by the PD-L1 (28-8) companion diagnostics (CDx) assay completed through the central laboratory. No/low PD-L1 expression is defined as positivity < 5% of tumor cells; high PD-L1 expression is defined as positivity ≥ 5% of tumor cells. Tumor samples used to establish PD-L1 expression for eligibility must have been collected after the most recent systemic therapy.

The main Phase 2 study will include 12 parallel evaluations of clinical activity of nivolumab combination regimens (depicted in the figure below). A Predictive Probability Design will be applied to each treatment arm, as described under Statistical Considerations. Patients enrolled in the lead-in dose escalation evaluation and receiving the dose of investigational study treatment selected for the Phase 2 study will be included in the analysis of the Phase 2 endpoints.


Non-
Squamous
Disease progression on or after prior checkpoint inhibitor
(CIT Experienced)


Expand if
≥ 1 Response: PD-L1 no/low
≥ 5 Response: PD-L1 high
Result of interest
if ≥ 3 Responses: PD-L1 no/low
if ≥ 17 Responses: PD-L1 high
Stage 1
Stage 2
Non-Squamous NSCLC
Disease progression on PLATINUM-BASED DOUBLET (CIT NAIVE)
Arm Aligned with Institution
Glesatinib + Nivolumab
Sitravatinib + Nivolumab
Mocetinostat + Nivolumab
PD-L1 no/low
PD-L1 high
n=9
n=17
n=8
n=27

Disease response and progression as documented by the Investigator in the Case Report Form (CRF) will be the basis for patient management and study expansion decision making. Unconfirmed objective responses recorded in the CRF may be used as the initial basis for expansion of study enrollment; however, follow-up evaluations on patients with unconfirmed responses must continue to support the decision to continue to the full number of patients to be included in the next stage. Disease assessments will be performed until objective disease progression is documented or subsequent anti-cancer therapy is begun. Central radiology review for disease response and progression may be added to the study during Stage 2. If this occurs, central review of all radiologic assessments performed in the study will be expected (including retrospective review of patients enrolled in Stage 1), and central radiology review for disease response will be the basis for the primary statistical analyses to estimate the objective response rate and its confidence interval, as well as the duration of response and PFS.

Study Treatments:

Throughout the study, nivolumab will be administered in accordance with approved labeling. Nivolumab is to be administered by intravenous infusion, using either regimen included in the approved label: 240 mg every 2 weeks (Q2W) or 480 mg every 4 weeks (Q4W). Guidance for adverse event management and associated nivolumab treatment modifications are provided in product labeling and replicated in Section 5.2.

The investigational agents will be administered in the following regimens:

1. Glesatinib tablets administered orally, twice daily (BID).
2. Sitravatinib capsules administered orally, once daily (QD).
3. Mocetinostat capsules administered orally, three times weekly (TIW, e.g., Monday, Wednesday and Friday).

The study will begin with a lead-in dose escalation evaluation of two dose levels of each investigational agent in combination with nivolumab in small cohorts of CIT-experienced patients. In addition, a dose de-escalation step may be undertaken as appropriate.

Investigational Study Drug Starting Dose Levels for Cohorts of Patients in the Lead-In Dose Evaluation

Drug	Regimen	Dose Escalation Steps		
		1	2	-1
Glesatinib Tablets	Twice Daily	500 mg	750 mg	350 mg
Sitravatinib Capsules	Once Daily	120 mg	150 mg	80 mg
Mocetinostat Capsules	Three Times Weekly	70 mg	90 mg	50 mg

Guidelines for adverse event management and associated treatment modifications of each agent are provided in Section 5.1.

The dose escalation phase of the study will employ the modified toxicity probability interval (mTPI) method for dose escalation and reduction decision making.

Statistical Considerations:

This Phase 2 study will use a Predictive Probability Design (Lee-2008) in each treatment arm and strata. In creating the statistical designs, the Type 1 error (α) is constrained to <0.05 and Power ($1-\beta$) is constrained to $\geq$0.90.

Statistical Design Applied to CIT-Experienced and CIT-Naïve with No/Low PD-L1 Expression

The ORR using nivolumab in the population with advanced non-squamous NSCLC having prior disease progression on a checkpoint inhibitor or patients with non-squamous NSCLC without prior checkpoint inhibitor therapy with no/low PD-L1 expression is assumed to be 5% (p_0); thus, this rate is considered uninteresting. The target ORR using the investigational agents in combination with nivolumab in this study is 30% (p_1). Stage 1 of enrollment will include a minimum of 9 evaluable patients in each treatment strata. With exactly 9 evaluable patients at Stage 1, if at least 1 patient has an Objective Response, 8 additional evaluable patients will be enrolled in the treatment stratum, for a total sample size of 17 evaluable patients. If at least 3 Objective Responses are observed in a treatment stratum, further investigation may be warranted. If the true ORR is 5% (null hypothesis), the probability of early termination during the study is 0.63; the Type 1 error is equal to 0.0466 and the power is equal to 0.9045.

Statistical Design Applied to CIT-Naïve with High PD-L1 Expression

The ORR using nivolumab in the population with non-squamous NSCLC having high PD-L1 expression is assumed to be 27% (p_0); thus, this rate is considered uninteresting. The target ORR using the investigational agents in combination with nivolumab is 50% (p_1).

Stage 1 of enrollment will include approximately 17 evaluable patients. With exactly 17 evaluable patients at Stage 1, if at least 5 patients have Objective Responses, 27 additional evaluable patients will be enrolled, for a total sample size of 44 evaluable patients. If at least 18 Objective Responses are observed, further investigation may be warranted. If the true ORR is 27% (null hypothesis), the probability of early termination during the study is 0.50; the Type 1 error is equal to 0.0303 and the power is equal to 0.9018.

The exact stopping rules for all cohorts will be calculated based on the Predictive Probability Design, once the exact number of patients evaluable at Stage 1 is known. The aim is to get a minimum of 9 evaluable patients at Stage 1 for CIT-experienced and CIT-naïve with no/low PD-L1 expression cohorts and a minimum of 17 evaluable patients at Stage 1 for CIT-naïve with high PD-L1 expression cohort.

Expansion Beyond Stage 2

The original protocol provided that if results in any strata were of high interest for efficacy, enrollment might be expanded to as many as 100 patients total in each cohort to narrow the 95% Confidence Interval (CI) around the ORR point estimate. Protocol Amendment 3 (Version 4.0) eliminates enrollment expansion beyond Stage 2 except in the sitravatinib segment of the study enrolling patients with CIT-experience.

For the sitravatinib segment of the study enrolling patients with CIT-experience, expansion of enrollment beyond Stage 2 will be managed as one cohort that includes all patients, regardless of prior clinical benefit during treatment with CIT. Based on preliminary clinical activity results (described in Section 1.5.3.2.2), enrollment into the combined cohort will expand to as many as 125 patients total, to further evaluate safety and efficacy in this setting.

Expansion of sitravatinib CIT-naïve cohorts beyond Stage 2 of enrollment is not anticipated.

Table 1: Schedule of Assessments

The Schedule of Assessments provides an overview of the protocol visits and procedures. Refer to Section 7 for detailed information on each assessment. Additional, unplanned assessments should be performed as clinically indicated, including for the purpose of fully evaluating adverse events.

Assessments	Screen/ Baseline	Cycle 1		Cycle 2 and 3		≥ Cycle 4		End of Treatment[15]	
	Within 28 days	Day 1	Day 15 (± 2 days)	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 1 (± 2 days)	Day 15 (± 2 days)	End of Treatment/ Withdrawal	Post Treatment Follow Up
Study Participation Informed Consent[1]	Before study specific assessments								
Tumor Tissue Collection for PD-L1 Expression and Tumor Gene Alterations[2]	X								
Medical History, Disease History, Prior Therapy	X								
ECOG Performance Status	X								
Physical Exam[3]	X							X	
Abbreviated Physical Exam[3]		X	X	X	X	X	X		
Vital Signs[4]	X	X	X	X	X	X	X	X	
Pregnancy Test[5]	X	As clinically indicated							
Hematology[6,7]	X	X	X	X	X	X		X	

Table 1: Schedule of Assessments (Continued)

Assessments	Screen/ Baseline	Cycle 1		Cycle 2 and 3		≥ Cycle 4		End of Treatment[15]	
	Within 28 days	Day 1	Day 15 (± 2 days)	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 1 (± 2 days)	Day 15 (± 2 days)	End of Treatment/ Withdrawal	Post Treatment Follow Up
Coagulation[6,7]	X	As clinically indicated							
Urinalysis[6,7]	X	As clinically indicated							
Serum Chemistry[6,7]	X	X	X	X	X	X		X	
Thyroid Function Test[6,7]	X	X		X		X		X	
Blood for Pharmacokinetics[8]		See Table 2, Table 3, and Table 4 and sub-study appendix Table 22, Table 23, Table 24, and Table 25							
Biopsy of Tumor for Biomarker Studies (Optional)[9]		Pre-dose X		Cycle 2 Only X				X	
Blood Samples – Flow Cytometry[10]	X	See Table 2, Table 3, and Table 4						X	
Blood Samples – Protein and Cytokine Biomarkers[10]		See Table 2, Table 3, and Table 4						X	
ctDNA blood sample[11]	X			Time of confirmation of disease response PR or CR				X	
Single 12-Lead ECG[12]	X	As clinically indicated except – Mocetinostat arm: Day 1 of each treatment cycle						X	
Triplicate 12-Lead ECG[12]		See Table 2, Table 3, and Table 4							

Table 1: Schedule of Assessments (Continued)

Assessments	Screen/ Baseline	Cycle 1		Cycle 2 and 3		≥ Cycle 4		End of Treatment[15]	
	Within 28 days	Day 1	Day 15 (± 2 days)	Day 1 (± 2 days)	Day 15 (± 2 days)	Day 1 (± 2 days)	Day 15 (± 2 days)	End of Treatment/ Withdrawal	Post Treatment Follow Up
Echocardiogram (Mocetinostat and Sitravatinib Treatment Arms Only)	X		X Mocetinostat arm only	X Cycle 3 only		X Mocetinostat arm only		X	
Disease Evaluation[13]	X	Every 8 weeks (± 10 days) for ~1 year and then every 16 weeks							
Investigational Agent Dispensing and/or Reconciliation		X		X		X			
Nivolumab Administration		X	X if Q2W	X	X if Q2W	X	X if Q2W		
Adverse Events[14] and Concomitant Medications	SAEs only	Throughout							
Long Term Follow-up[16]									X

1 Study Participation Informed Consent: May be performed more than 28 days prior to the first dose of study treatment and must be completed prior to initiation of any study specific assessments.

2 Tumor Testing for PD-L1 Expression and Tumor Gene Alterations: Encouraged for all patients. Archival tumor tissue allowed. For patients enrolled in CIT Naïve cohorts, the sample must have been collected following the completion of the most recent systemic treatment regimen and the central laboratory testing is to begin prior to study entry. Biopsy may precede informed consent if performed as Standard of Care (SOC) or to assess eligibility for a different clinical trial.

3 Physical Examinations: A complete physical examination required at Screening and End of Treatment only. Height will be recorded at screening only. All other evaluations will be symptom-directed, abbreviated evaluations.

4 Vital Signs: Weight, temperature, blood pressure, and pulse rate to be assessed prior to dosing as indicated.

5 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.

6 Selected Day 1 Assessments: Repeat assessment not required if screening assessment performed within 7 days before the first dose.

7 Safety Laboratory Assessments: Hematology, coagulation, chemistry, thyroid function and urinalysis evaluations (see Table 19) will be performed by local laboratories.

8 Pharmacokinetic Samples: Blood samples to be collected following ECGs and assessment of vital signs as scheduled in Table 2, Table 3 and Table 4 and sub-study appendix Table 22, Table 23, Table 24, and Table 25. In addition, unscheduled PK blood samples should be drawn in association with two kinds of safety events: 1) as soon as possible after a Serious Adverse Event (SAE), and 2) at a clinic visit at least one week following a dose modification of the investigational agent.

9 Tumor Biopsy for Biomarker Studies: Consent for serial sampling of tumor tissue (preferably the same lesion) is requested but is not mandatory for study entry. If tumor biopsy has been performed during screening, then that biopsy may be used for the baseline assessment. Markers of interest in tumor tissue include PD-L1 expression, CD8+ tumor infiltrating lymphocytes (TILs) including proliferating (Ki67+) CD8+ cells, natural killer cells (NK-cells), T regulatory cells (Tregs), macrophages and myeloid derived suppressor cells (MDSCs). Gene expression analyses may also be performed.

10 Blood Samples for Biomarker Studies: Blood samples for flow cytometry and protein/cytokine assays will be collected as outlined in Table 2, Table 3 and Table 4. Markers of interest in circulation include circulating PD-L1, Tregs, MDSCs, NK-cells, flow cytometry for T- and B-cell including CD4, CD8 and Ki67, monocytes and selected cytokines including CD8A, GZMB, IFNγ, CXCL9, CXCL10, CXCL11, and TBX21. Patients participating in the sitravatinib formulation and food effect sub-studies described in Appendix 5 and Appendix 6 are exempt from sample collection for biomarker studies, including flow cytometry and protein/cytokine assays.

11 Blood samples for ctDNA analysis: Blood will be collected in two 10ml Streck brand Cell-Free DNA Blood Collection tubes allowing shipping and stability at ambient temperatures.

12 12-Lead ECGs: Triplicate ECGs will accompany PK sampling as described in Table 2, Table 3 and Table 4. Only for the mocetinostat containing treatment arm, ECGs are to be performed on Day 1 of each cycle, either as a triplicate ECG accompanying PK or as a single ECG. In addition, ECGs are to be performed as clinically indicated. Assessments will include an evaluation of rhythm, heart rate, and PR, QRS, QT, and QTc intervals. RR interval should be recorded during each ECG assessment in order to calculate QTcF.

13 Disease Evaluations: To be performed at screening (28 day window allowed) and every 8 weeks from Cycle 1 Day 1 (± 10 days window for all other assessments except screening) until Week 49 (~1 year) and then every 16 weeks. All on-study disease evaluations should be based on a calendar beginning from the first day of dosing. At screening/baseline, assessments are to include CT with contrast of the chest, abdomen and pelvis, as well as brain Magnetic Resonance Imaging (MRI) with and without gadolinium or Computed Tomography Scan (CT) with contrast, a whole body bone scan and evaluation of any superficial lesions. Subsequent disease assessments should include all sites of disease identified at baseline or suspected to have developed; bone scans may be performed half as often (every 16 weeks) as other radiology evaluations and should be performed during assessment for confirmation of disease response. More detailed guidance on exceptional circumstances is provided in the protocol.

14 Adverse Events: SAEs will be reported from the time of informed consent until at least 28 days after the last administration of investigational agent or nivolumab. Adverse events will be reported from the first day of study treatment until at least 28 days after last dose of study drug, and until resolution or stabilization of acute AEs and/or ongoing SAEs.

15 End of Treatment: All patients will be followed for AEs for at least 28 days after the last dose of Study Treatment. Assessments that have been completed in the previous 4 weeks do not need to be repeated (8 or 16 weeks for tumor assessments in accordance with schedule).

16 Long Term Follow-up: Survival status and subsequent therapies will be collected during long term follow-up every 2 months (±14 days) from the End of Treatment visit until death or lost to follow-up. Follow-up may be performed by telephone contact.

Table 2: Glesatinib Schedule of PK, Biomarker Samples and Triplicate ECG Assessments

	Screen/ Baseline	**Cycle 1 Day 1**				**Cycle 1 Day 15 (± 2 days)**	**Cycle 2, 3, 5 Day 1 (± 2 days)**	**Cycle 2 Day 15 (± 2 days)**
Collection Time and Allowable Window	**Within 28 days**	**Pre-dose (-0.5-0 hour)**	**30 min (± 10 min)**	**3 hour (2-4 hour)**	**6 hour (5-8 hour)**	**Pre-dose (-0.5-0 hour)**	**Pre-dose (-0.5-0 hour)**	**Pre-dose (-0.5-0 hour)**
PK Sample [1]		X	X	X	X	X	X	X
Flow Cytometry [2]	X	X				X		
Protein and Cytokine Biomarkers [2]		X				X		
Triplicate ECG [3]		X		X		X	X	X

1 Scheduled vital signs and triplicate ECGs precede PK sample collection in all cases. Glesatinib dosing and sampling should precede nivolumab infusion.
2 The Day 1 blood samples for biomarker studies may be drawn up to 2 hours before dosing. The screen/baseline sample should not be collected on the same day as the pre-dose Cycle 1 Day 1 sample.
3 ECGs should be taken in triplicate, each reading at least 2 minutes apart. On Cycle 1 Day 1, two sets of triplicate ECGs should be done within 30 minutes prior to dosing (e.g., at 15 minute intervals) to firmly establish the baseline for the patient. In general, ECGs should be performed prior (within -30 to -5 minutes) to the respective PK blood collection.

Table 3: Sitravatinib Schedule of PK, Biomarker Samples and Triplicate ECG Assessments

	Screen/ Baseline	**Cycle 1 Day 1**				**Cycle 1 Day 15 (± 2 days)**	**Cycle 2, 3, 5 Day 1 (± 2 days)**	**Cycle 2 Day 15 (± 2 days)**
Collection Time and Allowable Window	**Within 28 days**	**Pre-dose**	**30 min (± 10 min)**	**4 hour (3-5 hour)**	**6 hour (5.5-8 hour)**	**Pre-dose (-0.5-0 hour)**	**Pre-dose (-0.5-0 hour)**	**Pre-dose (-0.5-0 hour)**
PK Sample [1, 4]		X	X	X	X	X	X	X
Flow Cytometry [2, 5]	X	X				X		
Protein and Cytokine Biomarkers [2, 5]		X				X		
Triplicate ECG [3, 6]		X (-1 hour)	X (-0.5 hour)		X		X	X	X

1 Scheduled vital signs and triplicate ECGs precede PK sample collection in all cases. Sitravatinib dosing and sampling should precede nivolumab infusion.

2 The Day 1 blood samples for biomarker studies may be drawn up to 2 hours before dosing. The screen/baseline sample should not be collected on the same day as the pre-dose Cycle 1 Day 1 sample.

3 ECGs should be taken in triplicate, each reading approximately 2 minutes apart. On Cycle 1 Day 1 only, two sets of triplicate ECGs should be done within 1 hour prior to dosing (e.g., at 30 minute intervals prior to dosing) to firmly establish the baseline for the patient. One set of triplicate ECGs is required at all other time points. In general, ECGs should be performed prior to the respective PK blood collection. Examples of the schedule are presented below:

- Example for Cycle 1 Day 1 pre-dose ECGs/PK: ~-1.0 hr (Triplicate ECGs); ~-30 mins (Triplicate ECGs); ~-15 mins (Vitals/PK)
- Example for all other pre-dose ECG/PK assessments: ~-30 mins (Triplicate ECGs); ~-15 mins (Vitals/PK).

4 Sample schedules for sitravatinib formulation and food effect evaluations are presented in Appendix 5 and Appendix 6, Table 22, Table 23, Table 24, and Table 25.

5 Patients participating in the sitravatinib formulation and food effect sub-studies described in Appendix 5 and Appendix 6 are exempt from sample collection for biomarker studies, including flow cytometry and protein/cytokine assays.

6 Patients participating in the sitravatinib formulation and food effect sub-studies described in Appendix 5 and Appendix 6 will undergo evaluation by triplicate ECG on Lead-In Day 1 instead of Cycle 1 Day 1.

Table 4: Mocetinostat Schedule of PK, Biomarker Samples and Triplicate ECG Assessments

	Screen/ Baseline	Cycle 1 Day 1				Cycle 1 Day 15 (± 2 days)		Cycle 2, 3, 5 Day 1 (± 2 days)	
Collection Time and Allowable Window	**Within 28 days**	**Pre-dose (-0.5-0 hour)**	**1 hour (0.5-1.5 hour)**	**3 hour (2-4 hour)**	**7 hour (6-8 hour)**	**Pre-dose (-0.5-0 hour)**	**1 hour (0.5-1.5 hour)**	**Pre-dose (-0.5-0 hour)**	**1 hour (0.5-1.5 hour)**
PK Sample [1]		X	X	X	X	X	X	X	X
Flow Cytometry [2]	X	X				X			
Protein and Cytokine Biomarkers [2]		X				X			
Triplicate ECG [3]		X	X			X		X	X

1 Scheduled vital signs and triplicate ECGs precede PK sample collection in all cases. On days mocetinostat and nivolumab are both administered and scheduled for PK assessment, mocetinostat dosing and sampling should precede nivolumab infusion.

2 The Day 1 blood samples for biomarker studies may be drawn up to 2 hours before dosing. The screen/baseline sample should not be collected on the same day as the pre-dose Cycle 1 Day 1 sample.

3 ECGs should be taken in triplicate, with readings at least 2 minutes apart. On Cycle 1 Day 1, two sets of triplicate ECGs should be done within 30 minutes prior to dosing (e.g., at 15 minute intervals) to firmly establish the baseline. In general, ECGs should be performed prior (within -30 to -5 minutes) to the respective PK blood collection.

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
APC	Antigen Presenting Cells
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
CFR	Code of Federal Regulations
CDx	Companion Diagnostics
CI	Confidence Interval
CIT	Checkpoint Inhibitor Therapy
C_{max}	Maximum Plasma Concentration
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography Scan
CTA	Clinical Trial Application
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumor Deoxyribonucleic Acid
DLT	Dose Limiting Toxicity
DR	Duration of Response
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EIU	Exposure In-Utero
FDA	Food and Drug Administration
FFPE	Formalin-Fixed, Paraffin-Embedded
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HDAC	Histone Deacetylases
HDPE	High-Density Polyethylene
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonization

LIST OF ABBREVIATIONS (CONTINUED)

IND	Investigational New Drug
INR	International Normalized Ration
irAE	Immune-related Adverse Event
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine Device
IV	Intravenous
MAb	Monoclonal Antibody
MDSC	Myeloid-derived Suppressor Cell
MDSCs	Myeloid-Derived Suppressor Cells
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MHC	Major Histocompatibility Complex
mITT	Modified Intent-to-Treat
mL	Milliliter
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
mTPI	Modified Toxicity Probability Interval
NCI	National Cancer Institute
NE	Not Evaluable
NK	Natural Killer
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PD	Objective Progression of Disease
PD-1	Programmed Cell Death 1
PD-L1	Programmed Cell Death Ligand 1
PFS	Progression-Free Survival
PK	Pharmacokinetics
PKAP	Pharmacokinetic Analysis Plan
PPD	Predictive Probability Design
PR	Partial Response

LIST OF ABBREVIATIONS (CONTINUED)

PTT	Partial Thromboplastin Time
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
TAA	Tumor Associated Antigens
TIW	Three Times Weekly
Treg	T Regulatory Cells
ULN	Upper Limit of Normal
WBC	White Blood Cell
WOCBP	Women of Child Bearing Potential

1 INTRODUCTION AND RATIONALE

1.1 Disease and Therapeutic Strategy

1.1.1 Non-Small Cell Lung Cancer

Lung cancer remains the leading cause of cancer-related death in the United States (US). Approximately 221,200 new cases of lung cancer are expected to be diagnosed in the US in 2015, and approximately 158,040 deaths will be attributed to lung cancer (Cancer Facts and Figures-2015). Non-small cell lung cancer (NSCLC) accounts for approximately 83% of lung cancer cases (Cancer Facts and Figures-2015), of which approximately half are classified as adenocarcinoma of the lung; squamous cell carcinoma accounts for approximately one-third of NSCLC cases and large cell carcinoma is less frequently diagnosed.

In 1995, the use of cisplatin-based chemotherapy was reported to lead to modest improvement in survival in patients with advanced NSCLC as compared to best supportive care, with a 27% reduction in death as reported in a meta-analysis of 11 trials (NSCLC Collaborative Group-1995). Subsequently, other chemotherapeutic agents have been reported to be active in NSCLC, leading to a comparison of 4 platinum-based doublets in the first-line treatment setting, all of which demonstrated similar activity (Schiller-2002). The importance of histology in the selection of first-line treatment for NSCLC was later described in the development of bevacizumab and pemetrexed. In a Phase 3 clinical trial, treatment with bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), demonstrated an improvement in survival when added to doublet chemotherapy, specifically in patients with non-squamous NSCLC (Sandler-2006). Similarly, treatment with pemetrexed, an antifolate chemotherapeutic agent, resulted in an improvement in survival when used as part of a chemotherapy doublet in patients with non-squamous NSCLC, but with a probable decrease in survival among patients with squamous cell NSCLC (Scagliotti-2008). Based on the results of these and other trials, platinum-based chemotherapy doublets, with or without bevacizumab in selected patients, remain a standard of care for most patients with advanced NSCLC in the first-line treatment setting.

Effective options are limited however for patients with advanced NSCLC whose disease progresses after first-line treatment. Over the past few years there has been increasing interest in treating cancer with immunotherapy, in particular manipulating the anticancer host immune response with human monoclonal antibodies (MAbs).

Nivolumab, a fully human IgG4, PD-1 receptor antagonist, was evaluated in a Phase 3 clinical trial of patients with squamous cell carcinoma of the lung with disease progression during or after first-line chemotherapy. This study demonstrated a significant improvement in survival compared with docetaxel, with a hazard ratio (HR) of 0.59 (95% CI: 0.44, 0.79, $p<0.001$) (Brahmer-2015). A similar Phase 3 trial of patients

with non-squamous NSCLC that had progressed during or after platinum-based doublet chemotherapy demonstrated an improvement in survival with nivolumab over docetaxel (HR 0.73, 96% [sic] CI 0.59, 0.89, p=0.002) (Borghaei-2015). OPDIVO® (nivolumab) was approved by the FDA for the treatment of patients with metastatic NSCLC with progression on or after platinum-based chemotherapy. Nivolumab was approved in the US in March 2015 for squamous NSCLC and October 2015 for non-squamous NSCLC.

Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. In a large international Phase 1 clinical trial, pembrolizumab was given to 495 patients with advanced NSCLC to evaluate safety, side-effect profile, and antitumor activity (Garon-2015). Patients (some of whom had received previous therapy and some of whom had not) were treated with various doses and regimens of pembrolizumab. Pembrolizumab had an acceptable side-effect profile and showed anti-tumor activity. Among all patients, the objective response rate was 19.4%, and the median duration of response was 12.5 months. The median duration of progression-free survival was 3.7 months, and the median duration of overall survival was 12.0 months. Keytruda® (pembrolizumab) was approved by the FDA in October 2015 for the treatment of patients with metastatic squamous or non-squamous NSCLC with progression on or after platinum-based chemotherapy. Despite these advances, most patients with advanced NSCLC have incurable disease, and additional, effective treatment options are needed. More recently, a trial of pembrolizumab, demonstrated an advantage of pembrolizumab over standard chemotherapy in patients with untreated, advanced NSCLC characterized by ≥ 50% tumor PD-L1 expression. Improvement was reported across multiple efficacy endpoints including survival along with a favorable safety profile (Reck-2016), leading to the approval of pembrolizumab in the first-line treatment setting in this patient population in the US.

1.2 Overall Rational for Proposed Combination Regimens

Immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway have demonstrated clinical activity across a range of cancer types, including non-small cell lung cancer (Brahmer-2015, Borghaei-2015, Garon-2015). While this therapy leads to durable clinical responses in a subset of patients, strategies to improve its clinical efficacy and overcome innate or acquired resistance to checkpoint inhibitor monotherapy are needed. Combination therapy with agents that target the molecular and cellular mechanisms of resistance to checkpoint inhibitor therapy is a rational approach to improving outcomes in patients.

Resistance mechanisms have been described based on fundamental knowledge of the immune system as well as emerging clinical data. Expression of PD-L1 appears to correlate with response in multiple clinical studies (Herbst-2014, Tumeh-2014). In the tumor microenvironment, PD-L1 can be upregulated in tumor cells via oncogenic signaling or in response to immune stimulatory factors such as interferon gamma (IFN-γ). Therefore, the absence of PD-L1 expression may reflect a tumor cell population and microenvironment with a suppressed immune response. A potentially related state

termed immunological ignorance was recently described and is characterized by a near complete absence of immune markers in the tumor. Tumors harboring a non-functional immune response or an excluded immune cell infiltrate represent additional cellular patterns found associated with resistance to checkpoint inhibition (Herbst-2014).

Several immune cell types normally function to suppress immune responses, are often found in abundance in cancer and may underlie these recently described resistance mechanisms to checkpoint blockade (Vanneman-2012). Regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs) and M2-polarized macrophages, in particular, are immunosuppressive in nature as they counteract pro-inflammatory immune responses and lead to tolerance. Inhibition of the accumulation and/or function of these cell types therefore represents a rational combination strategy to reprogram the immunosuppressive tumor microenvironment and increase the effectiveness of PD-1/PD-L1 therapy. As described in further detail below, both glesatinib and sitravatinib target key receptor tyrosine kinases present on these immune cell types. Moreover, in addition to inhibiting some of the same immunosuppressive cell types noted above, mocetinostat enhances tumor antigen presentation, increases immunologic cell death and recruits pro-inflammatory cell types through modulation of gene expression in the tumor cell compartment. In summary, these therapies selectively inhibit key molecular and cellular pathways strongly implicated in checkpoint inhibitor resistance and therefore represent rational strategies to enhance or restore anti-tumor immunity when combined with nivolumab.

1.3 Checkpoint Pathway

The PD-1 receptor along with the ligands PD-L1 and PD-L2 constitutes an immune checkpoint pathway that inhibits T-cell activation when engaged (Mellman-2011, Topalian-2015). PD-1 is expressed on T-cells whereas PD-L1 and PD-L2 are expressed on some cancer cells and immune cell types. PD-L1 is the predominant ligand expressed in solid tumors and is upregulated by IFNg. PD-L1 normally functions to limit collateral damage in normal tissues where an immune response has been triggered. When PD-L1 is upregulated in tumors, this functions to block the immune response and avoid elimination by the host. PD-L1 expression in tumor, including in lung cancer, has been associated with poor survival motivating the development of PD-1 pathway inhibitors (Mu-2011).

1.4 Glesatinib Background

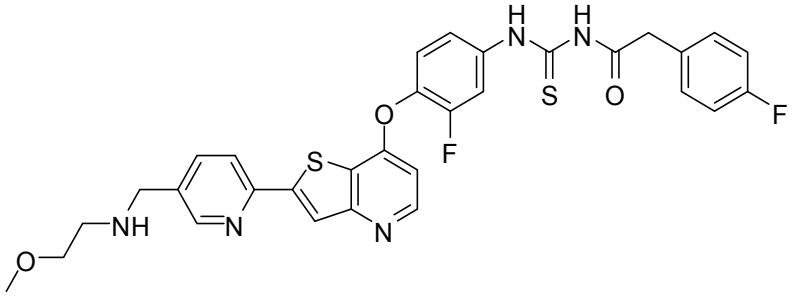
Glesatinib (MGCD265) is an orally administered multi-targeted receptor tyrosine kinase (RTK) inhibitor that primarily targets the Axl and MET receptors. Additional RTK targets potentially include MERTK, DDR2, and PDGFRα and β receptors. This subset of tyrosine kinases is involved in a number of processes implicated in human cancer including regulation of tumor growth and cell survival pathways, tumor invasion and metastatic progression, as well as tumor angiogenesis.

Background information in addition to that presented below is available in the MGCD265 Investigator's Brochure.

1.4.1 Glesatinib Drug Substance

The chemical structure of glesatinib (MGCD265) is as follows:

MGCD265 Free Base



Chemical Formula:	$C_{31}H_{27}F_2N_5O_3S_2$
Molecular Weight:	619.71 g/mol

1.4.2 Non-Clinical Data

Glesatinib demonstrated potent, concentration-dependent inhibition of the kinase activity of MET, Axl, MERTK, PDGFR family and DDR2 in biochemical assays and inhibited phosphorylation in cell-based assays. Glesatinib also inhibited MET-dependent cell viability and migration and endothelial tube formation and angiogenesis in cell-based experiments. In a variety of human tumor xenograft models, glesatinib demonstrated anti-tumor efficacy including robust tumor regression in models exhibiting genetic alterations of the MET RTK including *MET* mutations and gene amplification.

The potential for glesatinib cardiovascular effects was tested in vitro and in vivo. The IC_{50} for potassium (hERG/Kv11.1) and sodium channel (hNav1.5) inhibition were not calculated but were estimated to be >30 μM, a level that far exceeds exposures observed clinically. In a dog cardiovascular study, oral treatment with glesatinib did not affect hemodynamic functions (heart rate; systolic, mean and diastolic arterial pressure) or electrocardiogram parameters at dose levels up to 40 mg/kg.

In in vitro membrane permeability studies, Glesatinib was highly permeable and did not show significant efflux (efflux ratio 0.7) suggesting that glesatinib is not a substrate of Pgp or BCRP (efflux transporters).

Protein binding studies of glesatinib in mouse, rat, and human plasma demonstrated greater than 99.9% protein binding by an ultrafiltration assay; binding to dog plasma proteins was 99.8%. In addition, a serum shift experiment in a cell-based assay estimated glesatinib to be 98% bound to human plasma.

Glesatinib is relatively stable when incubated in human liver microsomes, suggesting that it is not extensively metabolized by the cytochrome P-450 system. Reaction phenotyping shows that metabolism of glesatinib that does occur appears to be mediated by several CYP enzymes without a specific enzyme predominance. Additionally, in vitro studies in human liver microsomes and in primary cultures of fresh human hepatocytes indicate that glesatinib is neither a potent inhibitor nor a potent inducer of CYP enzymes at the clinically observed concentration levels.

1.4.3 Clinical Experience

1.4.3.1 Glesatinib Pharmacokinetics

Following single dose administration of 750 mg BID SDD glesatinib tablets, MGCD265 was rapidly absorbed, with median C_{max} occurring 6 hours after dosing. The mean elimination half-life was 30.9 hours. Drug accumulation was observed after multiple dose administration, whereby C_{max} and AUC_{0-12} were 4.0- and 4.5-fold higher, respectively, than single dose administration. The mean peak to trough ratio at steady state was 1.12. At steady state, mean $C_{max,ss}$, $C_{ave,ss}$ and $AUC_{0-12,ss}$ values were 432 ng/mL, 396 ng/mL and 4751 ng•h/mL, respectively.

1.4.3.2 Glesatinib Clinical Safety

Single agent glesatinib has been evaluated using various oral formulations and regimens in Phase 1, 1/2, and 2 clinical trials in over 370 patients with advanced malignancies.

As of 17 January 2017, in Study No. 265-101, a total of 165 patients have been treated with single agent glesatinib daily dosing. Dose escalation started at 24 mg/m^2 administered once daily and progressed through multiple formulation changes. The maximum tolerated dose (MTD) with the non-aqueous suspension formulation was defined as 1050 mg BID, with diarrhea and fatigue being the most common dose-limiting adverse events. The SDD tablet formation was introduced with the expectation that the incidence and severity of diarrhea would be reduced as compared with the non-aqueous formulation that includes Miglyol® as an excipient. The dose escalation evaluation of the SDD formulation identified that the recommended dose when glesatinib is administered as a single agent is 750 mg BID; 1000 mg BID using the SDD formulation exceeded the maximum tolerated dose. The incidence, severity and speed of onset of diarrhea were less among patients receiving the SDD formulation as compared to the non-aqueous suspension formulation.

Across the clinical trial program, the most commonly observed treatment-emergent adverse events (TEAEs) reported as related to glesatinib when administered alone were

diarrhea (62%), nausea (39%), fatigue (31%), vomiting (26%), aspartate aminotransferase (AST) increase (25%), and alanine aminotransferase (ALT) increase (20%). Grade 3 TEAEs that were reported as related to treatment in more than one patient included diarrhea (8%), fatigue (5%), AST increase, ALT increase, lipase increase, nausea, and vomiting (2% each), and abdominal pain, anemia, blood alkaline phosphatase increase, blood phosphorus decrease, dehydration, hypertension, hypokalemia (1% each). Adverse events of grade 4 that were reported related to treatment included lipase increase in 3 patients (1%) and amylase increase and lymphocyte count decrease (< 1%). Events listed in the Investigator's Brochure as glesatinib Adverse Drug Reactions (ADRs) include diarrhea, nausea, vomiting, fatigue, asthenia, AST and ALT increase and dehydration.

Based on reported clinical experience with glesatinib and similar agents, and non-clinical data with glesatinib, guidance to the Investigator is provided for selected adverse events in Section 5.1.1.4.

1.5 Sitravatinib Background

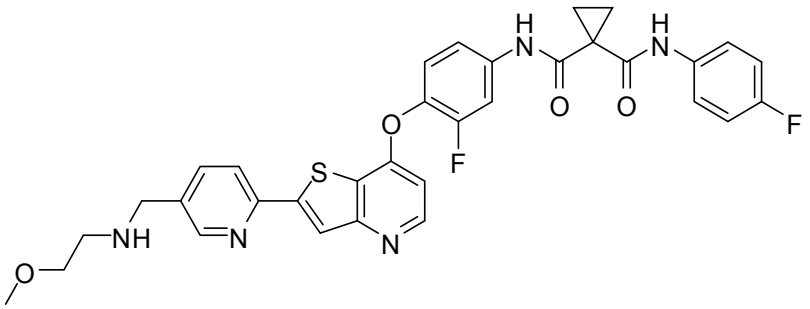
Sitravatinib (MGCD516) is an orally-available, potent small molecule inhibitor of a closely related spectrum of receptor tyrosine kinases (RTKs) including MET, Axl, MERTK, VEGFR family, PDGFR family, KIT, FLT3, Trk family, RET, DDR2, and selected Eph family members. Receptor tyrosine kinases (RTKs) are key regulators of signaling pathways leading to cell growth, survival, and migration (Blume Jensen-2001). These kinases are found dysregulated in many cancers through overexpression, genetic alteration or co-expression with high affinity ligands (Blume Jensen-2001). Multiple sitravatinib RTK targets are genetically altered in a variety of cancer indications and act as oncogenic drivers promoting cancer development and progression.

Background information in addition to that presented below is available in the Sitravatinib (MGCD516) Investigator's Brochure.

1.5.1 Sitravatinib Drug Substance

The chemical structure of sitravatinib (MGCD516) is as follows:

MGCD516 Free Base



Chemical Formula:	$C_{33}H_{29}F_2N_5O_4S$
Molecular Weight:	629.68 g/mol

1.5.2 Non-Clinical Data

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 vitro results from the hERG assay demonstrate an IC_{50} of 0.6 μM on the potassium current, which far exceeds exposures observed clinically. There were no adverse effects on the cardiovascular system, including no effect on the QTc interval, when sitravatinib was administered to dogs at doses up to 4 mg/kg (mean 6 hr concentration of 0.072 μg/mL). Minor increases in vascular pressures were observed during the dog cardiovascular study; however these were mild and considered of limited biological consequence. Assessment of the neurological functional observation battery (FOB) and respiratory evaluations (tidal volume, respiration rate, and minute volume) in rats did not reveal any sitravatinib-related effects at doses up to 25 mg/kg.

In a bidirectional permeability study with Caco-2 cell lines, sitravatinib is classified as a highly permeable compound, and not a substrate of P-gp and BCRP.

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

Sitravatinib was evaluated for cytochrome P-450-mediated metabolism using human liver microsomes and recombinant human enzymes. Results suggest that multiple enzymes, including CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1, and 3A4 are involved in the metabolism of sitravatinib with a low risk of one enzyme contributing to metabolism in a disproportionate manner. In vitro studies in human primary cultures of cryopreserved human hepatocytes and human liver microsomes indicate that sitravatinib is unlikely to inhibit or induce the tested enzymes at the systemic concentrations associated with 150 mg daily administration.

1.5.3 Sitravatinib Clinical Experience

1.5.3.1 Sitravatinib Pharmacokinetics

After single dose administration, sitravatinib reaches peak concentration in a median time of 3 to 9 hours. Exposure parameters (maximum concentration [C_{max}] and area under the curve [AUC]) are dose proportional with doses up to 150 mg. Mean elimination half-life varies between 35 and 53 hours after oral administration. Drug accumulation is observed after multiple dose administration and averaged 2.7-fold for C_{max} and 3.1-fold for AUC_{0-24}. Mean peak to through ratio at steady state is 1.8. Based on current data following administration of 150 mg once daily to patients, the steady state mean $C_{max,}$ $C_{ave,ss}$ and $AUC_{0-24,ss}$ values are 116 ng/mL, 95.1 ng/mL and, 2281 mg.h/mL, respectively.

1.5.3.2 Sitravatinib Clinical Trial Experience

1.5.3.2.1 Sitravatinib Monotherapy

Study 516-001 is a multi-center Phase 1/1b clinical trial of sitravatinib as monotherapy in patients with advanced solid tumor diseases. The Phase 1 dose-escalation segment of the study evaluated sitravatinib dose levels between 10 mg and 200 mg administered QD. Dose-limiting toxicity (DLT) was reported in four patients who developed palmar-plantar erythrodysesthesia, neuropathy, mucositis, or fatigue. The maximum tolerated dose was identified as 150 mg QD and, based on long-term tolerability, the recommended Phase 2 dose is 120 mg QD. The sitravatinib exposure achieved using 120 mg QD is expected to be adequate to inhibit the target TAM and VEGF receptors necessary to achieve antitumor activity in combination with nivolumab.

The Phase 1b segment is ongoing, evaluating the clinical activity of sitravatinib in patients having tumors with selected histological diagnoses and/or tumor gene alterations targeted by sitravatinib.

As of 26 June 2018, preliminary safety data are available for 153 patients treated in Study 516-001. Treatment-related adverse events reported in ≥ 10% of patients and Grade 3 or higher AEs reported in at least two patients are listed in Table 5.

Table 5: Summary of Adverse Events for Study 516-001 as of 26 June 2018 - Most Frequent (≥10%) Treatment-Related, Treatment Emergent Adverse Events and ≥ Grade 3 Events in At Least Two Patients

Adverse Event (Preferred Term)	N=153	
	All Grades n (%)	Grade ≥3 n (%)
Diarrhea	74 (48)	16 (11)
Fatigue	65 (43)	9 (6)
Hypertension	56 (37)	29 (19)
Nausea	45 (29)	5 (3)
Vomiting	40 (26)	4 (3)
Decreased appetite	38 (25)	1 (1)
Palmar-plantar erythrodysaesthesia	28 (18)	6 (4)
Aspartate aminotransferase increase	26 (17)	1 (1)
Alanine aminotransferase increase	25 (16)	1 (1)
Hypothyroidism	22 (14)	0
Weight decrease	21 (14)	2 (1)
Dysphonia	18 (12)	0
Stomatitis	18 (12)	0
Abdominal pain	16 (11)	0
Rash	15 (10)	0
Lipase increased	13 (9)	6 (4)
Mucosal inflammation	13 (9)	3 (2)
Anaemia	13 (9)	2 (1)
Rash maculo-papular	10 (7)	3 (2)
Hypophosphataeamia	9 (6)	5 (3)
Amylase increased	9 (6)	2 (1)
Ejection fraction decreased	7 (5)	3 (2)
Pulmonary embolism	6 (4)	6 (4)
Embolism	4 (3)	2 (1)
Left ventricular dysfunction	3 (2)	3 (2)
Pancreatitis	3 (2)	2 (1)

Grade 4 AE events reported as related to treatment in 1 patient each (0.7%) included dehydration, febrile neutropenia and lipase increased. Grade 5 treatment-related adverse event of cardiac arrest was reported in one patient. Treatment-related SAEs were reported in 24 patients (16%) and included diarrhea, nausea and vomiting (3% each); fatigue (2%); pancreatitis, pulmonary embolism, and hypertension (1.3% each); cardiac arrest, ejection fraction decreased, embolism, febrile neutropenia, headache, hypotension, left ventricular dysfunction, lipase increased, odynophagia, oropharyngeal pain, palmar-plantar erythrodysesthesia and tachycardia (0.7% each). Fifty patient deaths were reported in this study, with the primary cause of death being the disease under study (n=31), unknown (n=12), other (n=7), including sepsis (n=3), and hypoxic respiratory failure, respiratory failure, gastrointestinal bleed, or cardiac arrest (n=1 each).

Efficacy results are awaited from the Phase 1b segment of Study 516-001.

1.5.3.2.2 Sitravatinib in Combination with Nivolumab, Current Study Update as of June 2018

The current study began with a lead-in safety evaluation of sitravatinib in combination with nivolumab administered by intravenous infusion, 240 mg Q2W. The starting dose for sitravatinib was 120 mg administered orally, once daily, in 28-day cycles. No protocol defined DLTs were reported in the first 6 evaluable patients treated at the sitravatinib starting dose 120 mg daily in combination with nivolumab administered by intravenous infusion, 240 mg Q2W. Based on the experience of patients enrolled into the 516-001 study and the patients enrolled in the MRTX-500 study, 120 mg daily was selected as the Phase 2 dose of sitravatinib in combination with nivolumab.

As of 26 June 2018, preliminary safety data are available for 70 patients treated in the sitravatinib segment of Study MRTX-500. The data summarized below include the experience of patients enrolled in all sitravatinib patient strata in MRTX-500 (i.e., both CIT-experienced and CIT-naïve). Treatment-related AEs reported in ≥ 10% of patients and Grade 3 or higher AEs reported in at least two patients are listed in Table 6.

Table 6: Summary of Adverse Events for Study MRTX-500 as of 26 June 2018 - Most Frequent (≥10%) Treatment-Related (Sitravatinib and/or Nivolumab), Treatment Emergent Adverse Events and ≥ Grade 3 Events in At Least Two Patients

Adverse Event (Preferred Term)	N=70	
	All Grades n (%)	Grade ≥3 n (%)
Diarrhea	31 (44)	8 (11)
Nausea	28 (40)	0
Fatigue	27 (39)	2 (3)
Decreased appetite	18 (26)	0
Vomiting	18 (26)	1 (1)
Dysphonia	17 (24)	0
Weight decrease	16 (23)	1 (1)
Hypertension	16 (23)	9 (13)
Alanine aminotransferase increase	12 (17)	0
Aspartate aminotransferase increase	10 (14)	0
Stomatitis	10 (14)	1 (1)
Palmar-plantar erythrodysaesthesia	10 (14)	1 (1)
Hypothyroidism	10 (14)	0
Mucosal Inflammation	8 (11)	3 (4)
Lipase increase	4 (6)	2 (3)
Hyponatremia	5 (7)	2 (3)

Grade 4 events related to treatment were seen in 1 patient each (1.4%) included: hypertensive crisis, gastric ulcer perforation, and hypomagnesaemia. Grade 5 treatment-related cardiac arrest was reported in one patient. The Investigator stated that the death was due to the patient's disease process; however, the treating physician felt that sitravatinib could not be ruled out because of the known cardiac effects. The Sponsor assessed the Cardiac Arrest as unlikely related to sitravatinib and not related to nivolumab because of the Investigator statement and the event occurred 4 days after initiating treatment with sitravatinib (steady state PK is reached in a mean time of 11 to 15 days). Treatment-related SAEs were reported in 13 patients (19%); diarrhea (3%), and fatigue, vomiting, hypertension, cardiac arrest, hypertensive crisis, syncope, confusional state, myocarditis, gastric ulcer perforation, hypoxia, deep vein thrombosis, pulmonary embolism, anaemia, dehydration, hyponatraemia, and pancreatitis in one patient each (1.4% each). Immune-related AEs (irAEs) of special interest reported were pneumonitis and myocarditis in one patient each and attributed to treatment with sitravatinib and nivolumab. The case of pneumonitis was reported as Grade 3 on Cycle 1

Day 15 and resulted in permanent discontinuation of study treatment; the event did not meet the criteria for SAE reporting. The case of myocarditis was reported as Grade 3 on Cycle 1 Day 15, resolved following study treatment interruption, but recurred upon rechallenge. The patient permanently discontinued study treatment and the event was reported as an SAE. The patient subsequently developed clinically significant pericardial effusion requiring treatment. Three deaths were reported in this study, disease under study, staphylococcal sepsis, and cardiac arrest (n=1 each).

Nonclinical toxicology studies as well as clinical safety data from the Phase 1/1b and Phase 2 studies suggest that AEs associated with sitravatinib are similar to those observed with other small molecule inhibitors of the VEGFR pathway.

Based on reported clinical experience with sitravatinib and similar agents, and nonclinical data with sitravatinib, guidance to the Investigator is provided for selected AEs in Section 5.1.2.4.

Please refer to the latest Sitravatinib (MGCD516) Investigator's Brochure for more information.

1.6 Mocetinostat Background

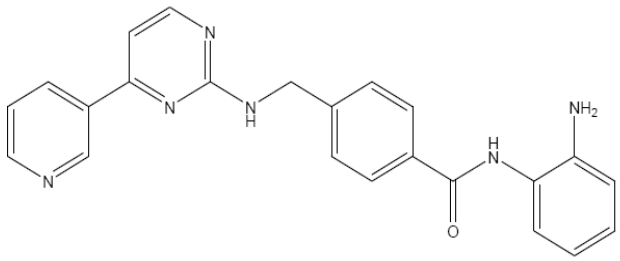
Mocetinostat (MGCD0103) is an oral, second generation benzamide inhibitor of HDAC 1, 2, 3 and 11 with broad spectrum antitumor activity in vitro and in vivo (Fournel-2008, Zhou-2008).

Background information in addition to that presented below is available in the MGCD0103 Investigator's Brochure.

1.6.1 Mocetinostat Drug Substance

The chemical structure of mocetinostat (MGCD0103) is as follows:

MGCD0103 Free Base



Chemical Formula:	$C_{23}H_{20}N_6O$
Molecular Weight:	396.45 g/mol

1.6.2 Mocetinostat Non-Clinical Data

Mocetinostat is a selective, potent, and dose-dependent inhibitor of human Class I (isoforms 1, 2, and 3) and Class IV (isoform 11) HDACs. There was weak or no activity against Class II HDACs or HDAC 8. Mocetinostat is a potent competitive inhibitor of HDAC 1, with a Ki of 64 nM. Binding was reversible, with high affinity and slow kinetics. Mocetinostat induced acetylation of core histones H4 and H3 in human bladder carcinoma (T24) cells, with an EC_{50} of 0.4 μM and 0.2 μM, respectively. Acetylation of histones was also observed in A549 human non-small cell lung carcinoma cells and A2780-S human ovarian carcinoma cells. Core histone acetylation was dose-dependent and was correlated with HDAC inhibition.

In the in vitro hERG assay, the IC_{50} for mocetinostat was > 50μM on the potassium current, which far exceeds exposures observed clinically. Results of a cardiovascular safety pharmacology study in Beagle dogs showed no test article-related changes in heart rate, arterial pressure (systolic, mean, or diastolic), or in ECG parameters at dose levels up to 100 mg/m^2 (5 mg/kg).

In a bidirectional permeability study with Caco-2 cell lines, mocetinostat is classified as highly permeable; the efflux ratio was < 2, hence it is not a P-gp or BCRP substrate.

The fractional binding of mocetinostat to human plasma was measured via equilibrium dialysis. At concentrations of 0.5, 1 and 10 μM, mocetinostat showed binding of 95.1%, 97.5%, and 95.2%, respectively.

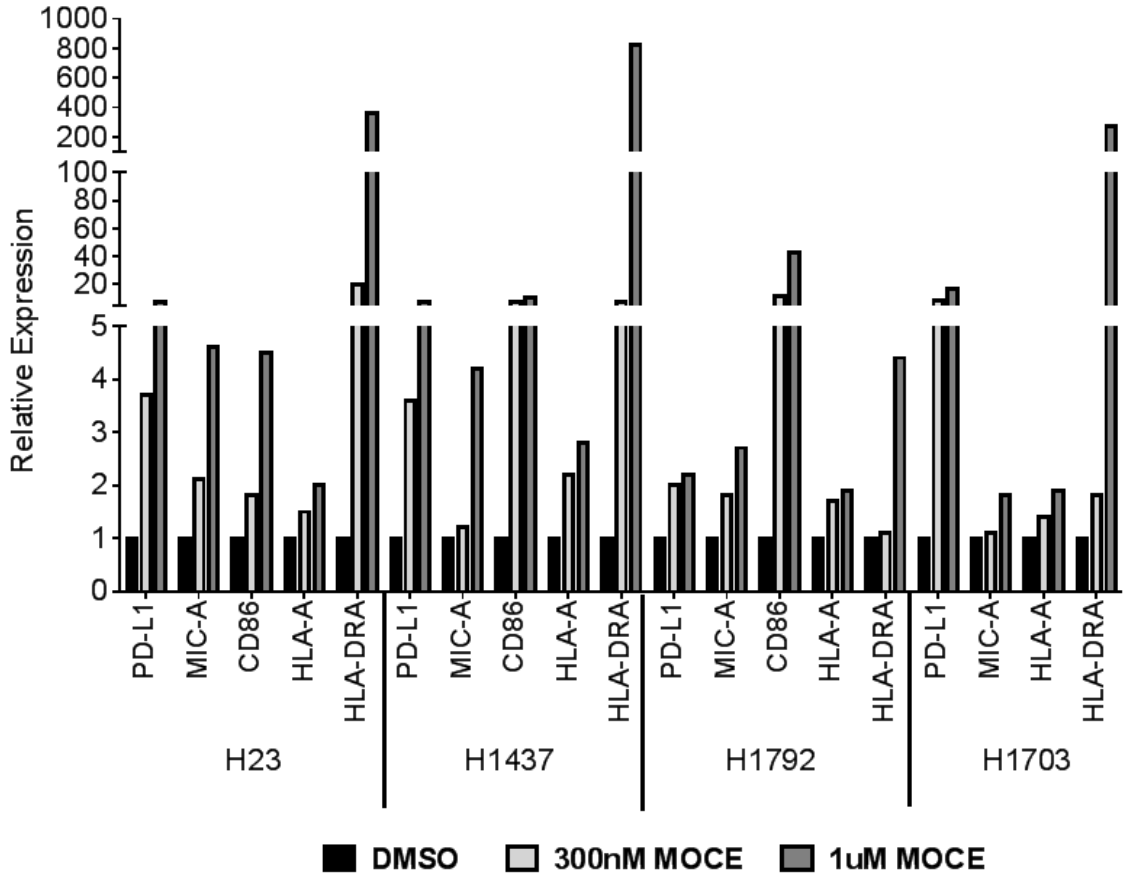
Mocetinostat is metabolized by cytochrome P-450 enzymes that include CYP 2E1 and 3A, and possibly also CYP 2C8 and 2C19. Caution should be used when mocetinostat is administered with concomitant medications that are inhibitors or inducers of CYP 2E1, or strong inhibitors or inducers of CYP 3A4. Mocetinostat does not appear to be a strong inducer of CYP enzymes but may be an inhibitor of CYP 2C9. Caution should be used when mocetinostat is administered with concomitant medications that are substrates for CYP 2C9. In vitro studies indicate that mocetinostat has a low potential for P-gp inhibition at the levels observed in patients.

Nonclinical Studies Supporting Mocetinostat and Checkpoint Inhibitor Combination

Nonclinical studies evaluated the mechanism of action of mocetinostat, its immune stimulatory properties, and the effect of combination treatment with immune checkpoint inhibitors. Initial studies were performed to assess the effect of mocetinostat on PD-L1, on major histocompatibility complex (MHC) class I and II molecules, and on immune co-stimulatory molecule gene and protein expression, across a panel of NSCLC cell lines in vitro. Mocetinostat demonstrated a concentration-dependent increase in PD-L1 gene expression ranging from 2- to 15-fold in all four NSCLC cell lines evaluated (H23, H1437, H1703, H1792) (Figure 1). In addition, mocetinostat increased PD-L1 cell-surface protein expression in 5 NSCLC cell lines, demonstrated by flow-cytometric

analysis utilizing a specific PD-L1 antibody. The increased expression of PD-L1 on tumor cells by mocetinostat may signal a shift in dependence of tumor cells on evading tumor-immune response via a PD-1-dependent mechanism. In addition, mocetinostat demonstrated a concentration-dependent increase in gene expression of several members of the human leukocyte antigen (HLA) gene complex, in all four NSCLC lines evaluated (Figure 1). HLA genes comprise the human MHC Class I and II molecules that regulate the presentation of tumor-associated antigens (TAAs) at the cell surface to enable recognition by cytotoxic T cells (CD8+). The induction of gene expression of MHC-class-I-related molecules, MIC-A and MIC-B, were also observed in all four NSCLC cell lines evaluated. The effector cytolytic responses of T cells and NK cells against tumor cells are mediated by NKG2D receptor-dependent engagement of MIC-A and MIC-B on target tumor cells, indicating that immune stimulatory properties of mocetinostat involve both innate and adaptive immune responses. Finally, mocetinostat induced the expression of the immune co-stimulatory molecule CD86, which is required for T-cell activation and antigen-dependent immune response against tumor cells expressing and presenting TAAs.

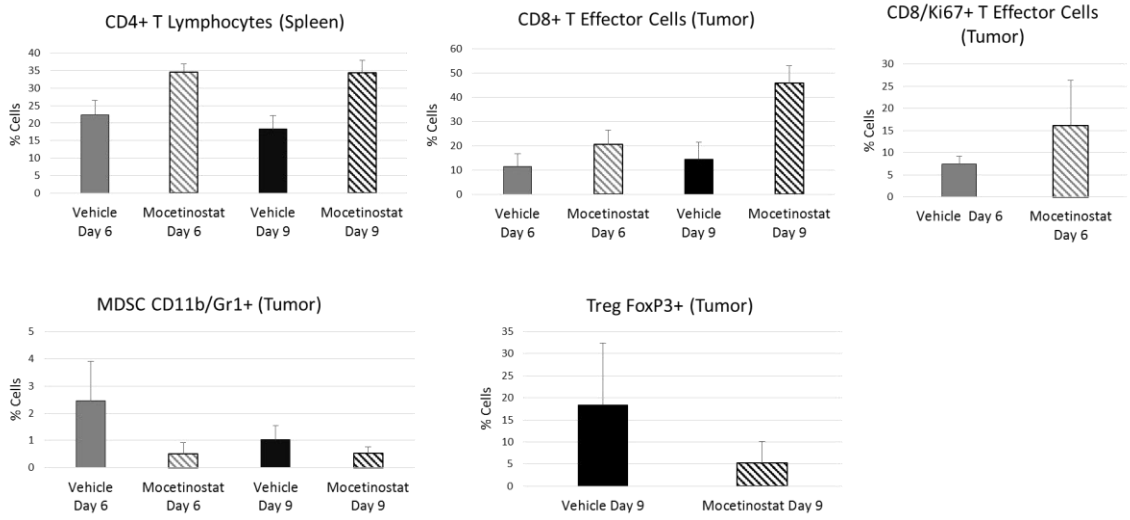
Figure 1: Mocetinostat Modulates Expression of PD-L1 and Antigen Presentation Regulatory Genes in NCSLC Cell Lines



Gene modulation in NSCLC post mocetinostat treatment. Cells were seeded in 10 cm dishes and incubated with various doses of mocetinostat or DMSO for 48 hours. RNA was extracted with Qiagen RNEasy plus kit. Relative gene expression, by quantitative polymerase chain reaction (PCR), was normalized to DMSO treatment.

To determine effect on CD4- and CD8-positive effector T cells and immunosuppressive cellular subsets including T regulatory cells (Tregs) and myeloid-derived suppressor cells (MDSCs), mice bearing syngeneic subcutaneous CT26 colon tumors were treated with 100 mg/kg mocetinostat by daily oral gavage. In these studies, mocetinostat demonstrated an increase in splenic CD4-positive T effector cells and mature cytolytic CD8-positive T cells in tumors compared to vehicle controls by day six of administration (Figure 2). In addition, mocetinostat treatment decreased tumor FoxP3-positive immunosuppressive Tregs and CD11b/Gr1-positive MDSCs in tumors compared to vehicle controls by day nine of administration.

Figure 2: Mocetinostat Modulates Key Immune Cell Populations In Vivo



Mocetinostat modulates immune cell populations. Fresh tumor and spleen samples in cold PBS were delivered within 45 minutes. Stained samples were loaded into Attune Autosampler for FACS analysis. Flow cytometry markers included percentages of: T-Cells (CD4+ and CD8+), Regulatory T-Cells (Tregs) Proliferation marker CD8+ cells that are Ki67+, MDSC (CD11b/Gr1+). Error bars represent standard deviation.

To determine the effects of mocetinostat and PD-L1 antibody combination therapy on tumor growth, CT26 tumor-bearing mice were treated with either agent alone or in combination over selected administration schedules. On Day 23, a statistically significant decrease in relative tumor volume was observed in the mocetinostat plus PD-L1 antibody combination group with a three day mocetinostat lead-in period compared with either single agent alone.

1.6.3 Mocetinostat Clinical Data

1.6.3.1 Mocetinostat Pharmacokinetics

The pharmacokinetics of mocetinostat has been evaluated in clinical trials, after single and repeated dose administration. In general, mocetinostat was rapidly absorbed following administration with 200 mL of a low pH beverage, with maximum concentration (C_{max}) occurring 0.5 to 1.5 hours after dosing. The elimination half-life ranged from approximately 7 to 12 hours. As determined from the C_{max} and AUC values, exposure to mocetinostat following oral dosing appears to increase with doses up to 110 mg. No significant drug accumulation is expected with administration of mocetinostat three times weekly.

1.6.3.2 Mocetinostat Clinical Safety

As of November 2016, mocetinostat has been administered orally as a single agent or in combination with chemotherapy to more than 489 clinical trial patients with various forms of hematological or solid tumor diseases. Regimens investigated included daily and three times weekly administration. The recommended Phase 2 treatment regimen for single agent mocetinostat is 90 mg as a fixed dose three times weekly (e.g., Monday, Wednesday and Friday)

Among 306 patients participating in clinical trials of mocetinostat single agent, treatment-related AEs were reported in 90.5% of patients. The most frequent AEs considered related to study drug (occurring in ≥5% of patients in a preferred term category) were reported for nausea (61.4%), fatigue (57.5%), diarrhea (46.7%), vomiting (37.3%), anorexia (26.8%), decreased weight (19.3%), anemia (15.4%), thrombocytopenia (13.1%), dyspepsia (11.8%) and abdominal pain (11.4%). The most frequent Grade 3/4 AEs considered related to study drug were the following fatigue (19.0%), thrombocytopenia (8.8%), neutropenia (6.5%), nausea (5.2%), anemia (5.6%), asthenia (4.6%), and anorexia (4.2%). Events listed in the Investigator's Brochure as mocetinostat ADRs include nausea, vomiting, diarrhea, anorexia, fatigue and asthenia.

Bladder toxicity resulting in dysuria and rarely hemorrhagic cystitis has been described in a few patients receiving mocetinostat. Symptoms may include dysuria, pollakiuria, hematuria, urgency, and bladder spasm and have been reported most commonly after multiple cycles of treatment.

Pericardial AEs have been reported in clinical trials of mocetinostat. The types of pericardial events included pericarditis, pericardial effusion, and cardiac tamponade. Of the pericardial adverse events, pericardial effusion was the most common. Findings of the analysis include a higher rate of pericardial SAEs among patients with Hodgkin lymphoma (9.5%) as compared to patients with leukemia or NHL (4.5% and 3.8%, respectively). Most of the pericardial AEs occurred during the first cycle of treatment. The majority of pericardial findings, including SAEs, resolved completely without sequelae, and no pericardial event was considered fatal. Screening assessments for

pericardial events were not included in the mocetinostat program during most of the prior clinical trial experience. The current study includes screening assessments and exclusion criteria to ensure that baseline status is known.

Grade 3 AEs of QTc prolongation (> 500 msec) were reported in 4 of 435 patients in clinical trials with mocetinostat; 3 of those 4 events were also reported as part of SAEs. Three of the 4 patients already had a prolonged QTc at baseline. Three of the events of QTc prolongation occurred in a setting of GI disturbances associated with dehydration and/or hypotension. In 2 cases, there was definite hypokalemia, with concomitant low magnesium in one patient, and in both cases, the QTc values decreased quickly to baseline levels after IV administration of potassium and magnesium. Concomitant treatment with drugs identified as having the potential to cause QTc prolongation may have been a factor in 2 patients.

Based on reported clinical experience with mocetinostat, guidance to the Investigator is provided for selected adverse events in Section 5.1.3.4.

1.7 Nivolumab

Nivolumab (OPDIVO) is a human monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Nivolumab is an IgG4 kappa immunoglobulin.

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

Background information in addition to that presented below is available in the USPI OPDIVO [nivolumab].

1.7.1 Nivolumab Drug Substance

Generic Name: Nivolumab

Other Name: OPDIVO

Molecular Weight: 146 kDa

1.7.2 Nivolumab Non-Clinical Data

Please refer to the latest US prescribing information USPI OPDIVO [nivolumab].

1.7.3 Nivolumab Clinical Data

Please refer to the latest US prescribing information USPI OPDIVO [nivolumab].

1.7.3.1 Nivolumab Pharmacokinetics

The PK of single-agent nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of OPDIVO every 2 or 3 weeks. The geometric mean (% coefficient of variation [CV%]) clearance (CL) is 8.2 mL/h (53.9%), geometric mean volume of distribution at steady state (V_{ss}) is 6.8 L (27.3%), and geometric mean elimination half-life ($t_{1/2}$) is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3.7-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks.

Based on a population PK analysis, the clearance of nivolumab increased with increasing body weight supporting a weight-based dose. The population PK analysis suggested that the following factors had no clinically important effect on the clearance of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1 expression, tumor type, tumor size, renal impairment, and mild hepatic impairment.

The effect of renal impairment on the clearance of nivolumab was evaluated by a population PK analysis in patients with mild (eGFR 60 to 89 mL/min/1.73 m2; n=313), moderate (eGFR 30 to 59 mL/min/1.73 m2; n=140), or severe (eGFR 15 to 29 mL/min/1.73 m2; n=3) renal impairment. No clinically important differences in the clearance of nivolumab were found between patients with renal impairment and patients with normal renal function.

The effect of hepatic impairment on the clearance of nivolumab was evaluated by population PK analyses in patients with mild hepatic impairment (total bilirubin [TB] less than or equal to the upper limit of normal [ULN] and AST greater than ULN or TB less than 1 to 1.5 times ULN and any AST; n=92). No clinically important differences in the clearance of nivolumab were found between patients with mild hepatic impairment and patients with normal hepatic function. Nivolumab has not been studied in patients with moderate (TB greater than 1.5 to 3 times ULN and any AST) or severe hepatic impairment (TB greater than 3 times ULN and any AST).

1.7.3.2 Nivolumab Anti-Drug Antibodies

Of 2085 patients who were treated with OPDIVO as a single agent at 3 mg/kg every 2 weeks and evaluable for the presence of anti-nivolumab antibodies, 233 patients (11.2%) tested positive for treatment-emergent anti-nivolumab antibodies by an electrochemiluminescent (ECL) assay and 15 patients (0.7%) had neutralizing antibodies against nivolumab. There was no evidence of altered pharmacokinetic profile or increased incidence of infusion reactions with anti-nivolumab antibody development.

1.7.3.3 Immune-Mediated Adverse Events

1.7.3.3.1 Immune-Mediated Pneumonitis

Immune-mediated pneumonitis, defined as requiring use of corticosteroids and no clear alternate etiology, including fatal cases, occurred with OPDIVO treatment.

In patients receiving OPDIVO as a single agent, immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients. The median time to onset of immune-mediated pneumonitis was 3.5 months (range: 1 day to 22.3 months). Immune-mediated pneumonitis led to permanent discontinuation of OPDIVO in 1.1%, and withholding of OPDIVO in 1.3% of patients. Approximately 89% of patients with pneumonitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 26 days (range: 1 day to 6 months). Complete resolution of symptoms following corticosteroid taper occurred in 67% of patients. Approximately 8% of patients had recurrence of pneumonitis after re-initiation of OPDIVO.

1.7.3.3.2 Immune-Mediated Colitis

Immune-mediated colitis, defined as requiring use of corticosteroids with no clear alternate etiology, can occur with OPDIVO treatment.

In patients receiving OPDIVO as a single agent, immune-mediated colitis occurred in 2.9% (58/1994) of patients; the median time to onset was 5.3 months (range: 2 days to 20.9 months). Immune-mediated colitis led to permanent discontinuation of OPDIVO in 0.7% and withholding of OPDIVO in 1% of patients. Approximately 91% of patients with colitis received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 23 days (range: 1 day to 9.3 months). Four patients required addition of infliximab to high-dose corticosteroids. Complete resolution occurred in 74% of patients. Approximately 16% of patients had recurrence of colitis after re-initiation of OPDIVO.

1.7.3.3.3 Immune-Mediated Hepatitis

Immune-mediated hepatitis, defined as requiring use of corticosteroids and no clear alternate etiology, can occur with OPDIVO treatment.

In patients receiving OPDIVO as a single agent, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients; the median time to onset was 3.3 months (range: 6 days to 9 months). Immune-mediated hepatitis led to permanent discontinuation of OPDIVO in 0.7% and withholding of OPDIVO in 1% of patients. All patients with hepatitis received high-dose corticosteroids (at least 40 mg prednisone equivalents) for a median duration of 23 days (range: 1 day to 2 months). Two patients required the addition of mycophenolic acid to high-dose corticosteroids. Complete resolution occurred in 74% of patients. Approximately 29% of patients had recurrence of hepatitis after re-initiation of OPDIVO.

1.7.3.3.4 Immune-Mediated Endocrinopathies

Hypophysitis

In patients receiving OPDIVO as a single agent, hypophysitis occurred in 0.6% (12/1994) of patients; the median time to onset was 4.9 months (range: 1.4 to 11 months). Hypophysitis led to permanent discontinuation of OPDIVO in 0.1% and withholding of OPDIVO in 0.2% of patients. Approximately 67% of patients with hypophysitis received hormone replacement therapy and 33% received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 14 days (range: 5 to 26 days).

Adrenal Insufficiency

In patients receiving OPDIVO as a single agent, adrenal insufficiency occurred in 1% (20/1994) of patients and the median time to onset was 4.3 months (range: 15 days to 21 months). Adrenal insufficiency led to permanent discontinuation of OPDIVO in 0.1% and withholding of OPDIVO in 0.5% of patients. Approximately 85% of patients with adrenal insufficiency received hormone replacement therapy and 25% received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 11 days (range: 1 day to 1 month).

Hypothyroidism and Hyperthyroidism

In patients receiving OPDIVO as a single agent, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 9% (171/1994) of patients; the median time to onset was 2.9 months (range: 1 day to 16.6 months). Approximately 79% of patients with hypothyroidism received levothyroxine and 4% also required corticosteroids. Resolution occurred in 35% of patients. Hyperthyroidism occurred in 2.7% (54/1994) of patients receiving OPDIVO as a single agent; the median time to onset was 1.5 months (range: 1 day to 14.2 months). Approximately 26% of patients with hyperthyroidism received methimazole, 9% received carbimazole, 4% received propylthiouracil, and 9% received corticosteroids. Resolution occurred in 76% of patients.

Type 1 Diabetes Mellitus

In patients receiving OPDIVO as a single agent, diabetes occurred in 0.9% (17/1994) of patients including two cases of diabetic ketoacidosis. The median time to onset was 4.4 months (range: 15 days to 22 months).

1.7.3.3.5 Immune-Mediated Nephritis and Renal Dysfunction

Immune-mediated nephritis, defined as renal dysfunction or ≥Grade 2 increased creatinine, requirement for corticosteroids, and no clear alternate etiology, can occur with OPDIVO treatment.

In patients receiving OPDIVO as a single agent, immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients; the median time to onset was 4.6 months (range: 23 days to 12.3 months). Immune-mediated nephritis and renal dysfunction led to permanent discontinuation of OPDIVO in 0.3% and withholding of OPDIVO in 0.8% of patients. All patients received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 21 days (range: 1 day to 15.4 months). Complete resolution occurred in 48% of patients. No patients had recurrence of nephritis or renal dysfunction after reinitiation of OPDIVO.

1.7.3.3.6 Immune-Mediated Rash

Immune-mediated rash including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) can occur with OPDIVO treatment.

In patients receiving OPDIVO as a single agent, immune-mediated rash occurred in 9% (171/1994) of patients; the median time to onset was 2.8 months (range: <1 day to 25.8 months). Immune-mediated rash led to permanent discontinuation of OPDIVO in 0.3% and withholding of OPDIVO in 0.8% of patients. Approximately 16% of patients with rash received high-dose corticosteroids (at least 40 mg prednisone equivalents per day) for a median duration of 12 days (range: 1 days to 8.9 months) and 85% received topical corticosteroids. Complete resolution occurred in 48% of patients. Recurrence of rash occurred in 1.4% of patients who resumed OPDIVO after resolution of rash.

1.7.3.3.7 Immune-Mediated Encephalitis

OPDIVO can cause immune-mediated encephalitis with no clear alternate etiology. Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture.

In patients receiving OPDIVO as a single agent, encephalitis occurred in 0.2% (3/1994). Fatal limbic encephalitis occurred in one patient after 7.2 months of exposure despite discontinuation of OPDIVO and administration of corticosteroids. In the other two patients encephalitis occurred post-allogeneic HSCT.

1.7.3.3.8 Other Immune-Mediated Adverse Reactions

Other clinically significant immune-mediated adverse reactions can occur with OPDIVO. Immune-mediated adverse reactions may occur after discontinuation of OPDIVO therapy. Across clinical trials of OPDIVO administered as a single agent or in combination with ipilimumab, the following clinically significant immune-mediated adverse reactions occurred in less than 1.0% of patients receiving OPDIVO: uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), myositis, myocarditis, rhabdomyolysis, motor dysfunction, vasculitis, and myasthenic syndrome.

1.7.3.3.9 Infusion Reactions

Severe infusion reactions have been reported in less than 1.0% of patients in clinical trials of OPDIVO.

In patients receiving OPDIVO as a single agent, infusion-related reactions occurred in 6.4% (127/1994) of patients.

1.7.3.4 Overall Safety Reported in NSCLC Trial

The safety of OPDIVO in metastatic NSCLC was evaluated in a randomized open-label, multicenter trial in patients with metastatic squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen (Trial 2) and a randomized, open-label, multicenter trial in patients with metastatic non-squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen (Trial 3).

Patients received 3 mg/kg of OPDIVO administered intravenously over 60 minutes every 2 weeks or docetaxel administered intravenously at 75 mg/m$_2$ every 3 weeks. The median duration of therapy in OPDIVO-treated patients in Trial 2 was 3.3 months (range: 1 day to 21.7+ months) and in Trial 3 2.6 months (range: 0 to 24.0+ months). In Trial 2, 36% of patients received OPDIVO for at least 6 months and 18% of patients received OPDIVO for at least 1 year and in Trial 3, 30% of patients received OPDIVO for greater than 6 months and 20% of patients received OPDIVO for greater than 1 year.

Trial 2 and Trial 3 excluded patients with active autoimmune disease, medical conditions requiring systemic immunosuppression, or with symptomatic interstitial lung disease. Across both trials, the median age of OPDIVO-treated patients was 61 years (range: 37 to 85); 38% were ≥65 years of age, 61% were male, and 91% were white. Ten percent of patients had brain metastases and ECOG performance status was 0 (26%) or 1 (74%).

OPDIVO was discontinued in 11% of patients and was delayed in 28% of patients for an adverse reaction. Serious adverse reactions occurred in 46% of patients receiving OPDIVO. The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were pneumonia, pulmonary embolism, dyspnea, pyrexia, pleural effusion, pneumonitis, and respiratory failure. In Trial 3, in the OPDIVO arm, seven deaths were due to infection including one case of *Pneumocystis jirovecii* pneumonia, four were due to pulmonary embolism, and one death was due to limbic encephalitis. Across both trials, the most common adverse reactions (reported in at least 20% of patients) were fatigue, musculoskeletal pain, cough, dyspnea, and decreased appetite.

Other clinically important adverse reactions observed in patients treated with OPDIVO and which occurred at a similar incidence in docetaxel-treated patients and not listed elsewhere in section 6 include: fatigue/asthenia (48% Grade 1-4, 5% Grade 3-4), musculoskeletal pain (33%), pleural effusion (4.5%), pulmonary embolism (3.3%).

1.8 Expectations for Combination of Study Investigational Agents and Nivolumab

1.8.1 Potential for Drug-Drug Interactions

The study investigational treatments glesatinib, sitravatinib or mocetinostat administered in combination with nivolumab are unlikely to result in clinically relevant drug-drug interactions (DDI) based on absorption, metabolism, elimination or protein binding. Nivolumab is a mAb and is intravenously administered, whereas the investigational agents are all small molecule therapeutics administered orally; no absorption interactions are expected.

No studies on the metabolism of nivolumab have been reported *in vitro* or in humans. Like most therapeutic proteins, nivolumab is not expected to be metabolized by liver cytochrome P-450 (CYP) or other drug metabolizing enzymes and is unlikely to have an effect on CYPs or other metabolizing enzymes in terms of inhibition or induction.

1.8.2 Evaluation of Potential for Increased Toxicities with Combination Use of Nivolumab and Study Investigational Agents

1.8.2.1 All Investigational Study Treatments in Combination with Nivolumab

Frequent adverse events, such as fatigue, musculoskeletal pain, decreased appetite, cough, and constipation, which are non-specific and typical of cancer treatment regimens have been observed with nivolumab, glesatinib, sitravatinib and mocetinostat monotherapy. Potential exists for these AEs to be observed with increased severity or frequency during use of the combined agents. Management of these effects in patients receiving cancer therapy is well precedented.

More importantly, immune-related AEs (irAEs) of Special Interest based on observed safety events using nivolumab monotherapy include pneumonitis, colitis, hepatitis, endocrinopathy, nephritis/renal dysfunction, rash, and encephalitis. While glesatinib, sitravatinib and mocetinostat may have immunostimulatory effects, autoimmune adverse effects have not been reported in clinical trials of these investigational study agents nor are they recognized as class effects for these agents. However, the potential for the investigational study treatments to exacerbate or promote these adverse events when administered in combination with nivolumab should be borne in mind.

A clinically relevant overlap in toxicity may arise between the immune-related colitis attributed to nivolumab and the non-specific, most often mild to moderate diarrhea observed with the three investigational agents. Immune-related colitis has been reported in 2.9% (58/1994) of patients treated with nivolumab, with a median time to onset of 5.3 months (range: 2 days to 20.9 months). Diarrhea of uncertain etiology has been reported in approximately 55% of patients treated with glesatinib, 48% of patients treated with sitravatinib monotherapy, and 46% of patients treated with mocetinostat, most often beginning within the first month of the start of treatment. Diarrhea (any grade) is less

common with nivolumab, occurring in approximately 8% (22/287) of NSCLC patients treated at 3 mg/kg Q2W in the CheckMate 057 clinical trial (USPI OPDIVO [nivolumab]). The time to onset may be helpful in distinguishing diarrhea that may be attributed to autoimmune effects versus non specific toxicity.

1.8.2.2 Glesatinib and Nivolumab

A clinically relevant overlap in toxicity may arise between the immune-related hepatitis attributed to nivolumab and the non-specific, most often mild to moderate elevation in liver enzymes observed with glesatinib. Immune-mediated hepatitis was reported in 0.3% (1/287) of NSCLC patients treated with nivolumab, with an onset of approximately 8 months following initiation of therapy. Increases in AST and ALT have been observed in approximately 18% and 12% of patients treated with glesatinib.

1.8.2.3 Sitravatinib and Nivolumab

Hypothyroidism, including thyroiditis, was reported in 7% (20/287) of NSCLC patients treated with nivolumab. Hypothyroidism has been reported in approximately 14% (22/153) of patients treated with sitravatinib monotherapy.

A clinically relevant overlap in toxicity may arise between the immune-related rash attributed to nivolumab and the non-specific, most often mild (Grade 1) rash observed with sitravatinib. Immune-related rash has been reported in 6% (17/287) of NSCLC patients treated with nivolumab. Rash of uncertain etiology has been reported in 10% (15/153) of patients treated with sitravatinib monotherapy.

1.8.2.4 Mocetinostat and Nivolumab

Two AEs observed in previous clinical trials of mocetinostat for which causality and mechanism are unclear are cystitis and pericardial effusion. Although the cause of these AEs is unknown, the potential for an immune-based mechanism exists, therefore increased risk may be associated with the combination of mocetinostat with nivolumab.

Robust toxicity management guidelines are in place to address or manage any immune mediated adverse reactions and drug-related toxicities associated with the study treatments.

1.9 Study Rationale

Immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway have demonstrated clinical activity in non-small cell lung cancer patients (Brahmer-2015, Borghaei-2015, Garon-2015). While this therapy leads to durable clinical responses in a subset of patients, strategies to improve its clinical efficacy and overcome innate or acquired resistance to checkpoint inhibitor monotherapy are needed. Combination therapy with agents that target the molecular and cellular mechanisms of resistance to checkpoint

inhibitor therapy is a rational approach to improving outcomes in both CIT-naïve and CIT-experienced patients.

The use of tyrosine kinase inhibitors (TKIs) to treat cancer is well established based on robust clinical efficacy achieved with well-tolerated inhibitors directed toward oncogenic tyrosine kinases. In addition, selected TKIs have been shown to modulate the immunogenic status of tumors, improve tumor perfusion by reducing intratumoral pressure and modulate subsets of immune cells, increasing the frequency and function of effector immune elements, while decreasing the number and function of immune suppressor cells. Taken together, these effects on the tumor microenvironment (TME) may lead to improved efficacy when TKIs are combined with checkpoint inhibitors. The TAM (Tyro3, Axl and MERTK) receptor tyrosine kinases (RTKs) are expressed by select innate immune cell subpopulations including macrophages and dendritic cells (Lemke-2008). The TAM receptors cooperate to create and maintain an immunosuppressive TME. MERTK suppresses the M1 macrophage pro-inflammatory cytokine response involving IL‑12, IL‑6 and TNF and enhances M2 macrophage anti-inflammatory cytokine production involving IL‑10, IL-4, TGFβ and HGF (Camenisch-1999, Tibrewal-2008). Given that anti-tumor host defense is usually mediated by cytotoxic T lymphocytes whose activation and stimulation is supported by Th1 type cytokines, the inhibition of Axl and MERTK are predicted to enhance an anti-tumor immune response. Furthermore, both Axl and MERTK are expressed by natural killer (NK) cells and negatively regulate NK cell activity in the TME as part of a feedback regulatory mechanism resulting in decreased NK cell anti-tumor activity and enhanced tumor progression and metastasis (Paolino-2014). Given the immunosuppressive function of TAM RTKs in the TME, inhibition of Axl and MERTK may complement PD-1/PD-L1 checkpoint inhibition to unleash the host anti-cancer immune response.

The MET (Mesenchymal-Epithelial Transition) RTK is implicated in modification of tumor immune responses based on its role in mediating an immunosuppressive TME as well as its role in regulating antigen presenting cell (APC) function. MET is expressed by immature CD14-positive monocytes and can induce an immunosuppressive phenotype when its ligand, hepatocyte growth factor (HGF), is secreted by tumor stroma and mesenchymal stem cells (MSCs) (Chen-2014). Depletion of CD14-positive monocytes or neutralization of HGF secretion by MSCs reverses the suppression of T effector proliferation and triggers a shift back toward a Th1 activated T cell phenotype (Chen-2014). MSCs are also implicated in expansion of immunosuppressive myeloid-derived suppressor cells (MDSCs), which are also dependent on the secretion of HGF (Yen-2013). APCs (i.e., dendritic cells) also express MET and the activation of MET by HGF results in suppression of APC function including both antigen presenting capacity and antigen-dependent T cell responses (Okunishi-2005, Singhal-2011, Benkhoucha-2010). Therefore, inhibition of MET may enhance the antitumor response by restoring APC function and reducing or eliminating MDSCs within the TME.

Glesatinib is an orally administered multi-targeted TKI that primarily targets the Axl and MET receptors. Additional RTK targets potentially include the MERTK, DDR2, and PDGFRα and β receptors. The TKI profile of glesatinib suggests the potential for synergistic anti-tumor effect when administered in combination with a checkpoint inhibitor.

Inhibition of the VEGF receptor family and KIT may further enhance antitumor immunoreactivity by depletion of immunosuppressive cellular subset from the TME including regulatory T cells and (MDSCs). T regulatory cells express VEGFR2 and the inhibition of VEGFR2 utilizing a specific VEGFR2 antibody antagonist or VEGFA neutralizing antibody (but not a VEGFR1 antagonist) inhibited Treg proliferation in vitro and in tumor-bearing mice and patient peripheral blood (Terme-2013). MDSCs notably express both KIT and VEGFR1 and the inhibition of these RTKs using pharmacologic or genetic approaches resulted in the inhibition of MDSC viability in vitro and depletion of this cell population in mouse tumor models (Ko-2009, Ozao-Choy-2009, Farsaci-2012).

Sitravatinib is an orally-available, potent small molecule inhibitor of a closely related spectrum of receptor tyrosine kinases (RTKs) including MET, Axl, MERTK, VEGFR family, PDGFR family, KIT, FLT3, Trk family, RET, DDR2, and selected Eph family members. In addition to the immunostimulatory effects of Axl and MET inhibition, sitravatinib may further condition the TME in favor of antitumor activity by its immunomodulatory effects mediated through VEGFR and KIT inhibition.

Taken together, TAM receptors, KIT, VEGFR family and MET activation work together to suppress anti-tumor immunity at several nodes and stages of the cancer-immunity cycle. The activation of TAM receptors functions as an innate immune cell checkpoint and inhibition of these receptors is predicted to complement and augment the activity observed with adaptive checkpoint inhibitor therapy (anti-PD-1) alone. Since activation of the TAM receptors functions as a mechanism to limit inflammation during the natural course of an immune response, it is likely that differing levels of TAM-dependent immunosuppression exists in most tumors, thus providing a rationale for testing inhibitors of these “innate checkpoints” in combination with adaptive checkpoint inhibitor therapy (anti-PD-1) in cancer patients that are immunotherapy naïve.

Histone deacetylases (HDACs) have been implicated in the epigenetic regulation of innate and adaptive immunity. Increasing evidence supports the proposal that spectrum-selective inhibitors of class I HDACs can reverse immune evasion and elicit antitumor host response through immunostimulatory mechanisms. The immunomodulatory properties of class I HDAC inhibitors are reported to be mediated through multiple mechanisms including: 1) induction of programmed cell death ligand 1 (PD-L1) expression on the tumor cell surface, 2) induction of tumor associated antigens (TAAs) and MHC Class I and Class II molecules on tumor cells, 3) induction of immunogenic cell death via activation and cross-presentation of tumor antigens by antigen presenting cells (APCs), 4) enhanced function of T effector cells, and 5) decreased function of immunosuppressive cell subsets including Tregs and MDSCs. In

addition, HDAC inhibitors are associated with anticancer effects through inhibiting cell cycle progression and inducing apoptosis in tumor cells (Kroesen-2014, Leggatt-2012, West-2012).

Mocetinostat is an orally administered spectrum-selective Class I/IV HDAC inhibitor specifically targeting HDACs 1, 2, 3 and 11. Given these pleiotropic immune activating effects of class I HDAC inhibitors, combination therapy of mocetinostat with checkpoint inhibition may result in increased efficacy compared to immunotherapy alone.

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response.

This study will evaluate the clinical activity of nivolumab in combination with 3 separate investigational agents, glesatinib, sitravatinib or mocetinostat. The study will begin with a lead-in dose escalation evaluation in small cohorts of patients administered one of the investigational study treatments in combination with nivolumab. Following identification of the dose level to be used in the Phase 2 evaluation for each investigational study treatment, full enrollment will proceed.

2 STUDY OBJECTIVES

2.1 Objectives

2.1.1 Primary Objective

- To evaluate the clinical activity of nivolumab in 3 combination regimens with the investigational agents glesatinib, sitravatinib, and mocetinostat, in patients with non-squamous NSCLC.

2.1.2 Secondary Objectives

- To evaluate the safety and tolerability of the combination regimens in the selected population.
- To evaluate secondary efficacy endpoints of the combination regimens in the selected population.
- To evaluate the pharmacokinetics (PK) of the investigational agents administered in combination with nivolumab.
- To evaluate the PK of different sitravatinib capsule formulations.

- To evaluate the PK of sitravatinib administered with food.

2.1.3 Exploratory Objectives

- [redacted]

[redacted]

[redacted]

2.2 Endpoints

2.2.1 Primary Endpoints

ORR as defined by RECIST 1.1.

2.2.2 Secondary Endpoints

- Safety characterized by type, incidence, severity, timing, seriousness and relationship to study treatment of adverse events and laboratory abnormalities.
- Secondary efficacy endpoints:
  - DR;
  - CBR;
  - PFS;
  - 1-Year Survival Rate; and
  - OS.
- Blood plasma concentrations of the investigational agents.

2.2.3 Exploratory Endpoints

- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3 STUDY DESIGN

Study MRTX-500 is an open-label, parallel Phase 2 evaluation of nivolumab in combination with 3 investigational agents, glesatinib, sitravatinib or mocetinostat, in patients with locally advanced, unresectable or metastatic non-squamous NSCLC. Patients who have experienced progression of disease on or after treatment with a checkpoint inhibitor (CIT- experienced) as well as those who have experienced disease progression after platinum-based doublet chemotherapy (CIT- naïve) will be enrolled. The primary objective is to evaluate the clinical activity of the combination study treatments using ORR in accordance with RECIST 1.1.

Secondary objectives include evaluation of safety, secondary efficacy endpoints, and PK for the investigational agents. The Schedule of Assessments to be performed in the study is presented in Table 1. Pharmacokinetic and blood biomarker sample collection and triplicate ECG assessment time points are presented in Table 2, Table 3, and Table 4. Specifics of two sitravatinib sub-studies are presented in appendices, including the PK evaluation of three sitravatinib capsule formulations (Appendix 5) and, the PK of sitravatinib administered with food (Appendix 6).

The treatment arms included in this study are the following:

1. Glesatinib plus nivolumab.

2. Sitravatinib plus nivolumab.

3. Mocetinostat plus nivolumab.

To control bias in assignment of individual patients to treatment arms and to mitigate the risk of medication errors with the 3 investigational study treatments administered in specific regimens, study sites will be aligned with one specified treatment combination. Site alignment may change as patient cohorts are filled or patient recruitment factors shift at sites.

3.1 Lead-In Dose Escalation Evaluation

The study will begin with a lead-in dose escalation evaluation of two dose levels of each investigational agent in combination with nivolumab, in cohorts of 3 to 8 CIT-experienced patients each. The starting dose for each agent (labeled Dose Level 1 in Table 7) represents a full reduction step as typically used in single agent Phase 2 trials. Dose Level 2 in Table 7 is the typical dose used in single agent Phase 2 trials. In addition, a dose de-escalation step may be undertaken as appropriate (labeled Dose Level -1 in Table 7). Table 7 lists the planned dose levels for each agent.

Table 7: Investigational Study Drug Starting Dose Levels for Cohorts of Patients in the Lead-In Dose Evaluation

Drug	Regimen	Dose Level		
		1	2	-1
Glesatinib Tablets	Twice Daily	500 mg	750 mg	350 mg
Sitravatinib Capsules	Once Daily	120 mg	150 mg	80 mg
Mocetinostat Capsules	Three Times Weekly	70 mg	90 mg	50 mg

Depending on experience in early cohorts of patients in the lead-in dose escalation evaluation, starting doses below those named in Table 7 may be implemented in new cohorts of patients after discussion among Investigators participating in the lead-in evaluation and the Sponsor. Depending on experience with early cohorts of patients, not all dose levels may be explored.

Throughout the study, nivolumab will be administered in accordance with approved labeling. Nivolumab is to be administered by intravenous infusion, using either regimen included in the approved label: 240 mg every 2 weeks (Q2W) or 480 every 4 weeks (Q4W). Guidance for adverse event management and associated nivolumab treatment modifications are provided in product labeling and replicated in Section 5.2.

3.1.1 Definition of Dose Limiting Toxicity

The National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 4.03 will be used throughout this study. The definition of DLT for the purpose of dose escalation decisions includes any of the following events considered to be causally related to treatment with an investigational study treatment in combination with nivolumab that occurs during the first 28-day treatment cycle:

- Any Grade 4 non-hematological toxicity.

- Any Grade 3 non-hematological toxicity or Grade 3 or 4 hematological toxicity that does not recover to ≤ Grade 2 as indicated by symptoms within 3 days and/or as indicated by laboratory assessment within 8 days after onset of the event despite optimal medical management with or without corticosteroids.
    - A special case is provided for hepatic transaminases – increase over baseline by two-fold or more and meeting Grade 3 or 4 criteria.
- Grade 2 pneumonitis or colitis that does not resolve to ≤ Grade 1 as indicated by symptoms within 3 days after onset of the event despite optimal medical management with or without corticosteroids.
- Febrile neutropenia or neutropenia associated with systemic infection.
- Any toxicity that requires suspension of treatment for more than 2 weeks.

The definition of DLT excludes the following conditions:

- Grade 3 fatigue lasting ≤ 7 days.
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that can be effectively managed with hormone replacement therapy.
- Acute infusion-related reaction.
- Lymphopenia without infection.
- Thrombocytopenia without clinically significant bleeding.

3.1.2 Enrollment and Dose Escalation Plan

Patients meeting eligibility criteria as outlined in this protocol may enroll into the lead-in dose escalation evaluation, regardless of whether they did or did not experience clinical benefit during prior treatment with a checkpoint inhibitor. Dose escalation cohorts are expected to include between 3 and 8 patients for each investigational study treatment and dose level evaluated. The first patient to be treated at the starting dose and at each new higher dose of investigational study treatment will be observed for at least one week prior to enrollment of subsequent patients in the cohort. As many as 5 patients may initially be enrolled into each cohort. For a patient within a dose cohort to be considered evaluable for the dose-escalation decision, the patient must have either been on study for one full cycle and have received treatment with nivolumab and at least 75% of scheduled investigational study treatment doses in Cycle 1 or have experienced a DLT in Cycle 1. Decision making for cohort expansion and dose escalation or de-escalation will be in accordance with the mTPI method (Dose-Finding Spreadsheet presented in Appendix 2). To ensure sufficient patient experience at the dose to be used in the Phase 2 study, enrollment at any dose level under consideration may be expanded to include at least 6 patients.

3.1.3 Definition of Maximum Tolerated Dose

The Maximum Tolerated Dose (MTD) is defined as the highest investigational study treatment dose administered in the combination regimen associated with the decision to "stay with the current dose" as determined from the Dose-Finding Spreadsheet (Appendix 2) using the experience of at least 6 patients during the first 28-day treatment cycle.

3.1.4 Selection of Phase 2 Dose for Investigational Study Drugs

For each investigational study drug, the dose to be selected for use in the Phase 2 study will be the highest dose evaluated in the lead-in evaluation that is associated with:

- sufficient safety/tolerability to anticipate that patients will typically be able to receive treatment with at least 75% of the intended dose intensity of investigational study treatment and 100% dose intensity of nivolumab; and
- no observed ≥Grade 3 or serious irAEs causally related to the combination regimen.

A dose level below the MTD may be selected for use in the Phase 2 study.

3.2 Phase 2 Study

Following completion of the lead-in dose escalation evaluation, enrollment into the Phase 2 study will proceed.

The treatment arms included in this study are the following:

1. Glesatinib plus nivolumab.
2. Sitravatinib plus nivolumab.
3. Mocetinostat plus nivolumab.

For patients who have experienced progression of disease on or after treatment with a checkpoint inhibitor (CIT-experienced), enrollment into each treatment arm will be stratified by prior outcome of treatment with a checkpoint inhibitor:

a. Clinical benefit (i.e., RECIST defined partial or complete response or stable disease for at least 12 weeks [-2 week window permitted for radiograph scheduling]) followed by radiographic progression of disease.

b. No prior clinical benefit (i.e., radiographic progression of disease ≤ 12 weeks after initiation of treatment [+2 week window permitted for radiograph scheduling]).

Thus, the study will include 6 parallel evaluations of clinical activity of nivolumab combination regimens (Figure 3) in patients with prior treatment with a checkpoint

inhibitor. Patients enrolled in the lead-in dose escalation evaluation and receiving the dose of investigational study treatment chosen for the Phase 2 study will be included in the analysis of the Phase 2 endpoints. Patients who discontinue the study prior to the first on-study disease assessment for reasons other than disease progression may be replaced.

For patients without prior checkpoint inhibitor therapy (CIT-naïve), each investigational study treatment arm (i.e., glesatinib, sitravatinib, and mocetinostat) will be stratified according to PD-L1 status:

a. Having tumor with no/low PD-L1 expression.
b. Having tumor with high PD-L1 expression.

Tumor PD-L1 expression will be determined by the PD-L1 (28-8) companion diagnostics assay completed through the central laboratory. No/low PD-L1 expression is defined as positivity < 5% of tumor cells; high PD-L1 expression is defined as positivity ≥ 5% of tumor cells. Tumor samples used to establish PD-L1 expression for eligibility must have been collected after the most recent systemic therapy.

Thus, the study will include 6 parallel evaluations of clinical activity of nivolumab combination regimens (Figure 3) in patients without prior treatment with a checkpoint inhibitor.

Disease response and progression as documented by the Investigator in the Case Report Form (CRF) will be the basis for patient management and study expansion decision making. Unconfirmed objective responses recorded in the CRF may be used as the initial basis for expansion of study enrollment; however, follow-up evaluations on patients with unconfirmed responses must continue to support the decision to continue to the full number of patients to be included in the next stage. Disease assessments will be performed until objective disease progression is documented or subsequent anti-cancer therapy is begun. Central radiology review for disease response and progression may be added to the study during Stage 2. If this occurs, central review of all radiologic assessments performed in the study will be expected (including retrospective review of patients enrolled in Stage 1), and central radiology review for disease response will be the basis for the primary statistical analyses to estimate the objective response rate and its confidence interval, as well as the duration of response and PFS.

Statistical Design Applied to CIT-Experienced and CIT-Naïve with No/Low PD-L1 Expression

This Phase 2 study will use a Predictive Probability Design (Lee-2008) in each treatment arm and strata. In creating the statistical designs, the Type 1 error (α) is constrained to <0.05 and Power ($1-\beta$) is constrained to ≥0.90.

The ORR using nivolumab in the population with advanced non-squamous NSCLC having prior disease progression on a checkpoint inhibitor or patients with non-squamous NSCLC without prior checkpoint inhibitor therapy with no/low PD-L1 expression is

assumed to be 5% (p_0); thus this rate is considered uninteresting. The target ORR using the investigational agents in combination with nivolumab in this study is 30% (p_1). Stage 1 of enrollment will include a minimum of 9 evaluable patients in each treatment strata. With exactly 9 evaluable patients at Stage 1, if at least 1 patient has an Objective Response, 8 additional evaluable patients will be enrolled in the treatment stratum, for a total sample size of 17 evaluable patients. If at least 3 Objective Responses are observed in a treatment stratum, further investigation may be warranted. If the true ORR is 5% (null hypothesis), the probability of early termination during the study is 0.63; the Type 1 error is equal to 0.0466 and the power is equal to 0.9045.

Statistical Design Applied to CIT-Naïve with High PD-L1 Expression

The ORR using nivolumab in the population with non-squamous NSCLC having high PD-L1 expression is assumed to be 27% (p_0); thus this rate is considered uninteresting. The target ORR using the investigational agents in combination with nivolumab is 50% (p_1).

Stage 1 of enrollment will include approximately 17 evaluable patients. With exactly 17 evaluable patients at Stage 1, if at least 5 patients have Objective Responses, 27 additional evaluable patients will be enrolled, for a total sample size of 44 evaluable patients. If at least 18 Objective Responses are observed, further investigation may be warranted. If the true ORR is 27% (null hypothesis), the probability of early termination during the study is 0.50; the Type 1 error is equal to 0.0303 and the power is equal to 0.9018.

The exact stopping rules for all cohorts will be calculated based on the Predictive Probability Design, once the exact number of patients evaluable at Stage 1 is known. The aim is to get a minimum of 9 evaluable patients at Stage 1 for CIT-experienced and CIT-naïve with no/low PD-L1 expression cohorts and a minimum of 17 evaluable patients at Stage 1 for CIT-naïve with high PD-L1 expression cohort.

In order to be part of the clinical activity evaluable population, the patient must have at least one on-study disease assessment or discontinue from treatment for progressive disease prior to this assessment. Patients who discontinue treatment prior to the first on-study disease assessment for an AE, toxicity, or withdraw consent are considered non-evaluable for disease assessment. These patients will not be part of the clinical activity evaluable population.

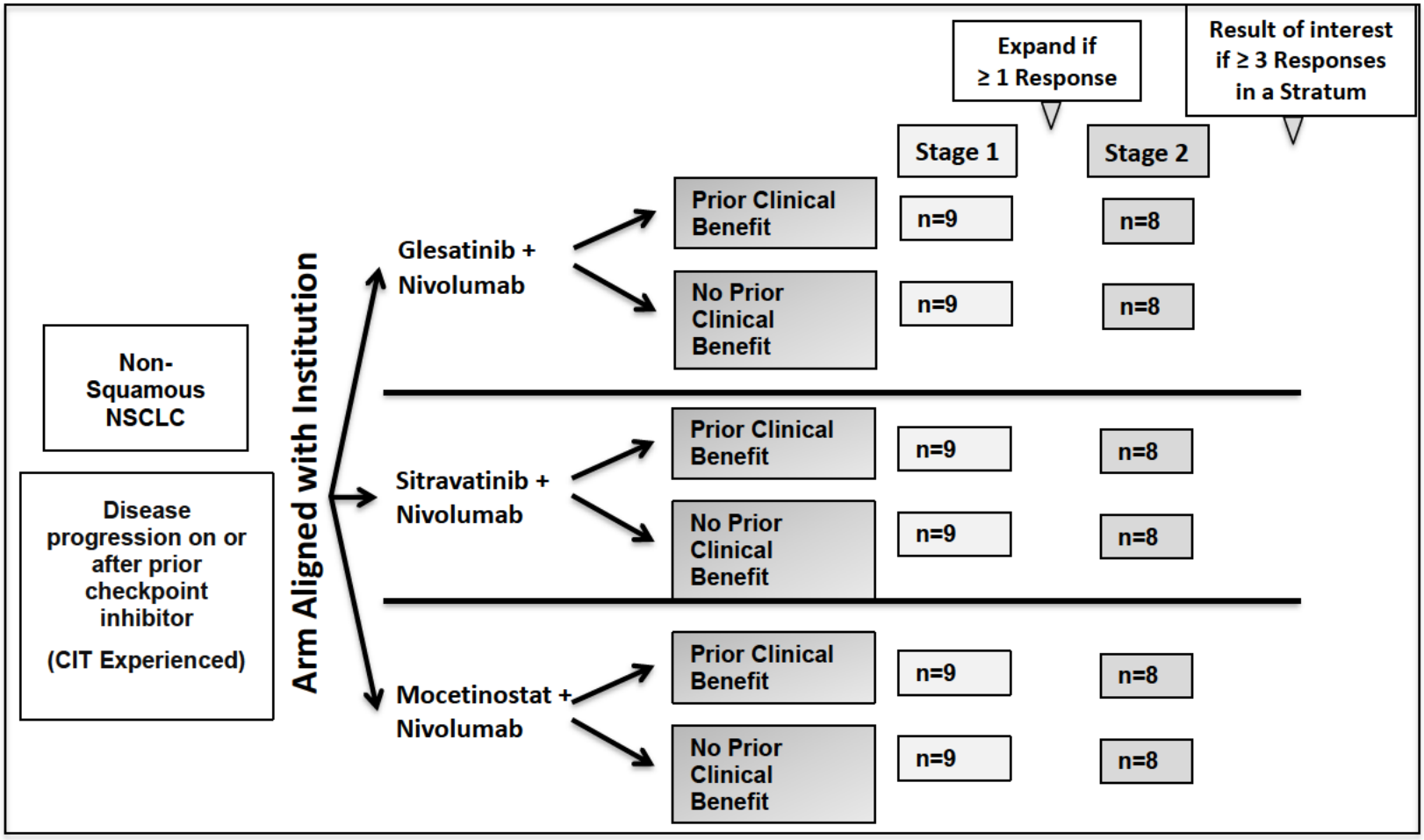
Expansion Beyond Stage 2

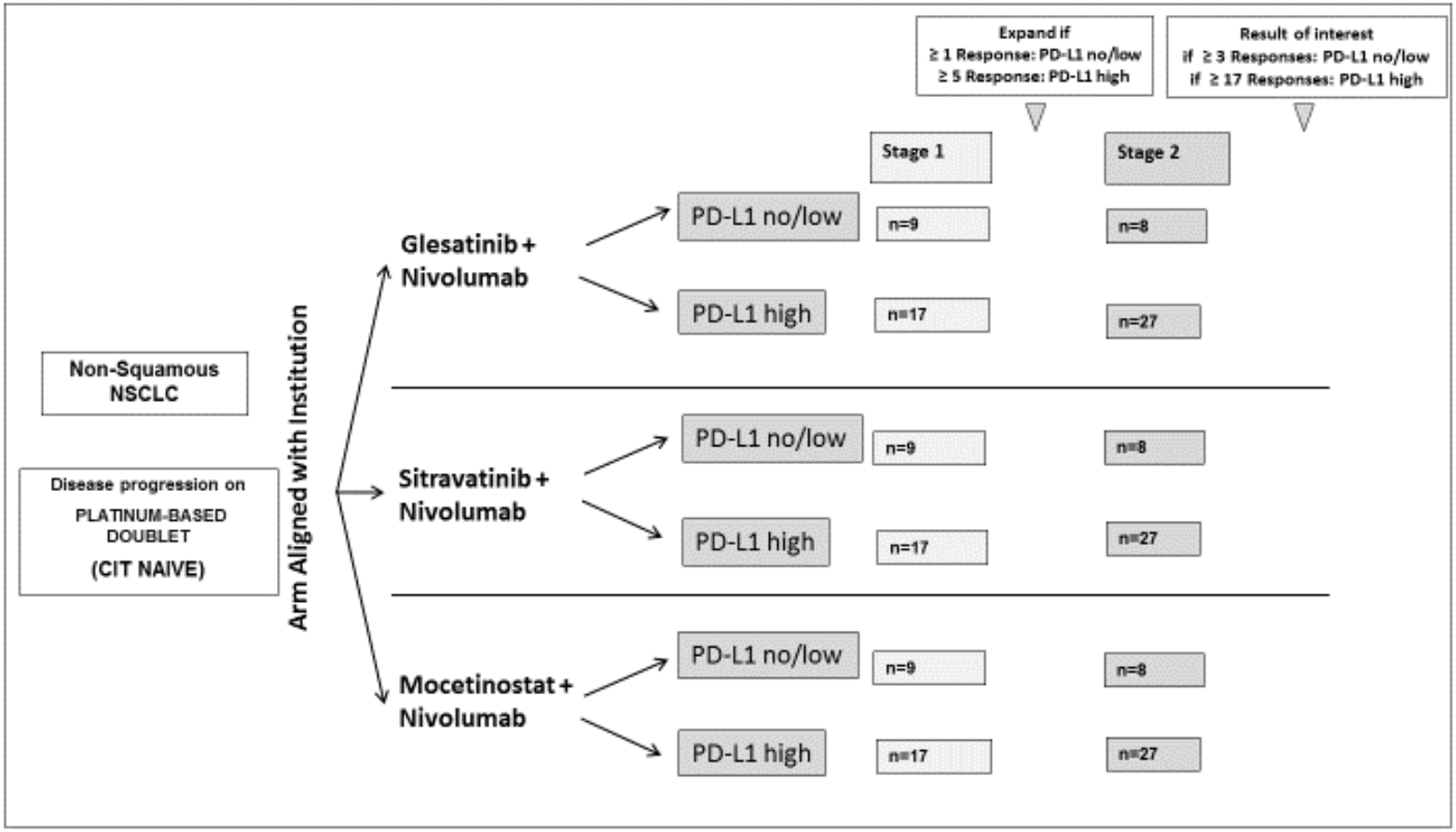
The original protocol provided that if results in any strata were of high interest for efficacy, enrollment might be expanded to as many as 100 patients total in each cohort to narrow the 95% Confidence Interval (CI) around the ORR point estimate. Protocol Amendment 3 (Version 4.0) eliminates enrollment expansion beyond Stage 2 except in the sitravatinib segment of the study enrolling patients with CIT-experience.

For the sitravatinib segment of the study enrolling patients with CIT-experience, expansion of enrollment beyond Stage 2 will be managed as one cohort that includes all patients, regardless of prior clinical benefit during treatment with CIT. Based on preliminary clinical activity results as of June 2018 (described in Section 1.5.3.2.2), enrollment into the combined cohort will expand to as many as 125 patients total, to further evaluate safety and efficacy in this setting.

Expansion of sitravatinib CIT-naïve cohorts beyond Stage 2 of enrollment is not anticipated.

Figure 3: Study Diagram




Expand if
≥ 1 Response: PD-L1 no/low
≥ 5 Response: PD-L1 high
Result of interest
if ≥ 3 Responses: PD-L1 no/low
if ≥ 17 Responses: PD-L1 high
Stage 1
Stage 2
Non-Squamous NSCLC
Disease progression on PLATINUM-BASED DOUBLET (CIT NAIVE)
Arm Aligned with Institution
Glesatinib + Nivolumab
Sitravatinib + Nivolumab
Mocetinostat + Nivolumab
PD-L1 no/low
PD-L1 high
n=9
n=17
n=8
n=27

4 PATIENT SELECTION AND ENROLLMENT

Patient eligibility must be reviewed and documented by an appropriately qualified member of the Investigator's study team before patients are included in the study. No exceptions to the patient eligibility requirements will be granted by the Sponsor.

4.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria as applicable for phase of the study to be eligible for enrollment into the study:

1. Histologically confirmed non-squamous NSCLC with metastatic or unresectable, locally advanced disease, not amenable to treatment with curative intent.

2. Receipt of at least one prior treatment in the advanced disease setting.

    a) CIT-experienced: Most recent treatment must have included a checkpoint inhibitor (i.e., anti-PD-1 or anti-PD-L1 including nivolumab, pembrolizumab, durvalumab, atezolizumab or avelumab) with the result of progression of disease on or after treatment.

    Note: For the PK sub-studies as outlined within Appendix 5 and Appendix 6, treatment with a checkpoint inhibitor (i.e., anti-PD-1 or anti-PD-L1) does not need to be included in the most recent treatment.

    b) CIT-naïve: Receipt of prior platinum-based doublet chemotherapy.

3. CIT-naïve: Molecular analysis of tumor sample collected following most recent therapy, assessed using the PD-L1 (28-8) CDx assay. Inclusion in the treatment arm will be based on documented no/low PD-L1 expression (positivity < 5% of tumor cells) or high PD-L1 expression (positivity ≥ 5% of tumor cells). ***Note: This criterion does not apply to the PK sub-studies as outlined within Appendix 5 and Appendix 6.***

4. Measurable disease as per RECIST version 1.1.

5. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1 or 2 (Appendix 1).

6. Adequate bone marrow and organ function demonstrated by:

    - Absolute neutrophil count ≥ 1,000/mm^3 (≥ 1.0 × 10^9/L)

    - Platelet count ≥ 50 × 10^9/L (> 50,000 per mm^3)

- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × Upper Limit of Normal (ULN), or ≤ 5.0 × ULN for patients with documented liver metastases.

- Serum bilirubin ≤ 1.5 × ULN or ≤ 3.0 × ULN for patients with Gilbert Syndrome or documented liver metastases.

- Serum creatinine ≤ 1.5 × ULN.

7. ≥ 18 years of age.

8. 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.

9. Completed informed consent process, including signing IRB/EC-approved informed consent form.

10. Willing to comply with clinical trial instructions and requirements.

4.2 Exclusion Criteria

Patients presenting with any of the following will not be included in the study:

1. Active brain metastases. Patients are eligible if brain metastases are adequately treated and patients are neurologically stable (except for residual signs or symptoms related to the central nervous system (CNS) treatment) for at least 2 weeks prior to enrollment without the use of corticosteroids, or are on a stable or decreasing dose of ≤10 mg daily prednisone (or equivalent).

   a. Patients with carcinomatous meningitis

2. Patients with any history of tumors that test positive for *EGFR, ROS1,* ALK mutations or *ALK* fusions or any other well characterized driver mutations (e.g., *RET* fusion, *TRK* alterations, *BRAF* mutations). ***Note: The following modification to this criterion applies to the PK sub-studies as outlined within Appendix 5 and Appendix 6: Patients with EGFR, ROS1, ALK mutations or ALK fusions are eligible if previously treated with targeted therapy and/or treatment with a targeted therapy is not indicated.***

3. Prior therapies: ***(Note: This exclusion criterion does not apply to the PK sub-studies as outlined within Appendix 5 and Appendix 6)***

   a) Immunotherapies not previously specified, including anti-CTLA-4, anti-OX40 and anti–CD137.

b) Combination therapy with a checkpoint inhibitor and cancer therapy having the same mechanism of action as the investigational agent intended for use in this study (e.g., tyrosine kinase target or HDAC inhibitor, except prior use of valproic acid for seizures).

4. Unacceptable toxicity on prior checkpoint inhibitor treatment (CIT- experienced patients only):

   a. ≥ Grade 3 immune-related AE related to checkpoint inhibitor.

   b. Grade 2 immune-related AE associated with checkpoint inhibitor unless the AE resolved or was well controlled by withholding the checkpoint inhibitor and/or treatment with steroids, with the exception of prior colitis, myocarditis, and pneumonitis, which are exclusionary.

   c. CNS or ocular AE of any grade related to checkpoint inhibitor.

      NOTE: Patients with a prior endocrine AE are permitted to enroll if they are stably maintained on appropriate replacement therapy and are asymptomatic.

5. Active or prior documented autoimmune disease:

   a. Inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis).

   b. History of interstitial lung disease (ILD), drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease.

   c. Active or prior documented autoimmune disease within the past 2 years.
      NOTE: Patients with Type I diabetes, vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.

6. Active or prior immunocompromising conditions:

   a. Current or prior use of immunosuppressive medication within 28 days before the first dose of study treatment, with the exceptions of topical, ocular, intranasal and inhaled corticosteroids (with minimal absorption) or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid. A brief course (≤ 3 days) of systemic corticosteroids >10 mg/day of prednisone (or equivalent corticosteroid) for prophylaxis (e.g., contrast dye allergy) or for treatment of non-immune conditions (e.g., delayed-type hypersensitivity reaction caused by a contact allergen) is permitted within the 28 days.

   b. Known acute or chronic human immunodeficiency virus (HIV).

c. History of primary immunodeficiency.

d. History of allogeneic transplant.

7. Known acute or chronic hepatitis B or hepatitis C. Patients treated for hepatitis C with no detectable viral load are permitted.

8. History of hypersensitivity to study treatment excipient.

9. History of stroke or transient ischemic attack within the previous 6 months.

10. Any of the following cardiac abnormalities:

    a. Unstable angina pectoris.

    b. Congestive heart failure ≥ NYHA Class 3.

    c. QTc >480 milliseconds.

    d. Sitravatinib and mocetinostat treatment arms:

        i. LVEF <40% (sitravatinib and mocetinostat only).

        ii. Current or history of a small, moderate or large pericardial effusion, and/or hemodynamic compromise due to pericardial effusion of any size. Minimal or trivial pericardial effusion is not excluded (mocetinostat only).

11. Concomitant medication known to cause prolonged QT which cannot be discontinued or changed to a different medication prior to enrollment (Appendix 3).

12. Known or suspected presence of another malignancy that could be mistaken for the malignancy under study during disease assessments.

13. Pregnancy. WOCBP must have a negative serum or urine pregnancy test documented within the screening period prior start of study drug.

14. Breast-feeding or planning to breast feed during the study or within 6 months after study treatment.

15. 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.

4.3 Life Style Guidelines

Patients who are biologically capable of having children and sexually active must agree to use an acceptable method of contraception 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 forms of contraception include:

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 condom or female condom used WITH a spermicide.

4. Male sterilization with confirmed absence of sperm in the post-vasectomy ejaculate.

5. Bilateral tubal ligation or bilateral salpingectomy.

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.

4.4 Enrollment into Study

Following completion of the study-specific informed consent process and review of all screening procedures, patient eligibility will be confirmed by appropriately qualified staff at the investigational site. Patients will be enrolled by entry into a patient registration log provided by the Sponsor and maintained by the study site, and completion of the patient registration procedure detailed in the Study Manual. Each patient will be assigned a sequential number by the study site. The patient number must be used on all documentation and correspondence with the Sponsor, Contract Research Organization (CRO) and laboratory vendors.

For the evaluation of tumor PD-L1 expression for CIT-naive patients, a 14-day turn-around time should be expected from the time of receipt of adequate samples at the central laboratory to test results returned to the study site.

5 STUDY TREATMENTS

5.1 Investigational Agents

5.1.1 Glesatinib

5.1.1.1 Glesatinib Formulation, Packaging and Storage

Glesatinib will be supplied by the Sponsor as 100 and 250 mg unit dosage strength tablets. The composition of the drug product consists of a blend of MGCD265 free base drug substance, hydroxypropylmethyl cellulose (HPMC), Avicel® (or equivalent), Kollidon® (or equivalent), sodium bicarbonate, sodium chloride, Syloid® (or equivalent), and magnesium stearate, as necessary.

Glesatinib tablets will be supplied in high-density polyethylene (HDPE), white opaque bottles. A tamper-proof heat induction seal and a child-resistant closure are used. Tablet bottles will be received by the pharmacy in foil pouches that are to be kept intact until the bottles are dispensed to the patient. The Sponsor provided bottles should be labeled for specific patient use and given to the patient.

While stored in the study site pharmacy, glesatinib tablets should be at refrigerated conditions (suggested temperature range 2-8°C, 36-46°F). Once dispensed to patients, tablets bottles should be stored at room temperature (suggested temperature range 15-30°C, 59-86°F).

Refer to the Pharmacy Study Manual for details on available unit dose strengths, bottle sizes, and number of units per bottle supplied.

5.1.1.2 Glesatinib Administration

Glesatinib tablets will be administered orally, twice daily (BID), in a continuous regimen expressed in 28-day cycles. The starting dose for glesatinib in the lead-in dose escalation evaluation will be 500 mg BID. Depending on safety observations, the glesatinib dose in the subsequent cohort of patients may escalate to 750 mg BID or de-escalate to 350 mg BID. Individual patients should not undergo dose escalation above their starting dose.

The following guidelines should be followed for glesatinib administration:

- Doses should be taken approximately every 12 hours at approximately the same times each day.

- At the beginning of the study, tablets should be taken on an empty stomach (at least a 1-hour fast before each dose and no food for a minimum of 1 hour after each dose). If results from an ongoing food-effect study indicate that fasting is unnecessary, an Administrative Letter to Investigators will communicate elimination of this guidance.

- Tablets should be taken with at least 200 mL (1 cup) of water.
- Patients should swallow the tablets whole and not chew them.
- If vomiting occurs after dosing, glesatinib doses should not be replaced.

On days when glesatinib and nivolumab dosing are both scheduled, the first daily dose of glesatinib should precede nivolumab infusion for logistical reasons. This order of dosing is of most interest on days when blood sampling is scheduled for glesatinib PK.

5.1.1.3 Glesatinib Dose Modification and Discontinuation

In the event of adverse events attributed to glesatinib and deemed intolerable by the Investigator, treatment should be either temporarily or permanently discontinued. For patients who temporarily discontinue treatment, treatment may resume following resolution of treatment-related adverse events to Grade 1 or baseline with the administration of glesatinib at a reduced dose level as outlined in Table 8. Once the dose has been reduced, re-escalation is generally not recommended but may be considered on a case-by-case basis. If the administration of glesatinib is interrupted for reasons other than toxicity, then treatment with the study drug may be resumed at the same dose.

Table 8: Glesatinib Sequential Dose Reductions for Individual Patients

750 mg twice daily
500 mg twice daily
350 mg twice daily
250 mg twice daily

Dose reduction below 250 mg BID may be undertaken after discussion with the Sponsor. If treatment with glesatinib is withheld for ≥ 28 consecutive days, then permanent discontinuation from this study drug should be considered.

5.1.1.4 Glesatinib Specific Adverse Event Management Guidelines

See Section 5.1.4.2 for management guidelines for non-hematological or hematological toxicities commonly associated with cancer therapies, which will be applied to all three investigational study treatments in this study.

The following are guidelines for management of potential adverse events more specific to treatment with glesatinib or agents in the same class of cancer treatment.

5.1.1.4.1 Diarrhea

See Section 5.1.4.2.2 for treatment management guidelines in patients experiencing diarrhea during study treatment. Patients treated with glesatinib should be made aware of

the potential of developing diarrhea while taking glesatinib. Prophylactic anti-diarrheal treatment may be implemented at the discretion of the Investigator. A regimen recommended for primary prophylaxis for diarrhea is loperamide 2-4 mg beginning with the first dose of glesatinib, followed by 2 mg every 6–8 hours. Loperamide use may be subsequently titrated as needed. If prophylactic treatment is not used, patients should start treatment with loperamide immediately upon the first sign of diarrhea. If there is no improvement in severity of symptoms within 24 hours, additional anti-diarrheal medication in the form of Lomotil® should be added. If this does not effectively control symptoms, patients should be instructed to contact their physician and their dose held until resolution of symptoms followed by a dose reduction as indicated per protocol. Patients with severe or prolonged diarrhea should be observed and treated for dehydration.

5.1.2 Sitravatinib

5.1.2.1 Sitravatinib Formulation, Packaging and Storage

Two formulations of sitravatinib capsules are being utilized in this study. The composition of the sitravatinib free base drug product consists of a blend of MGCD516 free base drug substance, microcrystalline cellulose (Avicel® PH302) and polysorbate 80 (Tween® 80) and Aerosil® 200 Pharma.

Sites that are participating in one or both of the PK Sub-Studies as referenced in Appendix 5 and Appendix 6 of the protocol will also receive Sitravatinib (MGCD516) malate formulation capsules.

Two manufacturing methods of the malate formulation were utilized to improve manufacturing process and scalability. The composition of the sitravatinib malate direct blend drug product consists of a blend of MGCD516 malate drug substance, microcrystalline cellulose (Avicel® PH302), colloidal silicon dioxide (Cab-O-Sil), croscarmellose sodium (Ac-Di-Sol) and magnesium stearate. The composition of the sitravatinib malate roller compaction drug product consists of a blend of MGCD516 malate drug substance, microcrystalline cellulose, mannitol, colloidal silicon dioxide, croscarmellose sodium, and magnesium stearate.

Sitravatinib drug product in all formulations is packaged in 30-count, 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 if the capsule count is the needed number, or the pharmacy may re-dispense the needed number of capsules into Sponsor provided HDPE bottles.

Sitravatinib capsule bottles should be stored under refrigerated conditions (2-8°C, 36-46°F) at the pharmacy in according to instructions on the label. After dispensing to the patient, bottles of sitravatinib capsules are to be stored at ambient room temperature for the duration of time specified in the Pharmacy Manual.

Refer to the Pharmacy Study Manual for details on available unit dose strengths, bottle sizes, and number of units per bottle supplied.

5.1.2.2 Sitravatinib Administration

Sitravatinib capsules will be administered orally, once daily (QD), in a continuous regimen expressed in 28-day cycles.

In the Phase 1 segment of the study, the starting dose for sitravatinib in the lead-in dose escalation evaluation will be 120 mg QD. Depending on safety observations, the sitravatinib dose in the subsequent cohort of patients may escalate to 150 mg QD or de-escalate to 80 mg QD. Individual patients should not undergo dose escalation above their starting dose.

The sitravatinib recommended Phase 2 starting dose is 120 mg QD.

The starting dose of sitravatinib for patients enrolled in the PK sub-studies is described in Appendix 5 and Appendix 6.

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). Instructions to be followed for patients enrolled in the sub-study dedicated to evaluating sitravatinib administered with food are provided in Appendix 6.
- Capsules should be taken with ~240 mL (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.

On days when sitravatinib and nivolumab dosing are both scheduled, the daily dose of sitravatinib should precede nivolumab infusion for logistical reasons. This order of dosing is of most interest on days when blood sampling is scheduled for sitravatinib PK.

5.1.2.3 Sitravatinib Dose Modification and Discontinuation

In the event of adverse events attributed to sitravatinib and deemed intolerable by the Investigator, treatment should be either temporarily or permanently discontinued. For patients who temporarily discontinue treatment, treatment may resume following resolution of treatment-related adverse events to Grade 1 or baseline with the administration of sitravatinib at a reduced dose level as outlined in Table 9. Once the dose has been reduced, re-escalation is generally not recommended but may be

considered on a case-by-case basis. 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.

Table 9: Sitravatinib Free Base Formulation Sequential Dose Reductions for Individual Patients

150 mg once daily (eliminated after lead-in evaluation)
120 mg once daily
80 mg once daily
60 mg once daily*

* Dose reduction below 60 mg QD may be undertaken after discussion with the Sponsor.

Sitravatinib Malate Direct Blend Formulation Sequential Dose Reductions for Individual Patients

60 mg once daily
40 mg once daily

Sitravatinib Malate Roller Compaction Formulation Sequential Dose Reductions for Individual Patients

100 mg once daily
80 mg once daily
60 mg once daily
40 mg once daily

A two-step dose reduction (e.g. 100 mg to 60 mg once daily) is permitted at the discretion of the investigator

In the event of sitravatinib-related AE, dose reduction with continuous treatment is preferred over repeated dose interruption. Following sitravatinib dose reduction and control of adverse event, re-challenge at a higher sitravatinib dose is permitted at the discretion of the Investigator. If treatment with sitravatinib is withheld for ≥ 28 consecutive days, then permanent discontinuation from this study drug should be considered. If one study drug is interrupted or discontinued, administration of the other study drug may continue at the discretion of the Investigator.

5.1.2.4 Sitravatinib Specific Adverse Event Management Guidelines

See Section 5.1.4.2 for management guidelines for non-hematological or hematological toxicities commonly associated with cancer therapies which will be applied to all three investigational study treatments in this study.

The following are guidelines for management of potential adverse events more specific to treatment with sitravatinib or agents in the same class of cancer treatment.

5.1.2.4.1 Hypertension

Hypertension, including Grade 3 events, has been reported with sitravatinib. Dihydropyridine calcium channel blockers such as nifedipine, amlodipine, and nicardipine may be considered if anti-hypertensive therapy is required and should be considered for patients with Grade 3 hypertension without clinically significant increases in blood pressure (BP) (see Table 10). On the other hand, in cases of Grade 3 hypertension with clinically significant increases in blood pressure (see Table 10), temporary suspension of sitravatinib dosing is recommended until blood pressure is controlled. Treatment with sitravatinib may resume at the same or a lower dose at the discretion of the Investigator. If significant hypertension recurs, options include change in medical management of the patient, reduction of sitravatinib dose, or discontinuation of study treatment, at the discretion of the Investigator. In the event of Grade 4 hypertension, sitravatinib should be permanently discontinued (see Table 10).

Table 10: Sitravatinib Dose Modification for Increased Blood Pressure

Toxicity	Treatment Delay	Reduction
Grade 1 or 2 hypertension	Investigator discretion, as per Table 15	
Grade 3 hypertension without clinically significant increases in BP as defined below	Investigator discretion. Consider anti-hypertensives per Section 5.1.2.4.1	
Grade 3 hypertension with clinically significant increases in BP *defined as* either an increase of ≥ 30 mmHg in systolic BP to ≥ 180 mmHg *or* increase of ≥ 20 mmHg in diastolic BP to ≥ 110 mmHg, confirmed with repeated testing after at least 5 minutes	Hold until ≤ Grade 2 or return to baseline	Investigator discretion
Grade 4 hypertension	Discontinue sitravatinib	Discontinue sitravatinib

5.1.2.4.2 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.

5.1.2.4.3 Diarrhea

See Section 5.1.4.2.2 for treatment management guidelines in patients experiencing diarrhea during study treatment. Diarrhea has been reported with sitravatinib treatment, though the mechanism remains unclear, as with other small molecule RTK inhibitors. Patients should be counseled that diarrhea is a possible side effect and advised to take loperamide or a similar medication as needed if diarrhea develops. Any patients developing dehydration or clinically significant electrolyte abnormalities should interrupt treatment, but treatment may be restarted once diarrhea is controlled.

5.1.2.4.4 Hemorrhagic Events

The risk of hemorrhagic events with sitravatinib is unknown; 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.

5.1.2.4.5 Thrombotic Events

Though thrombotic events (e.g., pulmonary embolism) have been reported with sitravatinib and with inhibitors of VEGFR, the risk of such events with sitravatinib is unknown. Precautions should be taken in patients with recent, clinically significant thrombotic events, and treatment should be discontinued in patients who develop clinically significant thromboembolic complications such as acute myocardial infarction or severe pulmonary embolism.

5.1.2.4.6 Thyroid Dysfunction Other than Immune-Mediated

Hypothyroidism and increases in TSH have been reported in patients taking sitravatinib. Patients diagnosed with hypothyroidism should be treated with thyroid replacement and may continue treatment with sitravatinib at the Investigator's discretion.

5.1.2.4.7 Decreased Left Ventricular Ejection Fraction

Decreased left ventricular ejection fraction (LVEF) has been reported with sitravatinib. In addition, decreases of LVEF to <50% on-study were observed in patients undergoing scheduled multigated acquisition (MUGA) scans or echocardiograms. The dose of sitravatinib should be interrupted and/or reduced in patients without clinical evidence of congestive heart failure (CHF) but with an ejection fraction <50% and >20% below baseline. Discontinuation should be considered in more severe cases.

5.1.2.4.8 Proteinuria

Although the risk with sitravatinib is unknown, proteinuria has been described with other inhibitors of the VEGFR pathway. Patients 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 restart when protein levels decrease to less than 2 grams/24 hours. Patients who develop nephrotic syndrome should be withdrawn from treatment with sitravatinib.

5.1.3 Mocetinostat

5.1.3.1 Mocetinostat Formulation, Packaging and Storage

Mocetinostat will be provided by the Sponsor as 10 mg (white opaque), 20 mg (white opaque), 25 mg (Swedish orange), and 50 mg (Swedish orange) unit dose strength capsules. The composition of the drug product consists of the free-base form of MGCD0103 and inert excipients: microcrystalline cellulose, sodium starch glycolate, colloidal silicon dioxide and non-bovine magnesium stearate.

Mocetinostat drug product is packaged in high-density polyethylene (HDPE), white opaque, bottles, with a desiccant packet. A tamper-proof heat induction seal and a child-resistant closure are used. Refer to the Pharmacy Study Manual for details on available unit dose strengths, bottle sizes, and number of units per bottle supplied.

Mocetinostat capsules should be stored protected from light, at room temperature (suggested range is 15-30°C, 59-86°F) according to instructions on the label.

5.1.3.2 Mocetinostat Administration

Mocetinostat capsules will be administered orally, three times per week (TIW), in a continuous regimen expressed in 28-day cycles. The starting dose for mocetinostat in the lead-in dose escalation evaluation will be 70 mg TIW. Depending on safety observations, the mocetinostat dose in the subsequent cohort of patients may escalate to 90 mg TIW or de-escalate to 50 mg TIW. Individual patients should not undergo dose escalation above their starting dose.

The following guidelines should be followed for mocetinostat administration:

- Patients should be instructed to take the dose of mocetinostat three days per week (e.g., Monday/Wednesday/Friday), in the morning, at approximately the same time each day.
- Mocetinostat capsules should be taken on an empty stomach (after an overnight fast or at least a 3-hour fast before each dose and no food for a minimum of 2 hours after each dose).
- Capsules should be taken with at least 200 mL (1 cup) of water.
- Patients should swallow the capsules whole and not chew them.
- If vomiting occurs after dosing, mocetinostat doses should not be replaced.

- Mocetinostat doses should not be taken 2 days in a row and gaps longer than 3 days (~72 hours) should be avoided when possible.

On days when mocetinostat and nivolumab dosing are both scheduled, the mocetinostat should precede nivolumab infusion for logistical reasons. This order of dosing is of most interest on days when blood sampling is scheduled for mocetinostat PK. Alignment of mocetinostat and nivolumab dosing days is not required. For instance, mocetinostat may be routinely administered on Monday, Wednesday and Friday, and nivolumab administered in the clinic on a Thursday.

5.1.3.3 Mocetinostat Dose Modification and Discontinuation

In the event of adverse events attributed to mocetinostat and deemed intolerable by the Investigator, treatment should be either temporarily or permanently discontinued. For patients who temporarily discontinue treatment, treatment may resume following resolution of treatment-related adverse events to Grade 1 or baseline with the administration of mocetinostat at a reduced dose level as outlined in Table 11. Once the dose has been reduced, re-escalation is generally not recommended but may be considered on a case-by-case basis. If the administration of mocetinostat is interrupted for reasons other than toxicity, then treatment with the study drug may be resumed at the same dose.

Table 11: Mocetinostat Sequential Dose Reductions for Individual Patients

90 mg three times per week
70 mg three times per week
50 mg three times per week
40 mg three times per week

Dose reduction below 40 mg TIW may be undertaken after discussion with the Sponsor. If treatment with mocetinostat is withheld for ≥ 28 consecutive days, then permanent discontinuation from this study drug should be considered.

5.1.3.4 Mocetinostat Specific Adverse Event Management Guidelines

5.1.3.4.1 Mocetinostat Management of Pericardial Adverse Events

Pericardial AEs will be defined as outlined in Table 12.

Table 12: Definitions of Pericardial Events

Event Term	Definition	Characteristics/Diagnosis
Pericarditis	Inflammation of the pericardium	The major clinical manifestations of acute pericarditis include: 1) chest pain, 2) pericardial friction rub, 3) ECG changes (with new, widespread ST elevation or PR depressions), and 4) pericardial effusion. At least 2 of these features are usually considered necessary to make the diagnosis.
Pericardial effusion	Excess exudate, or fluid, in the pericardium	Once a pericardial effusion is suspected, the diagnostic approach consists of 3 steps: 1) establish the presence of effusion, 2) assess the hemodynamic impact, and 3) establish the cause. Clinical evaluation and ECG findings may suggest the presence of a pericardial effusion, but imaging, usually ECHO, is required to establish a diagnosis.
Hemodynamic Compromise	Mechanical compression of the heart by large amounts of fluid or blood within the pericardial space that limits the normal range of motion and function of the heart	The diagnosis of hemodynamic compromise is based upon clinical and imaging evidence. The following physical findings 1) sinus tachycardia, 2) elevated jugular venous pressure, and 3) pulsus paradoxus are suggestive of frank tamponade. Echocardiogram or other imaging of the pericardium is essential to the diagnosis of hemodynamic compromise.

ECHOs will be used to assess and categorize pericardial fluid as minimal (or trivial), small, moderate or large and will assess for hemodynamic compromise. Pericardial effusions will be assessed and managed as follows (Table 13).

Table 13: Pericardial Effusion and Patient Management Guidelines

Category	Definitions	Patient Management
Minimal (or trivial)	A small echo-free space in the posterior atrioventricular groove that is visible only in systole when the heart has pulled away from the pericardium. Typically represents a normal amount of pericardial fluid in a disease-free state.	De novo (i.e., not present at baseline) pericardial effusion: • Study treatment may be continued at the discretion of the Investigator. • Increased ECHO and ECG monitoring weekly until effusion is no longer present or has not progressed over a period of 2 weeks. • Regular assessment schedule afterwards.
Small	< 1 cm of posterior echo-free space, with or without fluid accumulation elsewhere, present throughout the cardiac cycle, including diastole (and not only systole).	• Study drug will not be discontinued in these Patients, at the discretion of the Investigator, unless the effusion progresses. • Increased ECHO and ECG monitoring weekly for the first month after the new effusion first noted or until the effusion has regressed (if sooner). • Treatment for the effusion may be administered at the discretion of the Investigator.
Moderate	1 to 2 cm of echo-free space. Moderate effusions tend to be seen along the length of the posterior wall but not anteriorly.	• Remove immediately from study treatment. • Manage according to the standard of care at the discretion of the Investigator. • Refer to cardiologist for follow-up as clinically indicated, until resolution of stabilization.
Large	> 2 cm of maximal separation. Large effusions tend to be seen circumferentially.	
Hemodynamic Compromise	RV compression, IVC dilation without respiratory variation, abnormal flow variation across the AV valves without respiratory variation, enlarged or collapsed ventricles. RA diastolic collapse in isolation is too non-specific to signal hemodynamic compromise, but should be considered consistent with this diagnosis when accompanied by other findings	• Remove immediately from study treatment. • Refer to cardiologist for follow up as clinically indicated, until resolution or stabilization. • Collect blood and test for anti-nuclear antibody (ANA) and anti-histone antibody.

In exceptional circumstances where ECHO is not considered a technically optimal assessment of pericardial space (e.g., overweight patient), other methods (e.g., MRI) should be used for pericardial assessments. In such cases, the guidelines provided in Table 13 would not apply, and the evaluation should be performed in consultation with the Sponsor. In the event that a pericardial effusion is first identified by a method other than ECHO, efforts should be made to obtain an ECHO for assessment of effusion size.

5.1.4 Instructions Common to Investigational Study Treatments

5.1.4.1 Clinical Trial Material Specifics and Management Common to the Investigational Study Treatments

Investigational study treatment medication labels comply with the legal requirements of the United States and will be printed in the languages required in the countries in which the study is conducted.

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 chemotherapeutic agents.

Investigational study treatment clinical trial material should be stored in an area that is secure, with limited access and monitored for temperature using a calibrated thermostat.

Study site personnel will dispense investigational study treatment tablets or capsules on Day 1 of each dose cycle for the first 12 cycles on study, and then may reduce the frequency to every 2 cycles, at the discretion of the Investigator. Sufficient supply will be provided for each cycle and extra tablets/capsules may be provided to cover an additional 2 days in case of delayed clinic visits or lost tablets/capsules. Study tablets/capsules will be dispensed in HDPE bottles provided by the Sponsor.

All investigational study treatment supplies will be accounted for in the drug accountability inventory forms supplied by the Sponsor or using locally approved forms that include all required information. The drug accountability inventory forms must identify the study drug, including batch or lot numbers and account for its disposition on a patient-by-patient basis, including specific dates and quantities. The forms must be signed by the individual who dispensed the drug.

Patients will be asked to record their daily dosing on Sponsor provided diary cards and report any missed doses or lost doses at the next clinic visit. On the back of each Sponsor provided diary card, written dosing instructions for the specified investigational study treatment tablets or capsules are provided (e.g., fasting instructions, take with water, etc.). 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 tablet/capsule count. Study site personnel will retain the bottle(s) until a monitor has completed reconciliation and retain dosing diaries with site study files.

At the end of the study, all unused investigational study treatment drug supplies must be destroyed in accordance with local Standard Operating Procedure provided to the Sponsor for the Trial Master File, or returned to the Sponsor or its appointed agent, as directed by the Sponsor.

5.1.4.2 Adverse Event Management Guidelines Common to the Investigational Study Treatments

Guidance on size of dose reduction steps in response to investigational study treatment toxicity are specified for glesatinib, sitravatinib and mocetinostat in Sections 5.1.1.3, 5.1.2.3 and 5.1.3.3, respectively.

Adverse event management guidance specific to investigational study treatments for glesatinib, sitravatinib and mocetinostat in Sections 5.1.1.4, 5.1.2.4 and 5.1.3.4, respectively.

5.1.4.2.1 Investigational Study Treatment Management in Event of Immune-Related Adverse Events

None of the three investigational study treatments has been associated with immune-mediated AEs. However, the potential exists for one or more of the treatments to contribute to immune-mediated AEs associated with nivolumab treatment. In the event of an immune-related AE during study treatment, administration of the investigational study treatment and nivolumab should be interrupted until the event stabilizes to Grade ≤1 (consistent with guidance provided in the OPDIVO US Prescribing Information replicated in Section 5.2.5). At the time of resumption of investigational study treatment dosing, a dose reduction may be implemented at the discretion of the Investigator.

5.1.4.2.2 Diarrhea/Colitis

The management of diarrhea should be guided by clinical judgment and an assessment of the most likely causative etiology, with special consideration given to the potential for immune-mediated colitis. Non-specific, most often mild to moderate diarrhea has been observed with all three investigational study treatments and nivolumab. Diarrhea has been reported in approximately 55% of patients treated with glesatinib, 23% of patients treated with sitravatinib, and 46% of patients treated with mocetinostat, most often beginning within the first month of treatment. Diarrhea (any grade) is less common with nivolumab, occurring in approximately 8% (22/287) of patients treated for NSCLC with 3 mg/kg Q2W in the CheckMate 057 clinical trial (USPI OPDIVO [nivolumab]). Immune-related colitis has been reported in 2.4% (7/287) of patients treated with nivolumab for NSCLC, with median time to onset of 2.7 months (range: 4 weeks to 19 months). The presence of abdominal pain, mucus or blood in the stool or peritoneal signs should raise the index of suspicion for immune-mediated colitis, as these features are generally not observed with glesatinib, sitravatinib or mocetinostat treatment-associated diarrhea. The diarrhea observed with the investigational study treatments generally improves within several days of interrupting study medication and therefore dechallenge, with close observation may help establish the most likely causality. However, if any features of the clinical presentation, including timing of presentation, failure to improve with dechallenge, laboratory or radiologic tests suggests

the presence of immune-mediated colitis, all study medications should be withheld and treatment with immuno-suppressive therapy initiated as detailed in Table 17.

5.1.4.2.3 Increased Transaminases

The management of increases in AST and ALT should be guided by the clinical judgment of the Investigator, including an assessment of the most likely causative etiology, with special consideration given to the potential for immune-mediated hepatitis. Increased transaminases should be evaluated to determine whether confounding factors exist, such as viral infection, metastatic lesions or biliary obstruction. Tyrosine kinase inhibitors in general, and MET inhibitors in particular, have been associated with non-specific, most often mild to moderate elevation in AST and ALT. The observed effects of MET inhibitors likely reflect on-target impact on the ligand, hepatocyte growth factor (HGF). Among patients treated with glesatinib, increases in AST and ALT have been observed in approximately 18% and 12%, respectively. Mild to moderate elevations in liver transaminases have also been observed in less than 10% of patient treated with sitravatinib. The elevations observed with both glesatinib and sitravatinib generally occur within the first cycle of treatment and resolve with interruption of treatment. Nivolumab-related immune-mediated hepatitis was reported in 0.3% (1/287) of patients treated for NSCLC, with an onset of approximately 8 months following initiation of therapy.

For cases where transaminases increases are not likely to be immune-mediated, treatment management decisions should be made using Investigator discretion in consideration of clinical factors. Recommended treatment modifications are provided in Table 14. However, if any features of the clinical presentation, including timing of presentation, failure to improve with dechallenge, laboratory or radiologic tests suggests the presence of immune-mediated hepatitis, all study medications should be withheld and treatment with immuno-suppressive therapy initiated as detailed in Table 17.

Table 14: Investigational Study Treatment Modification for Increased Hepatic Transaminase[1]

Toxicity	Treatment Delay	Dose Modification
Grade 1 (>ULN to 3.0 × ULN)	May be implemented based on Investigator and patient discretion	
Grade 2 (>3.0 to 5.0 × ULN)	Not required	Decrease by 1 dose level
Grade 3/4 (>5.0 × ULN)	Hold until ≤ Grade 1 or return to baseline	Decrease by at least 2 dose levels for a first dose reduction; decrease by at least 1 dose level if dose is already reduced.

1. See Sections 5.2.4 and 5.2.5 for guidelines on treatment modification for nivolumab

5.1.4.2.4 Management of Hy's Law Cases

In the event a patient develops concurrent increase in AST and/or ALT ≥ 3 × ULN, bilirubin ≥ 2 × ULN but without concurrent increases in alkaline phosphatase (i.e., alkaline phosphatase < 2 × ULN), that is not attributable to liver metastases or biliary obstruction, investigational study treatment should be permanently discontinued.

5.1.4.2.5 Management of Investigational Study Treatment in Event of Non-Hematological Toxicities

Per protocol, a complete review of adverse events should be conducted at each clinic visit. Symptomatic Grade 2 sitravatinib-related non-hematological adverse events occurring any time on study, particularly early in treatment (e.g., Cycle 1 Day 15 or Cycle 2 Day 1), are recommended to be managed using dose reduction to the next lower dose level, per the reduction schedule outlined in Table 9, rather than continued dosing until interruption becomes necessary.

Non-hematological toxicities ≥ Grade 3 and considered to be treatment-related should be managed with investigational study treatment interruption 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; if not, treatment may be resumed at a reduced dose (Table 15). Treatment with sitravatinib may continue without dose modification (e.g., interruption or reduction) in cases of asymptomatic amylase and/or lipase increases in the absence of other clinical evidence of pancreatitis (e.g., symptoms, electrolyte abnormalities, radiographic changes) at the investigator's discretion. Recurrence of the toxicity may be managed similarly. If treatment is interrupted for ≥ 28 days, permanent discontinuation from sitravatinib should be considered.

Table 15: Investigational Study Treatment Dose Modifications – Non-Hematological Drug-Related Toxicities[1, 2]

Toxicity	Treatment Delay	Dose Modification
Grade 1	Continue treatment unchanged	
Grade 2 Asymptomatic	May be implemented based on Investigator or patient discretion[2]	
Grade 2 Symptomatic	May be implemented based on Investigator or patient discretion[2] Early dose reduction to the next lower dose level is recommended over treatment interruption	
Grade 3 or 4	Hold until ≤ Grade 1 or return to baseline[2]	Resume at dose one or more levels below that inducing the toxicity. Exceptions presented in footnote.[2,3]

1 Management of selected adverse events for each investigational study treatment are presented in Sections 5.1.1.4, 5.1.2.4 and 5.1.3.4.

2 The current OPDIVO® US Prescribing Information (USPI OPDIVO [nivolumab]) must be consulted to determine appropriate dose modifications for nivolumab.

3 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 manifestations (e.g., electrolyte abnormalities, radiographic changes) of pancreatitis.

5.1.4.2.6 Management of Investigational Study Treatment in Event of Hematological Toxicities

Hematological toxicities are not a frequent cause of treatment interruption or discontinuation with any of the three investigational study treatments. Observed ≥ Grade 3 hematological events that are considered to be causally related to the administered investigational study treatment should be managed using treatment interruption or dose reduction at the discretion of the Investigator. If treatment is interrupted for ≥ 28 days, permanent discontinuation from study treatment should be considered.

5.2 Nivolumab Study Drug

Nivolumab will be obtained from commercial sources and managed in accordance with the OPDIVO US Prescribing Information. The following sections provide reprints of information and guidance included in the OPDIVO US Prescribing Information dated April 2018. Refer to the current OPDIVO US Prescribing Information provided by the manufacturer for updates during the conduct of this clinical trial (https://packageinserts.bms.com/pi/pi_opdivo.pdf).

5.2.1 Formulation and Packaging

OPDIVO is a sterile, preservative-free, non-pyrogenic, clear to opalescent, colorless to pale-yellow liquid that may contain light (few) particles. OPDIVO injection for intravenous infusion is supplied in single-dose vials. Each mL of OPDIVO solution contains nivolumab 10 mg, mannitol (30 mg), pentetic acid (0.008 mg), polysorbate 80 (0.2 mg), sodium chloride (2.92 mg), sodium citrate dihydrate (5.88 mg), and Water for Injection, USP. The formulation may contain hydrochloric acid and/or sodium hydroxide to adjust pH to 6.

5.2.2 Preparation and Dispensing

Visually inspect drug product solution for particulate matter and discoloration prior to administration. OPDIVO is a clear to opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.

- Withdraw the required volume of OPDIVO and transfer into an intravenous container.

- Dilute OPDIVO with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with a final concentration ranging from

1 mg/mL to 10 mg/mL. For patients with weight less than 40 kg, the total volume of infusion must not exceed 4 mL/kg.

- Mix diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials of OPDIVO.

The product does not contain a preservative. After preparation, store the OPDIVO infusion either:

- at room temperature for no more than 4 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or
- under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of infusion preparation.

Do not freeze.

5.2.3 Administration

The recommended dose of OPDIVO is 240 mg every 2 weeks (Q2W) or 480 mg every 4 weeks (Q4W) administered as an intravenous infusion over approximately 30 minutes, until disease progression or unacceptable toxicity. Administer the OPDIVO infusion through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer). Flush the intravenous line at end of infusion.

5.2.4 Infusion Modification and Discontinuation

There are no recommended dose modifications for hypothyroidism or hyperthyroidism.

Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. Discontinue OPDIVO in patients with severe or life-threatening infusion reactions.

Dose modifications recommended in OPDIVO US Prescribing Information dated April 2018 are reprinted in Table 16. Required dose modifications (i.e., interruption or discontinuation) for nivolumab should be performed per the current OPDIVO US Prescribing Information (USPI OPDIVO [nivolumab]) Section 2.10 and Section 5, in addition to potential dose modifications for sitravatinib in accordance to Section 5.1.2.3.

Table 16: Recommended Dose Modifications for OPDIVO – Reprinted from OPDIVO US Prescribing Information

Adverse Reaction	**Severity ***	**Dose Modification**
Colitis	Grade 2 diarrhea or colitis	Withhold dose [a]
	Grade 3 diarrhea or colitis	
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold dose [a]
	Grade 3 or 4 pneumonitis	Permanently discontinue
Hepatitis	Aspartate aminotransferase (AST)/or alanine aminotransferase (ALT) more than 3 and up to 5 times the upper limit of normal or total bilirubin more than 1.5 and up to 3 times the upper limit of normal	Withhold dose [b]
	AST or ALT more than 5 times the upper limit of normal or total bilirubin more than 3 times the upper limit of normal	Permanently discontinue
Hypophysitis	Grade 2 or 3 hypophysitis	Withhold dose [a]
	Grade 4 hypophysitis	Permanently discontinue
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Withhold dose [a]
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue
Type 1 Diabetes Mellitus	Grade 3 hyperglycemia	Withhold dose [a]
	Grade 4 hyperglycemia	Permanently discontinue
Nephritis and Renal Dysfunction	Serum creatinine more than 1.5 and up to 6 times the upper limit of normal	Withhold dose [a]
	Serum creatinine more than 6 times the upper limit of normal	Permanently discontinue
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose [a]
	Grade 4 rash or confirmed SJS or TEN	Permanently discontinue
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Withhold dose [a]
	Immune-mediated encephalitis	Permanently discontinue
Other	Other Grade 3 adverse reaction First occurrence Recurrence of same Grade 3 adverse reactions	 Withhold dose [a] Permanently discontinue
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
	Grade 3 myocarditis	Permanently discontinue
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
	Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer	Permanently discontinue

* Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI CTCAE v4).
a Resume treatment when adverse reaction returns to Grade 0 or 1.
b Resume treatment when AST/ALT returns to baseline.

5.2.5 Nivolumab Adverse Event Management Guidelines

Table 17 reproduces AE management guidelines provided in OPDIVO US Prescribing Information, Section 5.

Table 17: Management of Nivolumab Immune-Related Adverse Events – Reprinted from OPDIVO US Prescribing Information

Immune-mediated AE Defined as Requiring Use of Corticosteroids and no Clear Alternate Etiology	
Immune-mediated pneumonitis	Monitor patients for signs with radiographic imaging and symptoms of pneumonitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for moderate (Grade 2) or more severe pneumonitis, followed by corticosteroid taper. Permanently discontinue nivolumab for severe (Grade 3) or life-threatening (Grade 4) pneumonitis and withhold nivolumab until resolution for moderate (Grade 2) pneumonitis.
Immune-mediated colitis	Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) colitis. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) colitis of more than 5 days duration; if worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day prednisone equivalents. Withhold OPDIVO for moderate or severe (Grade 2 or 3) colitis. Permanently discontinue OPDIVO for life-threatening (Grade 4) or for recurrent colitis upon restarting OPDIVO.
Immune-mediated hepatitis	Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for severe (Grade 3) or life-threatening (Grade 4) transaminase elevations, with or without concomitant elevation in total bilirubin. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents for moderate (Grade 2) transaminase elevations. Withhold OPDIVO for moderate (Grade 2) and permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) immune-mediated hepatitis.
Immune-mediated endocrinopathies	
Hypophysitis	Administer hormone replacement as clinically indicated and corticosteroids at a dose of 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) or greater hypophysitis. Withhold OPDIVO for moderate (Grade 2) or severe (Grade 3). Permanently discontinue OPDIVO for life-threatening (Grade 4) hypophysitis.

Table 17: Management of Nivolumab Immune-Related Adverse Events – Reprinted from OPDIVO US Prescribing Information (Continued)

Immune-mediated endocrinopathies (continued)	
Adrenal Insufficiency	Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by a corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. Withhold OPDIVO for moderate (Grade 2) and permanently discontinue OPDIVO for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency.
Hypothyroidism and Hyperthyroidism	Administer hormone-replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism. There are no recommended dose adjustments of OPDIVO for hypothyroidism or hyperthyroidism.
Type 1 Diabetes Mellitus	Withhold OPDIVO in cases of severe (Grade 3) hyperglycemia until metabolic control is achieved. Permanently discontinue OPDIVO for life-threatening (Grade 4) hyperglycemia.
Other Immune-mediated AEs	
Immune-Mediated Nephritis and Renal Dysfunction	Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for life-threatening (Grade 4) increased serum creatinine. Administer corticosteroids at a dose of 0.5 to 1 mg/lg/day prednisone equivalents for moderate (Grade 2) or severe (Grade 3) increased serum creatinine, if worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/day prednisone equivalents.
Immune-Mediated Skin Adverse Reactions	For symptoms or signs of SJS or TEN, withhold OPDIVO and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue OPDIVO. For immune-mediated rash, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by a corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) rash. Withhold OPDIVO for severe (Grade 3) rash and permanently discontinue OPDIVO for life-threatening (Grade 4) rash.
Immune-Mediated Encephalitis	Withhold OPDIVO in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out infectious or other causes of moderate to severe neurologic deterioration. If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for patients with immune-mediated encephalitis, followed by corticosteroid taper. Permanently discontinue OPDIVO for immune-mediated encephalitis.
Other Immune Mediated Adverse Reactions	For any suspected immune-mediated adverse reactions, exclude other causes. Based on the severity of the adverse reaction, permanently discontinue or withhold OPDIVO, administer high-dose corticosteroids, and if appropriate, initiate hormone-replacement therapy. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider restarting OPDIVO after completion of corticosteroid taper based on the severity of the event.
Infusion Reactions	Discontinue OPDIVO in patients with severe or life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions.

5.3 Medication Error

Medication errors may involve patient exposure to a wrong study drug, at a wrong dosing frequency, or at a wrong dose level (e.g., a dose that is not planned in the study). Medication errors occurring during the conduct of this study will be documented as AEs (regardless of whether clinical signs or symptoms are observed) and if serious consequences are observed, will be reported on Serious Adverse Event (SAE) forms. In all cases of medication error, the sponsor should be notified immediately.

There is currently no specific treatment in the event of an overdose of glesatinib, sitravatinib, mocetinostat or nivolumab. The Investigator will use clinical judgment to treat any overdose.

5.4 Concomitant Therapies

5.4.1 Concomitant Medication(s)

Concomitant medications must be locally-approved and used at doses and regimens that are considered standard-of-care for the treated indication. Treatment for co-morbidities, disease signs and symptoms and treatment emergent adverse events should be provided as necessary in the judgment of the Investigator. Patients may continue to use any ongoing medications not prohibited by the inclusion/exclusion criteria or treatment plan.

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.

- Glesatinib specific – Patients treated with glesatinib may received prophylactic anti-diarrheal treatment at the discretion of the Investigator. A regimen recommended for primary prophylaxis for diarrhea is loperamide 2-4 mg beginning with the first dose of glesatinib, followed by 2 mg every 6–8 hours. Loperamide use may be subsequently titrated as needed.

Anti-Emetics: Patients may be premedicated for nausea and vomiting. Recommended anti-emetic agents include granisetron 1 mg as premedication, and then granisetron and/or prochlorperazine as needed.

- **Gastric Acid Medications:** Proton pump inhibitors and H_2 antagonists should be avoided during treatment on study but are not exclusionary. Switch from use of proton pump inhibitors or H_2 antagonists to use of antacids is preferred. Use of antacids should be avoided 4 hours before and 2 hours after administration of investigational study treatment.

Medications with QTc Prolonging Activity (Sitravatinib and Mocetinostat only): The risk of QTc prolongation in patients receiving the investigational study treatments has not been characterized. Use of medications known to prolong QTc and pose risk of Torsades de Pointes (examples listed in Appendix 3) is to be avoided.

P-450 Considerations, Mocetinostat Specific:

- **Warfarin or Coumarin Derivatives** – Therapeutic doses of warfarin or other coumarin derivative anticoagulants are not permitted in patients treated with mocetinostat. Warfarin has a narrow therapeutic range and mocetinostat can have inhibitory effects on CYP2C9, the main metabolizing enzyme of warfarin. Patients may adopt a different anticoagulant.

- **Contraceptives –** Hormonal contraceptives may be affected by cytochrome P-450 interactions, and are therefore not considered effective for this study, since induction of CYP3A4 may not be excluded in patients receiving mocetinostat.

- **Cautioned Medications –** Caution should be used when mocetinostat is administered to patients taking medications metabolized by CYP2C9, or that inhibit or induce metabolism by CYP2E1 or CYA3A4. See Appendix 3 for examples of medications of interest. If a patient is taking a drug on one these lists, it is encouraged to substitute a different medication if possible.

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

Transfusions: Patients may receive transfusions as necessary.

Antibiotics: Antibiotics should be used as needed. Patients with neutropenic fever or infection should be treated promptly.

Supportive Care/Palliative Care: Supportive and palliative care for disease related symptoms may be administered at the Investigator's discretion, including the use of analgesics.

Growth Factors: Therapeutic colony-stimulating factors should be used in accordance with ASCO guidelines.

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 immune-mediated AEs and the extent required to manage comorbidities and symptoms of disease.

Vaccines: Live attenuated vaccines within 100 days of nivolumab dosing are to be avoided. Inactivated vaccines, such as the injectable influenza vaccine, are permitted.

5.4.2 Concomitant Surgery or Radiation Therapy

The use of surgery to manage cancer lesions during study treatment is discouraged. The impact of the investigation study treatments on wound healing has not yet been characterized. For patients with bone involvement, 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 micro-fractures or painful lesions). However, these treatments may be used in cases where it is medically necessary.

In the event that major surgery is needed during study treatment, the patient should, if possible, interrupt dosing with the assigned investigational study treatment for the duration specified in Table 18.

Table 18: Treatment Interruption for Major Surgery

Drug	Discontinue in Advance	Resume Following
Glesatinib Tablets	1 week	1 week
Sitravatinib Capsules	2 weeks	2 weeks
Mocetinostat Capsules	1 week	1 week

5.4.3 Other Anticancer or Experimental Therapy

Use of approved or investigational anticancer treatment will not be permitted during the study treatment period, including chemotherapy, biological response modifiers, hormone therapies* or immunotherapy. No other investigational drug may be used during treatment on this protocol. Concurrent participation in another therapeutic clinical trial 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's Medical Monitor.

6 STUDY ASSESSMENTS

6.1 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 did not enroll on the study will be considered as screen failures. Limited information will be recorded in the CRF for these patients.

6.2 Study Period

For details on procedures during the study period, see Schedule of Assessments as shown in Table 1.

6.3 End of Treatment Assessment

All patients will be followed for AEs for at least 28 days after the last dose of Study Treatment. See the Schedule of Assessments (Table 1) for evaluations to be performed at the End of Treatment visit.

6.4 Long-Term Follow-up and End of Study Assessment

Survival status and subsequent therapies will be collected during long term follow-up as outlined in the Schedule of Assessments (Table 1) until death or lost to follow-up. Beyond 28 days after last treatment, follow-up may be performed by telephone contact. Treatments received following participation in the study will be collected in the CRF.

6.5 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 Investigator or Sponsor 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 Investigator);
- Global deterioration of health status requiring discontinuation;
- Adverse event;
- Significant protocol violation;
- Lost to follow-up;
- Refusal for further treatment;
- Study termination by Sponsor;
- Death.

Reasons for discontinuation from study follow-up may include:

- Study terminated by Sponsor;
- 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 adverse events.

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 may retain and continue to use any data collected before such refusal for further follow-up.

7 PROCEDURES

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that there may be circumstances outside of the control of the Investigator that may make it infeasible to perform a protocol-specified assessment. In these cases, the Investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol required test cannot be performed, the Investigator will document in the source document and CRF the reason and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1 Efficacy

All patients enrolled in the study are to be evaluated for disease activity as outlined in the Schedule of Assessments (Table 1). Screening/baseline tumor assessments should include CT or MRI of the chest, abdomen, and pelvis, whole body bone scan, MRI of the brain and evaluation of any superficial lesions. On-study assessments will include all known and suspected sites of disease and will be performed at 8-week intervals until approximately 1-year and then every 16 weeks; bone scans may be performed half as often as other radiology evaluations (i.e., every 16 weeks). The allowable windows for assessments are 4 weeks prior to first study treatment for screening/baseline assessments and ±10 days for on-study disease assessments. All known and suspected sites of disease

should be evaluated at each assessment. Assessments will be performed until objective disease progression is documented or subsequent anti-cancer therapy is begun.

CT scans should be performed with contrast agents unless contraindicated for medical reasons. If intravenous contrast is medically contraindicated, the imaging modality to be used (either CT without contrast or MRI) should be the modality which best evaluates the disease, and the choice should be determined by the Investigator in conjunction with the local radiologist. Depending on the adequacy for evaluation of disease, a combination of CT without contrast and MRI should most often be used. CT without contrast is preferred for evaluation of lesions in lung parenchyma. MRI is not adequate for evaluation of lung parenchyma but should also be performed to evaluate all other aspects of the chest. MRI of the abdomen and pelvis should substitute for CT with contrast unless the method does not adequately depict the individual's disease, in which case CT without contrast is preferred.

For patients having effusions or ascites, cytological proof of malignancy should be obtained prior to selection of the effusion as a non-target lesion. Effusions that have not been evaluated using cytology or were found to be non-malignant should not be considered to be cancer lesions.

Disease response will be assessed in accordance with RECIST 1.1 (Eisenhauer-2009). Appendix 4 provides guidance in using the response criteria and includes modifications to RECIST 1.1 to address potential temporary treatment effects such as tumor lesion cavitation or flare response. Assessments will be performed until objective disease progression is documented by the Investigator, or subsequent anti-cancer therapy is begun.

Patients experiencing tumor response (Partial Response [PR] or Complete Response [CR]) should undergo confirmatory assessment at least 4 weeks after initial documentation of response. It is acceptable to perform confirmatory assessments at the next appointed evaluation per protocol. Bone scan is required as an element of the confirmation of PR or CR if bone lesions were identified at the baseline assessment.

The Investigator's assessment of disease response and progression will be the basis for patient management and study expansion decision making. Potential exists for individual tumor lesions to cavitate or become otherwise difficult to evaluate for a period of time as the result of beneficial study treatment impact. For example, tumor necrosis and cavitation may result in minor increase in overall individual lesion size or unclear tumor margins prior to recovery to a smaller lesion, development of scar tissue, or complete resolution. For this reason, Investigators may delay reaching the conclusion of disease progression until subsequent on-study disease assessments are performed.

Central radiology review to assess RECIST outcome may be undertaken after Stage 1 of the study. Materials to be forwarded for independent review will be all imaging studies performed at screening and on study, preferably in digital format, using an electronic

transfer through a portal to the review vendor or transfer on compact disc or optical disc. All digital media must be in DICOM format. Films may be forwarded for review if necessary; all films should be originals (second original films acceptable) rather than copies of films.

7.2 Safety Assessments

7.2.1 Adverse Events

Assessment of adverse events will include type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE, Version 4.03]), timing, seriousness, and relatedness to study treatment.

Signs and symptoms of the patient's cancer diagnosis and/or comorbidities present at baseline will be recorded in the CRF as AEs beginning on Day 1 of study treatment and onward throughout the study. 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.

7.2.2 Physical Examination and Vital Signs

A physical examination including all major body systems is mandated at Screening and End of Treatment Visits only. During study treatment, symptom directed physical examinations will be performed.

Vital signs to be assessed include weight, body temperature, blood pressure, and pulse rate. Height will be recorded at screening only. On days were both vital signs and PK sampling are scheduled, the vital signs should be assessed prior to blood sampling.

Clinically significant findings noted during screening will be reflected on the medical history CRF, while those noted during study treatment will be collected on the AE CRFs.

7.2.3 Laboratory Safety Assessments

Laboratory safety assessments for which data will be collected in this study will include hematology, coagulation, thyroid tests, urinalysis and chemistry parameters presented in Table 19.

Laboratory tests will be drawn at the time points described in the Schedule of Assessments (Table 1) and analyzed at local laboratories. Additional laboratory tests may be performed per standard of care, at the Investigator's discretion for the purpose of planning treatment administration, dose modification, following adverse events, or as clinically indicated.

Table 19: Laboratory Safety Parameters

Hematology Panel	**Blood Chemistry Panel**
Hemoglobin	Aspartate aminotransferase (AST)
Platelet count	Alanine aminotransferase (ALT)
White blood cell count (WBC)	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	Lipase
	Amylase
Coagulation	Sodium
International normalized ratio (INR)	Potassium
Partial thromboplastin time (PTT)	Chloride
	Bicarbonate [CO^2]
Urinalysis (dip stick)	Blood urea nitrogen (BUN)
Blood	Creatinine
Protein	Glucose (non-fasted)
	Albumin
Thyroid Function Test	Total Calcium
Thyroid-stimulating hormone (TSH)	Magnesium
Free-T4	Uric acid

Pregnancy Testing: For patients of childbearing potential, a serum or urine pregnancy test will be performed by the local laboratory at screening. Pregnancy tests will also be done whenever pregnancy is suspected during the study. Additional pregnancy testing may be necessary if required by local practices or regulations.

7.2.4 Electrocardiogram (ECG)

Single and triplicate ECGs are to be performed as outlined in the Schedule of Assessments (Table 1). It is preferable that the machine used has a capacity to calculate the standard intervals automatically. Assessments reported by automated read as prolongation of QTc should be over-read by a cardiologist to ensure accuracy of interpretation.

7.2.5 Echocardiogram (ECHO)

Echocardiograms will be performed in the sitravatinib and mocetinostat treatment arms at screening, and thereafter as in the Schedule of Assessments (Table 1). Additional

assessments of LVEF and evaluation of pericardial effusions may be performed as clinically indicated at the Investigator's discretion if there are signs or symptoms of cardiotoxicity. Where abnormalities indicating pericardial effusion exist, weekly assessments should be performed until normalization as described in Section 5.1.3.4.1. In exceptional circumstances where ECHO is not considered a technically optimal assessment of pericardial space (e.g., overweight patient), other methods (e.g., MRI) should be used for pericardial assessments.

7.3 Laboratory Studies

Full details on sample collection, processing, storage and shipment are presented in the Study Laboratory Manual.

7.3.1 Pharmacokinetic Evaluation

The PK of the investigational study treatments will be determined using blood samples collected at specified time points prior to and following study treatment dosing. Every effort will be made to collect these PK samples at the exact nominal times relative to dosing. A variation window is allowed for each time point as outlined in Table 2, Table 3, and Table 4. The actual time of each sample collection will be recorded on the source document and CRF.

All plasma or serum samples will be stored frozen and shipped on dry ice according to instructions provided. Analysis of samples will be performed using specific validated bioanalytical methods. Full details on sample collection, processing, storage and shipment will be provided in the Study Laboratory Manual.

7.3.2 Pharmacodynamic Evaluation in Tumor Tissue

[redacted]

7.3.3 Pharmacodynamic Evaluation in Blood

[redacted].

7.3.4 Circulating Tumor DNA

[redacted]

7.3.5 Sample Collection for PD-L1 Expression and Tumor Gene Alterations

Tumor tissue testing for PD-L1 expression is required for patients enrolling in the CIT-naïve patient cohort through the central laboratory. The sample tested must have been collected following completion of the most recent systemic treatment regimen.

For CIT-experienced patients, tumor tissue collection for testing for PD-L1 expression and/or evaluation of tumor gene alterations is an optional but highly desirable assessment. Archival samples are acceptable if more recent tumor specimens are not available.

Samples should be collected via a core needle of 18 gauge or larger or be collected by an incisional or excisional tumor biopsy. Where institutional practice uses a smaller gauge needle, samples should be evaluated for tumor cell quantity (i.e., > 100 tumor cells) to allow for adequate PD-L1 immunohistochemistry analyses.

Samples should be formalin fixed and embedded in paraffin. Samples from fine needle aspirates (FNA) or decalcified bone are not appropriate for these evaluations.

Further guidance on sample preparation and submission can be found in the Study Laboratory Manual.

7.4 Post-treatment Follow-up

Survival status and subsequent therapies will be collected during long term follow-up as outlined in the Schedule of Assessments (Table 1) until death or lost to follow-up. Beyond 28 days after last treatment, follow-up may be performed by telephone contact. Treatments received following participation in the study will be collected in the CRF.

8 ADVERSE EVENT REPORTING

8.1 Sponsor Medical Monitor Personnel

The contact information for the sponsor's Medical Monitor personnel for this trial is available in the study contact list located in the Study Manual.

8.2 Adverse Events

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. A treatment emergent AE (TEAE) is an AE that occurs after the first dose of any study treatment or any preexisting condition that increases in severity after the first dose of study treatment.

All observed or volunteered AEs will be recorded in source documents and reported in the CRF. 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 AE when available; follow all recorded AEs to resolution. Examples of AEs include but are not limited to:

- Signs or symptoms of co-morbidity, illness, or toxicity of study treatment;
- Signs or symptoms of worsening malignancy under study (disease progression assessed by measurement of malignant lesions should not be reported as an AE).
- Laboratory abnormalities (see Section 8.2.1 for guidance for reporting in CRF);
- Hypersensitivity;
- Drug abuse, dependency, overdose, withdrawal or misuse;
- Signs or symptoms of drug interactions;
- Extravasation;
- Exposure during pregnancy or via breastfeeding;
- Medication error; or
- Occupational exposure.

8.2.1 Laboratory Abnormalities

An abnormal laboratory test result should be reported as an AE in the CRF only if it is associated with one or more of the following:

- Clinical symptoms;
- Requires additional tests (beyond repeats), treatment or intervention;
- Results in change in study treatment dosing;
- Requires discontinuation from study treatment; and/or
- Considered by the Investigator or Sponsor to be an AE.

Hy's Law

Hepatic function abnormality defined by an increase in AST and/or ALT to ≥ 3 × ULN concurrent with an increase in total bilirubin to ≥ 2 × ULN but without increase in alkaline phosphatase (i.e., alkaline phosphatase < 2 × ULN) meets the criteria for Hy's Law and raises the concern for drug-induced liver injury when no other cause of the abnormal laboratory results are identified. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (e.g., cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product.

Cases meeting Hy's Law should be reported as SAEs. Study drug should be permanently discontinued for a Hy's Law case.

8.2.2 Severity Assessment

AEs occurring during this study will be graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03). Documentation of AE grading in the source documents and CRF should be consistent with provided definitions.

8.2.3 Causality

For each AE, the Investigator should determine and document whether there exists a reasonable possibility that the study treatment caused or contributed to the AE. The Investigator's assessment should be recorded in the source document. The CRF will provide the options for attribution to study treatment as "related" and "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.

Collection of causal relationship for AEs associated with study procedures (e.g., tumor biopsy) is provided for separately in the CRF.

8.3 Serious Adverse Events

8.3.1 Definition of a Serious Adverse Events

An 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

Progression of the malignancy under study, including any signs or symptoms of progression that may require hospitalization, should not be reported as an SAE unless the outcome is fatal within the safety reporting period.

Definition of Terms

Life threatening: An AE is life threatening if the patient was at immediate risk of death from the event as it occurred; i.e., it does not include a reaction that if it had occurred in a more serious form might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

Hospitalization: In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious. Hospitalization for elective surgery or routine clinical procedures that are not the result of AE (e.g., elective surgery for a preexisting condition that has not worsened) need not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'non-serious' according to the usual criteria.

Disability/permanent damage: An AE is disabling or caused permanent damage if it resulted in a substantial disruption of a person's ability to conduct normal life functions, e.g., a significant, persistent or permanent change, impairment, damage or disruption in body function/structure, physical activities and/or quality of life.

Adverse Event of Special Interest (AESI): AESIs are of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring and rapid communication by the Investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

Immune-related Adverse Events (irAE): An irAE is defined as an adverse event that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

8.3.2 Exposure During Pregnancy

Exposure during pregnancy (i.e., exposure in-utero [EIU]) may occur in a female study participant, the female partner of a male study participant or study site personnel working with the investigational product (e.g., occupational exposure) 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 prior to or around the time of conception or during the pregnancy of his partner.

If exposure in-utero occurs, the Investigator must submit an SAE form and an EIU Supplemental Form within 24 hours of awareness of the exposure, regardless of whether an AE or SAE has occurred.

In the event of pregnancy in a female study participant, if the pregnancy is continued, study treatment will be immediately discontinued.

In the event of exposure of the pregnant partner of a male study participant, the study participant should be asked to deliver an EIU Pregnant Partner Release of Information Form to his partner. The Investigator must document on the EIU Form that the patient was given this letter to provide to his partner.

Follow-up to obtain pregnancy outcome information is to be conducted for all EIU reports. In the case of a live birth, the health of the neonate should be assessed at the time of birth and for up to 3 months after birth. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays). In the event the pregnancy is terminated, the reason(s) for termination should be reported and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection.

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 the Sponsor.

8.4 Reporting of SAEs and AEs

8.4.1 Reporting Period

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 28 days post last administration of either therapy. All SAEs will be followed until the event has resolved or stabilized to a chronic condition, whichever is later. Death must be reported if it occurs during the active reporting period for SAEs regardless of whether a subsequent anticancer therapy is administered. Serious adverse events occurring to a patient after the active reporting period has ended should be reported to the Sponsor if the Investigator becomes aware of them and if the Investigator assesses at least a reasonable possibility of being related to study drug.

The reporting period for non-serious AEs begins from the day of first dose of study treatment and continues until at least 28 days after last administration of study treatment and/or until recovery from all acute toxicities associated with the drug administration to a chronic condition, whichever is later. If a patient begins a subsequent anticancer therapy, the AE reporting period ends at the time the new treatment is started.

8.4.2 Reporting Requirements

All SAEs must be reported within 24 hours of Investigator/site knowledge of the event, irrespective of the extent of available AE information, by faxing the SAE report to the Sponsor's pharmacovigilance representative designated in the Study Manual. The 24-hour timeframe also applies to additional new information (follow-up) on previously

forwarded SAE reports and to the initial and follow-up reporting of exposure during pregnancy and exposure via breastfeeding. The need for an expedited report to regulatory authorities will be determined by the Sponsor and necessary reporting will be performed by the Sponsor. The Sponsor will notify study Investigators of all Suspected, Unexpected (as judged against the Investigator Brochure) Serious Adverse Reaction (SUSAR) reports. The Investigator is responsible for reporting all SUSARs to the IRB/EC.

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.

9 STATISTICS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be maintained by the Sponsor. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1 Hypothesis and Sample Size

9.1.1 Lead-In Dose Escalation Evaluation

Approximately 24 patients may be enrolled into the lead-in dose escalation portion of the study. A precise sample size cannot be defined, as it is dependent on the number of dose escalations based on the mTPI method, and the number of patients enrolled in the expansion cohorts.

The mTPI method (Ji-2013) will be employed in decision making concerning dose escalation within each regimen investigated. The assumptions to be applied in establishing the mTPI methodology are:

- each specific regimen exploration will include up to 30 patients;
- the MTD is defined to have 0.25 probability of toxicity; and
- the acceptable variance around the MTD is ± 0.05 (i.e., the region of the MTD is 20% to 30% incidence of dose limiting toxicity).

9.1.2 Phase 2

This Phase 2 study will use a Predictive Probability Design (Lee-2008) in each treatment arm and strata. In creating the statistical designs, the Type 1 error (α) is constrained to <0.05 and Power ($1-\beta$) is constrained to $\geq$0.90.

Statistical Design Applied to CIT-Experienced and CIT-Naïve with No/Low PD-L1 Expression

The ORR using nivolumab in the population with advanced non-squamous NSCLC having prior disease progression on a checkpoint inhibitor or patients with non-squamous NSCLC without prior checkpoint inhibitor therapy with no/low PD-L1 expression is assumed to be 5% (p_0); thus this rate is considered uninteresting. The target ORR using the investigational agents in combination with nivolumab in this study is 30% (p_1). Stage 1 of enrollment will include a minimum of 9 evaluable patients in each treatment strata. With exactly 9 evaluable patients at Stage 1, if at least 1 patient has an Objective Response, 8 additional evaluable patients will be enrolled in the treatment stratum, for a total sample size of 17 evaluable patients. If at least 3 Objective Responses are observed in a treatment stratum, further investigation may be warranted. If the true ORR is 5% (null hypothesis), the probability of early termination during the study is 0.63; the Type 1 error is equal to 0.0466 and the power is equal to 0.9045.

Statistical Design Applied to CIT-Naïve with High PD-L1 Expression

The ORR using nivolumab in the population with non-squamous NSCLC having high PD-L1 expression is assumed to be 27% (p_0); thus this rate is considered uninteresting. The target ORR using the investigational agents in combination with nivolumab is 50% (p_1).

Stage 1 of enrollment will include approximately 17 evaluable patients. With exactly 17 evaluable patients at Stage 1, if at least 5 patients have Objective Responses, 27 additional evaluable patients will be enrolled, for a total sample size of 44 evaluable patients. If at least 18 Objective Responses are observed, further investigation may be warranted. If the true ORR is 27% (null hypothesis), the probability of early termination during the study is 0.50; the Type 1 error is equal to 0.0303 and the power is equal to 0.9018. The exact stopping rules for all cohorts will be calculated based on the Predictive Probability Design, once the exact number of patients evaluable at Stage 1 is known. The aim is to get a minimum of 9 evaluable patients at Stage 1 for CIT-experienced and CIT-naïve with lo/no PD-L1 expression cohorts and a minimum of 17 evaluable patients at Stage 1 for CIT-naïve with high PD-L1 expression cohort.

Expansion Beyond Stage 2

For the sitravatinib segment of the study enrolling patients with CIT-experience, expansion of enrollment beyond Stage 2 will be managed as one cohort that includes all patients, regardless of prior clinical benefit during treatment with CIT. Based on preliminary clinical activity results as of June 2018 (described in Section 1.5.3.2.2), enrollment into the combined cohort will expand to approximately 125 patients total. The purpose for enrollment expansion is to further evaluate safety and efficacy in this setting.

Expansion of sitravatinib CIT-naïve cohorts beyond Stage 2 of enrollment is not anticipated.

Table 20 presents estimates of the 95% CI around the observed ORR for several potential outcomes using the sample size of 125 patients, and the Clopper-Pearson method.

Table 20: Estimates of 95% CI Using Clopper-Pearson After Enrollment of 125 Patients

Number of Observed Responses Among 125 Patients	ORR	95% CI
19	15%	9.4-22.7
25	20%	13.4-28.1
31	25%	17.5-33.3
38	30%	22.5-39.3
44	35%	26.9-44.3
50	40%	31.3-49.1
63	50%	41.3-59.5

9.2 Data Handling

Listings of all patient data will be prepared. Data summaries will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. Further details of planned analyses will be described in the SAP.

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 with specific rules defined in the SAP.

9.3 Analysis Populations

9.3.1 Modified Intent-to-Treat Population

The Modified Intent-to-Treat (mITT) population is defined as all patients who receive treatment with both an investigational study treatment and nivolumab on this study.

The primary efficacy analyses of the primary and secondary efficacy endpoints will be performed in the mITT population. In addition, the mITT population will be used in making decisions to expand the study to the next stage of enrollment.

9.3.2 Clinical Activity Evaluable Population

In order to be considered eligible for the clinical activity evaluable population, the patient must have at least one on-study disease assessment or discontinue from treatment for progressive disease. Patients who discontinue treatment prior to the first on-study disease assessment for an AE, toxicity, or withdraw consent are considered non-evaluable for disease assessment and will not be part of the clinical activity evaluable population.

This population will be used to present tumor responses as well as to make decision on the Predictive Probability design.

9.3.3 Safety Population

The Safety population is defined as all patients who received at least 1 dose of either investigational study treatment or nivolumab. The Safety population will be used for all safety analyses.

9.3.4 Molecular Marker Evaluable Population

The molecular marker evaluable population will consist of all patients who receive at least one dose of either investigational study treatment or nivolumab for whom PD-L1 expression or circulating PD-L1 results are available.

9.3.5 Pharmacokinetic Evaluable Population

The Pharmacokinetic evaluable population will consist of all patients who received treatment with an investigational study drug and had sufficient concentration-time data to permit calculation of PK parameters for the investigational agent. For patients who were noncompliant with respect to administration of investigational agent, or for patients with incomplete data, a decision as to their inclusion in the analysis will be made on a case-by-case basis.

9.3.6 Pharmacodynamic Evaluable Population

The Pharmacodynamic evaluable population will consist of all patients who receive at least one dose of investigational agent or nivolumab for whom PD results are available.

9.4 Efficacy Endpoint Definitions and Analyses

9.4.1 Objective Response Rate

Objective disease response will be categorized in accordance with RECIST v1.1 (Appendix 4). Objective Response Rate (ORR) is defined as the percent of patients documented to have a confirmed Complete Response (CR) or Partial Response (PR). If central review of disease response is undertaken, ORR as reported by the central radiology review laboratory will be used to calculate ORR and the exact 95% confidence intervals (CI). ORR as reported by the Investigator will be used in study expansion decision making (PPD design) and supportive analyses.

Descriptive statistics (frequency and percentage) for ORR, CR, and PR will be presented. The exact 95% CI of these response rates will be calculated. An exact test for single proportion (two-sided α=5%) will be performed to test H_0: ORR $\leq$ 5% against H_1: ORR > 5%. Other details will be described in the SAP.

9.4.2 Clinical Benefit Rate

Clinical Benefit Rate (CBR) is defined as the percent of patients documented to have a confirmed Complete Response (CR), Partial Response (PR), or Stable Disease (SD) documented during at least 2 on-study assessments and including at least 14 weeks on study (e.g., allowance for 2-week window around Week 17 assessment).

9.4.3 Duration of Response

Duration of Response (DR) is defined as the time from date of the first documentation of objective tumor response (CR or PR) to the first documentation of Objective Progression of Disease (PD) or to death due to any cause in the absence of documented PD. Censoring for the DR endpoint will be assigned on the date of the last tumor assessment if no assessment of tumor progression is identified and the patient does not die while on study. DR will only be calculated for the subgroup of patients with an objective response. The Kaplan-Meier method will be used to obtain the estimate of median DR.

9.4.4 Progression Free Survival

Progression-free survival (PFS) is defined as the time from date of first study treatment to first PD or death due to any cause in the absence of documented PD. Censoring for the PFS endpoint will be assigned on the date of the last tumor assessment if no assessment of tumor progression is identified and the patient does not die while on study. For patients in whom two or more sequential assessments are missed, followed by the finding of tumor progression, the PFS endpoint will be censored on the date of the last tumor assessment before the gap. Patients lacking an evaluation of disease after first study treatment will have their PFS time censored on the date of first dose with duration of 1 day. Patients who start a new anti-cancer therapy prior to documented PD will have the endpoint censored at the date of the last tumor assessment prior to the start of the new

therapy. The Kaplan-Meier method will be used to obtain the estimate of median progression-free survival time.

9.4.5 Overall Survival

Time to death is defined as the time from date of first study treatment to death due to any cause. Censoring for the survival endpoint will be assigned on the date of the last on-study follow-up that the patient is reported to be alive. The Kaplan-Meier method will be used to estimate the median OS and 1-year Survival Rate; the 95% confidence interval of the 1-year survival rate will also be reported.

9.5 Safety Data Presentations and Summaries

9.5.1 Adverse Events

Adverse events will be classified using the medical dictionary for regulatory activities (MedDRA) classification system. Listings will include the verbatim term, preferred term, and system organ class (SOC). The number of patients with treatment emergent AEs and the incidence of TEAEs by SOC and preferred term will be summarized. TEAEs will be summarized by maximum intensity and relationship to study therapy. Separate summaries will be provided for TEAEs, TESAEs, treatment-related AEs, treatment-related SAEs, and other significant AEs (e.g., AEs leading to study discontinuation).

9.5.2 Prior and Concomitant Medications

Collected prior and concomitant medications will be coded using the WHO medical dictionary; patients who received these medications will be listed and summarized.

9.5.3 Clinical and Laboratory Assessments

Clinical and laboratory assessments include clinical laboratory tests (hematology, coagulation, urinalysis, thyroid function tests and chemistry), vital signs, ECHO and 12-lead ECGs.

Clinical laboratory results will be listed by patient and, as appropriate, summarized descriptively, which will include a display of change from baseline. Selected parameters will be presented in shift tables of baseline against worst grade test result. Laboratory values outside of the normal ranges will be identified. Laboratory values that meet Grade 3 or 4 criteria according to NCI CTCAE v.4.03 will be listed and summarized.

ECG assessments will be evaluated for change of QTc from baseline as an exposure: response analysis. The Investigator's interpretation of QTc will be used in the clinical management of patients. The study analysis will use Fridericia's formula applied programmatically to the ECG data collected in CRFs.

Vital signs, ECHO and ECG measurements will be listed for each patient at each visit. Descriptive statistics of observed values and changes from baseline will be summarized by treatment group.

9.5.4 Patient Demographics, Baseline Characteristics and Disposition

Presentations of patient characteristics will include a summary of the following for all patients enrolling in the study:

- Demographics
- Baseline disease characteristics
- Pre-existing conditions/concurrent illness
- Prior therapies/surgeries

A summary of patient enrollment and disposition will include reasons for study discontinuation.

9.5.5 Analysis of Study Treatment Dosing

Study treatment administration will be described in terms of the total number of cycles administered, the median (range) of cycles administered for each agent separately and for the combination, dose intensity, and reasons for the deviations from planned therapy.

9.6 Other Study Endpoints

9.6.1 Pharmacokinetic Analysis

The PK sparse exposure data from this study may be used in the development of population PK and PK/PD models for each investigational agent. Pharmacokinetic parameters will be determined, listed, and summarized for the PK evaluable population in the Pharmacokinetic Analysis Plan (PKAP). Only samples with acceptable PK (as defined in the PKAP) will be included in the summary statistics and a listing of individual data points or patients excluded from the analysis will be presented. Plasma concentrations will be listed by patient for the PK Population. Summary statistics of investigational agent concentrations will be reported by dose level, Day and Cycle. The exposure levels as well as the PK parameters of the investigational drugs reported in earlier studies will be compared to the current study PK exposure and parameters to evaluate the potential effect of nivolumab on investigation drugs' PK. Details of this analysis will be provided in the PKAP. Possible relationships between PK parameters, PD variables, safety, and clinical activity may be examined.

9.6.2 Pharmacodynamic and Exploratory Analyses

[redacted]

9.7 Interim Analysis

No interim statistical analysis is planned during this study.

9.8 Data Monitoring Committee

No Data Monitoring Committee is planned during this study.

10 ETHICS AND RESPONSIBILITIES

10.1 Ethical Conduct of the Study

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 Conference on Harmonization [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; the study will be conducted under a protocol reviewed and approved by an IRB/EC; 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 Obligations of Investigators

The Investigator is responsible for complying with the protocol and all applicable regulations and guidelines governing clinical research. Additionally, he/she is responsible for ensuring that all participating staff members are adequately trained and competent to perform his/her assigned tasks.

All Investigators must provide the sponsor with a current *curriculum vitae*. Only Investigators and designated Sub-Investigators are permitted to sign CRFs and examination findings (e.g., laboratory results or ECGs).

The Investigator or designee is responsible for informing the patient of all available information relevant to his/her safety and obtaining signed, written consent from all participating patients. Additionally, the Investigator is responsible for monitoring patient safety and providing periodic and requested reports to the IRB/EC.

The Investigator is responsible for the accuracy and completeness of all study records including CRFs, source documents, and the Site Trial Master File. The Investigator will allow the study monitor, Sponsor, auditor, regulatory agencies, and IRB/EC full access to the study and source documents.

10.3 Institutional Review Board/Ethics Committee/Research Ethics Board (IRB/EC)

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/EC for written approval. The Investigator will provide the Sponsor with a copy of the IRB/EC's written approval, as well as the membership list or a compliance statement from the IRB/EC. The Investigator is responsible for notifying the IRB/EC of any Sponsor-approved amendments to the protocol or ICF, SAEs occurring in patients treated at the study site in accordance with local IRB/EC practice, and all expedited safety reports from SAEs occurring at other study sites participating in the drug development program.

10.4 Informed Consent Form

The ICF must contain all elements required by the Food and Drug Administration (FDA) under 21 Code of Federal Regulations (CFR) Part 50 and the ICH GCP guidelines (ICH E6) in addition to any other elements required by applicable national, state, provincial, and local regulations, or institutional policies.

All patients who choose to participate in the study must provide written consent after having had adequate time to consider whether they will participate in the study. The written consent must be obtained prior to any protocol-related procedures that are not part of the patient's normal medical care. The patient must be advised of his/her right to withdraw from the study at any time.

Written documentation of consent must be recorded in the patient's source documents, study records and CRF indicating the date the consent was signed. The patient should receive a signed copy of the consent form according to GCP guidelines.

10.5 Confidentiality

All information generated in this study is considered confidential, is patient to applicable privacy rules and regulations, and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from the Sponsor

and otherwise except in accordance with applicable law or regulations. However, authorized regulatory officials, IRB/EC personnel, the Sponsor and its authorized representatives (as and to the extent authorized in the patient's ICF) are allowed access to the records.

Identification of patients in CRFs shall be by study assigned patient numbers only. If required, the patient's full name may be made known to an authorized regulatory agency or other authorized official.

10.6 Reporting of Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction (i.e., clinical hold) imposed by an applicable Regulatory Authority, or if the Investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, the Sponsor must be informed immediately. In addition, the Investigator will inform the Sponsor immediately of any serious breaches of this protocol or of ICH GCP of which the Investigator becomes aware.

11 RECORDS MANAGEMENT

11.1 Source Documentation

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.

11.2 Study Files and Records Retention

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 Principal Investigator has responsibility for ensuring the authenticity, accuracy, completeness and timeliness of all data collected in the CRF. CRFs must be signed by the Principal Investigator or by an authorized Sub-Investigator to attest that the information included is true.

The study site will maintain a Site Trial Master File in accordance with GCPs.

The Investigator shall retain all records for the longest of the following periods: (i) 15 years; (ii) the period of time that conforms to ICH GCP guidelines; (iii) the period of time required by applicable law or regulations, or (iv) the period of time specified in the Clinical Research Agreement.

12 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Monitoring Procedures

Sponsor appointed Site Monitor(s) must be allowed access to all study records, original source documents, and investigational products throughout the duration of the study. These personnel are responsible to assess compliance with the protocol, appropriate health authority regulations, ICH GCP guidelines, and Sponsor requirements.

The study monitor is responsible for complying with the monitoring guidelines established by the Sponsor for the study, assessing the site's needs, and liaising with the assigned Sponsor staff.

If the Investigator withdraws from the study and relinquishes his/her responsibility for the maintenance and retention of records, he/she must notify the Sponsor in writing so arrangements can be made to properly store the study materials.

12.2 Auditing and Inspection Procedures

The Sponsor's Quality Assurance representatives, IRB/EC reviewers, or inspectors from regulatory agencies may perform an audit or inspection at any time during or after completion of the clinical study. All study-related documentation must be made available to the designated auditor. In addition, representatives of applicable regulatory health authorities may choose to inspect a study. A Sponsor representative will be available to assist in the preparation for such an inspection.

13 CHANGES IN STUDY CONDUCT

13.1 Protocol Amendments

Changes to the study protocol, except those intended to reduce immediate risk to study patients, may be made only by the Sponsor. A protocol change intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRB/EC 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.

Any permanent change to the protocol must be handled as a protocol amendment. The change and the justification will be documented in writing by the Sponsor, as an Administrative Letter or amended protocol. Protocol amendments will be provided with a separate document describing each change and rationale. The written Administrative Letter or amendment must be submitted to the IRB/EC and the Investigator must await approval before implementing the changes. The Sponsor will be responsible for submitting protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the IRB/EC, the Investigator, and/or the Sponsor, the amendment to the protocol substantially changes the study design and/or increases the potential risk to the patient and/or has an impact on the patient's involvement as a study participant, the currently approved written informed consent form will require similar modification. In such cases, informed consents (revised as appropriate to address protocol amendments) will be obtained for patients enrolled in the study before continued participation.

13.2 Protocol Deviations

Prospective permission to deviate from the eligibility criteria for this protocol will not be provided by the Sponsor. Study specified assessments should not be omitted and the study treatment regimen should not deviate from protocol specifications. Minor, occasional adjustments in the clinic visit schedule may be necessary for logistical reasons (e.g., due to weather conditions) but must not become routine or systematically alter the study schedule. The IRB/EC should be informed of any deviations that may affect a patient's treatment or informed consent, especially those increasing potential risks, which must receive prior written approval by the IRB/EC.

14 END OF TRIAL

14.1 End of Trial in a European Union Member State

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient patients have been recruited and completed the study as stated in the regulatory application (i.e., Clinical Trial Application [CTA]) and ethics application in the Member State.

14.2 End of Trial in all other Participating Countries

End of Trial in all other participating countries 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.

14.3 Premature Termination

Premature termination of this study may occur at any time because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety concerns, or at the discretion of the Sponsor. In addition, the Sponsor retains the right to discontinue development of glesatinib, sitravatinib or mocetinostat at any time. If termination becomes necessary, the Sponsor will inform the appropriate regulatory authorities of the termination and the reason. The Principal Investigator will inform the IRB/EC of the same. In terminating the study, the Sponsor and the Principal Investigator will assure that adequate consideration is given to the protection of the patients' interests.

15 STUDY REPORT AND PUBLICATION POLICY

The Sponsor is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

The publication of study results will be governed by the applicable Clinical Research Agreement between the Sponsor and the Study Site and Investigator (as applicable).

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Appendix 1. ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
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 house work, office work
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair
5	Dead

Appendix 2. DOSE-FINDING SPREADSHEET OF THE MODIFIED TOXICITY PROBABILITY INTERVAL (MTPI) METHOD

Number of Patients Treated at Current Dose

Number of Dose Limiting Toxicities	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
2		U	D	D	S	S	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
3			U	U	U	D	S	S	S	S	S	S	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E
4				U	U	U	U	U	D	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	E	E	E	E	E
5					U	U	U	U	U	U	D	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
6						U	U	U	U	U	U	U	U	D	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
7							U	U	U	U	U	U	U	U	U	U	S	S	S	S	S	S	S	S	S	S	S	S	S	S
8								U	U	U	U	U	U	U	U	U	U	U	U	S	S	S	S	S	S	S	S	S	S	S
9									U	U	U	U	U	U	U	U	U	U	U	U	U	U	S	S	S	S	S	S	S	S
10										U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	S	S	S	S	S	S
11											U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	S	S	U	U	S
12												U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
13													U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
14														U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
15															U	U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
16																U	U	U	U	U	U	U	U	U	U	U	U	U	U	U
17																	U	U	U	U	U	U	U	U	U	U	U	U	U	U
18																		U	U	U	U	U	U	U	U	U	U	U	U	U
19																			U	U	U	U	U	U	U	U	U	U	U	U
20																				U	U	U	U	U	U	U	U	U	U	U
21																					U	U	U	U	U	U	U	U	U	U
22																						U	U	U	U	U	U	U	U	U
23																							U	U	U	U	U	U	U	U
24																								U	U	U	U	U	U	U
25																									U	U	U	U	U	U
26																										U	U	U	U	U
27																											U	U	U	U
28																												U	U	U
29																													U	U
30																														U

E = Escalate to the next higher dose
S = Stay at the current dose
D = De-escalate to the next lower dose
U = The current dose is unacceptably toxic
MTD = 0.25
Sample Size = 30
$\varepsilon_1 = 0.05$
$\varepsilon_2 = 0.05$

Appendix 3. MEDICATIONS OR SUBSTANCES TO BE AVOIDED OR USED WITH CAUTION DURING STUDY TREATMENT

Bold font indicates medications or substances that might be relatively commonly used.

Italic font indicates medications for indications that are exclusionary for the current study or would likely result in discontinuation from study treatment with mocetinostat and sitravatinib for management of a concurrent illness.

DRUGS THAT MAY PROLONG QT INTERVAL

Drugs To Be Avoided

Drugs with a Known Risk of Torsades de Pointes	Amiodarone, anagrelide, *arsenic trioxide*, astemizole (off US market), **azithromycin**, bepridil (off US market), chloroquine, **chlorpromazine**, cisapride (off US market), **citalopram**, **clarithromycin**, cocaine, disopyramide, dofetilide, domperidone (not on US market), dronedarone, **droperidol**, **erythromycin**, **escitalopram**, flecainide, halofantrine, haloperidol, ibutilide, levomethadyl (off US market), mesoridazine (off US market), **methadone**, moxifloxacin, **ondansetron**, *pentamidine*, pimozide, probucol (off US market), procainamide, quinidine, sevoflurane, sotalol, sparfloxacin (off US market), sulpiride (not on US market), terfenadine (off US market), thioridazine, *vandetanib*.

Drugs To Be Used with Caution

Drugs with a Conditional Risk of Torsades de Pointes	**Amantadine**, amisulpride, amitriptyline, amoxapine, chloral hydrate, **ciprofloxacin**, clomipramine, desipramine, **diphenhydramine**, doxepin, **fluconazole**, **fluoxetine**, **furosemide**, galantamine, **hydrochlorothiazide**, imipramine (melipramine), indapamide, **itraconazole**, ivabradine, **ketoconazole**, metronidazole, *nelfinavir*, nortriptyline, **paroxetine**, posaconazole, protriptyline, quinine sulfate, *ritonavir*, **sertraline**, solifenacin, *telaprevir*, trazodone, **trimethoprim-sulfa**, trimipramine, voriconazole.

CAUTION WHEN TAKING THE FOLLOWING MEDICATIONS AND SUBSTANCES DURING TREATMENT WITH MOCETINOSTAT

Enzyme	
Inhibitor of CYP 2E1	Disulfiram
Inducers of CYP 2E1	**Ethanol**, isoniazid, **tobacco**
Strong Inhibitors of CYP 3A4	*Boceprevir*, **clarithromycin**, *conivaptan*, grapefruit juice, *indinavir*, **itraconazole**, **ketoconazole**, *lopinavir/ritonavir*, *mibefradil (withdrawn from US market)*, nefazodone, *nelfinavir*, **posaconazole**, *ritonavir*, *saquinavir*, *telaprevir*, **telithromycin**, **voriconazole**
Strong Inducers of CYP 3A4	Carbamazepine, phenytoin, rifampin
Substrates of CYP 2C9	Celecoxib, diclofenac, fluvastatin, **glipizide**, **ibuprofen**, **irbesartan**, **losartan**, **naproxen**, phenytoin, piroxicam, **rosiglitazone**, **sulfamethoxazole**, *tamoxifen*, tolbutamide, torsemide

Appendix 4. ABBREVIATED PRESENTATION OF RECIST VERSION 1.1 GUIDELINES

A modification to RECIST 1.1 has been made to account for the possibility of temporary changes resulting from the potentially beneficial treatment responses of tumor necrosis, cavitation or flare response.

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 patiented to other local treatment) are non-measurable unless it 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 treatment. If the baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

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 indeterminate.

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.

- Indeterminate: Progression has not been documented, and

    - 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.

- Indeterminate: Progression has not been determined and 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.

Lesion Changes That May Be Transient

Potential exists for individual tumor lesions to develop necrosis, to cavitate, have a flare response to treatment or become otherwise difficult to evaluate for a period of time as the result of beneficial study treatment impact. For example, tumor necrosis, cavitation or flare may result in increase in overall size of individual lesions or unclear tumor margins prior to recovery to smaller lesions, development of scar tissue, or complete resolution. The true tumor measurements of lesions should be recorded but the conclusion of progressive disease may be suspended until continued assessment clarifies the nature of the tumor change. If repeat assessments indicate progression of disease, then PD should be recorded on the date of the first assessment giving the impression of progression. If repeat assessments indicate that the change was a process of transition, then NE (not evaluable) should be recorded during the period of transition, and PR or CR may be recorded for subsequent evaluations. The CRF will collect information on the observations during the period of transition to support the assessment conclusions.

Supplemental Investigations

If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

Best Objective Response

Target Lesions	Non-Target Lesions	New Lesion	Point in Time Response	Best Response
CR	CR	No	CR	CR and PR require confirmation at least 4 weeks after first observation
CR	Non-CR/Non-PD	No	PR	
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	SD requires an on-study assessment after at least 6weeks on treatment. Unconfirmed PR or CR are reported as SD.
PD	Any	Yes or No	PD	
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	

Patientive Progression

Patients requiring discontinuation of treatment due to worsening health status attributable to advancement of the malignancy under study but without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status.

Appendix 5. SITRAVATINIB SUB-STUDY TO EVALUATE THE PHARMACOKINETICS OF THREE FORMULATIONS

This sub-study within Study MRTX-500 will be conducted at selected study sites. It is an open-label evaluation of sitravatinib PK using three formulations of capsules. The sitravatinib formulations to be studied are free base hard gelatin capsules with 10% polysorbate 80 (Tween® 80), the formulation used in the main study and reference product, and as many as two new malate formulations: malate capsules, and free base softgel capsules. Investigation of alternative formulations is for the purpose of optimizing product characteristics and manufacturing efficiency. This investigation is being performed within the context of Study MRTX-500 to enable evaluation in one of the patient populations of interest for future sitravatinib clinical trials and in patients whose steady-state PK may be evaluated, and long-term sparse PK samples may be collected.

In preparation for this sub-study, a non-clinical PK study was conducted in dogs after administration of single and multiple doses of the three sitravatinib capsule formulations. Groups of 6 dogs (3 male and 3 female) were included in each evaluation. PK sampling was performed on Day 1 and at steady state on Day 7. The PK parameters C_{max}, AUC_{0-24}, and $AUC_{0-\infty}$ (for Day 1 only) were estimated (Table 21). The ratios of the geometric means were used to compare the free base Tween capsule (reference product) to the malate salt capsule and the free base softgel capsule. Preliminary data indicate that the malate salt capsule to reference product ratios were 2.52, 2.19, and 2.15 for C_{max}, AUC_{0-24}, and $AUC_{0-\infty}$, respectively, on Day 1 and, 1.85 and 1.65 for C_{max} and AUC_{0-24}, respectively, on Day 7. The free base softgel capsule to reference product ratios were 2.18, 2.29, and 2.26 for C_{max}, AUC_{0-24}, and $AUC_{0-\infty}$, respectively, on Day 1 and, 1.70 and 1.81 for C_{max} and AUC_{0-24}, respectively, on Day 7. Concentration time profiles for the formulations were comparable, with a median t_{max} of 4, 3 and 4 hrs and a mean half-life of 5.6, 4.9 and 5.1 hrs for the reference product, malate salt capsule and free base softgel capsule, respectively. The new formulations showed lower variability as compared to the reference product, expressed as lower geometric mean CV% values for all the PK parameters.

Table 21: Pharmacokinetic Parameters in Dog Following Oral Administration of Three Sitravatinib Capsule Formulations

Day	Dose (mg) (Formulation)		C_{max} (ng/mL)	AUC_{0-24} (ng·hr/mL)	AUC_{0-inf} (ng·hr/mL)
Day 1	20 Malate Salt Capsule	Geo. Mean	57.61	451.22	470.64
		Geo. CV%	51.4	45.5	44.7
		N	6	6	6
	20 Free Base Softgel Capsule	Geo. Mean	49.91	472.04	495.13
		Geo. CV%	21.3	18.6	21.0
		N	6	6	6
	20 Free Base 10% Tween Capsule	Geo. Mean	22.85	205.82	219.28
		Geo. CV%	110.0	118.7	125.5
		N	6	6	6
	Malate Salt to: Free Base 10% Tween	Ratio[a]	**2.52**	**2.19**	**2.15**
	Free Base Softgel to: Free Base 10% Tween	Ratio[a]	**2.18**	**2.29**	**2.26**
Day 7	20 Malate Salt Capsule	Geo. Mean	73.85	637.62	
		Geo. CV%	44.8	41.2	
		N	6	6	
	20 Free Base Softgel Capsule	Geo. Mean	67.98	698.55	
		Geo. CV%	32.2	32.3	
		N	6	6	
	20 Free Base 10% Tween Capsule	Geo. Mean	39.92	385.99	
		Geo. CV%	115.1	130.2	
		N	6	6	
	Malate Salt to: Free Base 10% Tween	Ratio[a]	**1.85**	**1.65**	
	Free Base Softgel to: Free Base 10% Tween	Ratio[a]	**1.70**	**1.81**	

[a] Ratio calculated based on Geo. Mean.

The exposure levels observed in the dog study were higher for both of the new formulations as compared to the reference product. For this reason, a dose escalation approach will be implemented in this sub-study for the new formulations. The starting dose for each was determined by applying the Day 1 and Day 7 (steady state) exposure ratios to the starting dose using the reference product in the main study (120 mg QD). If

the exposure ratios observed in dogs reflect exposure in patients, administration of 50-70 mg of either new formulation would be expected to result in exposure comparable to the reference product (free base 10% Tween capsule) administered at 120 mg QD. The starting dose for the malate direct blend formulation will be 60 mg QD. This is considered conservative for two reasons, 1) the magnitude of exposure differences between oral formulations observed in dogs is most often attenuated when subsequently studied in humans, and 2) sitravatinib has been administered at 150 mg QD in a clinical trial (Study 516-001) and was tolerated. As described below, each new formulation may also be evaluated at a higher dose level.

As described in Section 1.8.1 of this protocol, sitravatinib administered in combination with nivolumab is unlikely to result in a clinically relevant drug-drug interaction based on absorption, metabolism, elimination or protein binding. Nivolumab is a mAb and is intravenously administered, whereas sitravatinib is a small molecule therapeutic administered orally; no absorption interactions are expected. No studies on the metabolism of nivolumab have been reported in vitro or in humans. Like most therapeutic proteins, nivolumab is not expected to be metabolized by liver cytochrome P-450 (CYP) or other drug metabolizing enzymes and is unlikely to have an effect on CYPs or other metabolizing enzymes in terms of inhibition or induction.

This sub-study will include dedicated patient cohorts for the free base formulation, malate direct blend formulation and malate roller compaction formulation. Data evaluable for PK are needed from as many as 10 patients in each cohort; as many as 12 patients may be enrolled into each cohort to ensure sufficient PK data are evaluable. Patients eligible for this sub-study will meet applicable entry criteria in the main study. Specifically, patients will have locally advanced, unresectable or metastatic non-squamous NSCLC and will have experienced progression of disease on or after at least one prior treatment in the advanced disease setting.

Enrollment of the cohort of patients to receive the sitravatinib free base 10% Tween capsule formulation (reference product) may proceed upon approval of Protocol Amendment 4 (Version 5.0) by the IRB/EC. Enrollment into cohorts evaluating the new formulations is expected to begin in the fourth-quarter 2018. The sitravatinib malate salt capsule formulation is expected to be evaluated first, with evaluation of the free base softgel capsule undertaken if results using the malate salt are unfavorable.

Reference sitravatinib exposure data using the sitravatinib free-base 10% Tween capsule formulation administered at 120 mg QD will be generated in one cohort of patients. Due to the observation in the dog study of increased exposure using the two new sitravatinib capsule formulations, two dose levels are planned for each of these formulations. The starting dose for both the malate salt capsule and free base softgel capsule formulation will be 60 mg QD, as described above. The PK data generated using the starting dose in patients will be used to extrapolate the dose of each capsule formulation needed to achieve exposure comparable to the reference product administered at 120 mg QD.

The potential patient cohorts are listed below:

1. Sitravatinib free base 10% Tween (free base) capsule formulation – 120 mg QD.

2. Sitravatinib malate direct blend salt capsule formulation – 60 mg QD.

3. Sitravatinib malate roller compaction capsule formulation – 100 mg QD.

This starting dose of 100 mg sitravatinib malate roller compaction capsule is extrapolated based on the safety and PK results in Cohort 2. The 60 mg QD sitravatinib malate exposure was compared to the 120 mg sitravatinib free base exposure and the 100 mg QD of sitravatinib malate is projected to achieve exposure comparable to the 120 mg QD sitravatinib free base.

The following patient cohorts will no longer be explored and hence patient enrollment within these cohorts will not open at this time.

4. Sitravatinib free base softgel capsule formulation – 60 mg QD.

5. Sitravatinib free base softgel capsule formulation – dose to be extrapolated based on results in Cohort 4 to achieve exposure comparable to Cohort 1.

In the event that early results at a dose level are not within the exposure range expected, adaptations, including truncated enrollment into a cohort or addition of a limited number of cohorts may be undertaken after discussion between the Investigators participating in the sub-study and the Sponsor.

Sitravatinib Administration and PK/ECG Timepoints

The sub-study will begin with a 7-day lead-in period comprised of a single dose of the assigned sitravatinib formulation/dose followed by sample collection for PK analysis over a 168-hour period as defined in Table 22.

At only the Lead-in Day 1 and C1D15 visits: following an overnight fast of at least 10 hours, patients enrolled in this sub-study will receive the assigned sitravatinib capsule formulation administered with ~240 mL (a cup) of water. Patients will continue to fast for at least 4 hours before the next meal. Water is allowed as desired except for one hour before and one hour after sitravatinib administration.

All other doses of sitravatinib (with the exception of Lead-in Day 1 and C1D15) should be taken, at the assigned daily dose, in the modified fasted state, specifically, at least a 2-hour fast before each dose and no food for a minimum of 1 hour after each dose. On days of PK sampling, patients should delay taking the daily sitravatinib dose until the pre-dose PK sample has been collected in the clinic.

Several changes to the assessment schedule outlined in the main study will apply to patients enrolled in this sub-study.

1 Patients enrolled in this sub-study are exempt from sample collection for the purposes of flow cytometry and protein or cytokine biomarker studies.

2 Triplicate ECGs will be performed on Day 1 of the lead-in period as described in Table 22 instead of later, on Cycle 1 Day 1, as described in Table 3.

3 The PK sample collection schedule describe in Table 22 and Table 23 are to be followed up to Cycle 1 Day 15, after which the sparse sampling schedule described in Table 3 applies.

Please see the central lab manual for collection, processing, and shipping instructions of PK blood samples.

Upon completion of the lead-in period, patients will begin Cycle 1 Day 1 (same visit as lead-in period Day 8) of study treatment as described in the main study, using the assigned sitravatinib formulation and dose in combination with nivolumab. On Cycle 1 Day 15 (± 2 days), a steady-state PK profile will be evaluated with sample collection over a 24-hour period (Table 23). Treatment of patients beyond Cycle 1 Day 15 will continue using the assigned sitravatinib formulation and dose in combination with nivolumab. Individual patient escalation from the starting dose using a new capsule formulation to any subsequent higher dose may be considered, at the discretion of the Investigator, after PK data at the higher dose are available. Patient assessment and management will be as described in the main study.

Table 22: PK Sample Collection and Triplicate ECG Schedule During Lead-In Period

	PK Lead-In Period Following a Single Dose of Sitravatinib											
	Day 1								**Day 2**	**Day 3**	**Day 4**	**Day 8 /C1D1**
Collection Time and Allowable Window	**Pre-dose (-30 min)**	**30 min (± 10 min)**	**1 hour (±15 min)**	**2 hour (±15 min)**	**4 hour (±30 min)**	**6 hour (±30 min)**	**8 hour (±30 min)**	**12 hour [1] (±2 hours)**	**24 hour (±2 hours)**	**48 hour[1] (±5 hours)**	**72 hour[1] (±7 hours)**	**168 hour (±7 hours)**
PK Sample	X	X	X	X	X	X	X	X	X	X	X	X
Triplicate ECG [2]	X twice				X							

1 Sample collections at 12 hours, 48 hours and 72 hours after dosing is optional. While sample collection at these timeframes are highly desirable to strengthen PK analysis, they are not mandatory in the event of logistical constraints.

2 ECGs should be taken in triplicate, each reading approximately 2 minutes apart. On Lead-in Day 1 only, two sets of triplicate ECGs should be done within 1 hour prior to dosing (e.g., at 30-minute intervals prior to dosing) to firmly establish the baseline for the patient. One set of triplicate ECGs is required at all other time points. In general, ECGs should be performed prior to the respective PK blood collection. An example of the schedule on Lead-in Day 1 would be triplicate ECG

approximately -1.0 hr and again approximately -30 mins, followed by vital signs and PK sample approximately -15 min.

Table 23: PK Sample Collection and Triplicate ECG Schedule Cycle 1 Day 15 (± 2 Days)

	Cycle 1 Day 15								
Collection Time and Allowable Window	**Pre-dose (-30 min)**	**30 min (± 10 min)**	**1 hour (±15 min)**	**2 hour (±15 min)**	**4 hour (±30 min)**	**6 hour (±30 min)**	**8 hour (±30 min)**	**12 hour [1] (±2 hours)**	**24 hour (±2 hours)**
PK Sample	X	X	X	X	X	X	X	X	X
Triplicate ECG [2]	X								

1 Sample collection at 12 hours after dosing is optional. While sample collection at this timeframe is highly desirable to strengthen PK analysis, it is not mandatory in the event of logistical constraints.
2 ECGs should be taken in triplicate, each reading approximately 2 minutes apart.

The PK evaluable population will consist of all patients who received treatment with sitravatinib and had sufficient concentration-time data to permit calculation of PK parameters for sitravatinib. For patients who were noncompliant with respect to administration of sitravatinib, or for patients with incomplete data, a decision as to their inclusion in the analysis will be made on a case-by-case basis.

After completion of the PK sub-study specific assessments and depending on the duration of treatment of individual patients and the long-term availability of various sitravatinib capsule formulations, patients may be transferred from the formulation assigned at the time of study entry to a more available formulation. The need for any such transfers will be communicated to Investigators by the Sponsor in writing (to be retained with patient source documents).

PK concentration and parameter data will be descriptively derived and displayed. A descriptive comparison will be conducted using AUC_{0-t}, $AUC_{(0-\infty)}$, C_{max}, T_{max}, $t_{1/2}$, and steady state PK exposure parameters. Steady state exposure comparison will also be assessed and accounted for. Descriptive statistics will be used to summarize patient characteristics, treatment administration and safety variables between the formulation cohorts. Details of this analysis will be provided in the PKAP.

Appendix 6. SITRAVATINIB SUB-STUDY TO EVALUATE PHARMACOKINETICS WHEN ADMINISTERED WITH FOOD

This sub-study within Study MRTX-500 will be conducted at selected study sites. It is an open-label evaluation of PK when sitravatinib capsules are administered orally in the fed state. The potential to administer sitravatinib in the fed or fasted state is being investigated to provide flexibility and convenience for future patients enrolling in sitravatinib clinical trials. Reference data in the fasted state will be generated in the sub-study described in Appendix 5. Depending on timing of availability of drug product for different sitravatinib capsule formulations and results from the formulation PK sub-study, evaluation of sitravatinib PK in the fed state may be undertaken with one or more capsule formulation(s).

Sitravatinib administered in combination with nivolumab is unlikely to result in a clinically relevant drug-drug interaction based on absorption, metabolism, elimination or protein binding. Nivolumab is a mAb and is intravenously administered, whereas sitravatinib is a small molecule therapeutic administered orally; no absorption interactions are expected. No studies on the metabolism of nivolumab have been reported in vitro or in humans. Like most therapeutic proteins, nivolumab is not expected to be metabolized by liver cytochrome P-450 (CYP) or other drug metabolizing enzymes and is unlikely to have an effect on CYPs or other metabolizing enzymes in terms of inhibition or induction.

This sub-study will be conducted in as many as three dedicated patient cohorts. Data evaluable for PK are needed from at least 6 patients in each cohort; as many as 8-10 patients may be enrolled into each cohort to ensure 6 patients are evaluable for PK. The sitravatinib dose to be administered using either of the new capsule formulations will be determined in the PK sub-study described in Appendix 5.

Patients eligible for the sub-study will meet applicable entry criteria in the main study. Specifically, patients will have locally advanced, unresectable or metastatic non-squamous NSCLC and will have experienced progression of disease on or after at least one prior treatment in the advanced disease setting.

The definition of the fed state for the purpose of this sub-study is consumption of a high-fat (approximately 50% of total caloric content of the meal), high-calorie (800-1000 calories) meal at the time of sitravatinib dosing. For the purposes of this sub-study, a high-fat meal consists of approximately 150, 250, 500-600 calories from protein, carbohydrates and fat respectively. An example meal consists of two eggs fried with butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes and eight ounces of whole milk. The nutritionist at the study site may recommend an alternative meal that follows the guidance for fat and calorie content.

Sitravatinib Administration and High-Fat Meal/PK/ECG Timepoints

The sub-study will begin with a 7-day lead-in period comprised of a single dose of the assigned sitravatinib formulation followed by sample collection for PK analysis over a 168-hour period (Table 24).

At only Lead-in Day 1 and C1D15 visits: Patients will be seen in clinic at the end of an overnight fast of at least 10 hours. The pre-dose PK sample will be obtained and then the patient will consume a high-fat, high-calorie meal (as described above). Patients should start the recommended meal 30 minutes prior to sitravatinib dosing. Patients should eat this meal in 30 minutes or less. Sitravatinib is to be administered 30 minutes after the start of the meal with ~240 mL of water. If the meal is not finished in 30 minutes, patients should not complete the meal post sitravatinib administration. No food should be consumed for at least 4 hours after the dose. Water can be allowed as desired except for 1 hour before and 1 hour after the drug administration.

C1D1 to C1D14: Patients should consume their typical meal within 30 minutes prior to each dose of sitravatinib. Sitravatinib should be taken with ~240 mL of water.

C1D16 and beyond: Sitravatinib should be taken in the modified fasted state, specifically, at least a 2-hour fast before each dose and no food for a minimum of 1 hour after each dose. On days of PK sampling, patients should delay taking the daily sitravatinib dose until the pre-dose PK sample has been collected in the clinic.

Patients enrolled in this sub-study will receive sitravatinib administered orally at the daily dose of 120 mg QD for the reference product and, for the new capsule formulations, at the dose recommended after conduct of the PK sub-study described in Appendix 5.

Several changes to the assessment schedule outlined in the main study will apply to patients enrolled in this sub-study.

1 Patients enrolled in this sub-study are exempt from sample collection for the purposes of flow cytometry and protein or cytokine biomarker studies.

2 Triplicate ECGs will be performed on Day 1 of the lead-in period as described in Table 22 instead of later, on Cycle 1 Day 1, as described in Table 3.

3 The PK sample collection schedule describe in Table 22 and Table 23 are to be followed up to Cycle 1 Day 15, after which the sparse sampling schedule described in Table 3 applies.

PK blood samples will each collect 4 mL of blood. PK samples collected during this sub-study will be analyzed by the central laboratory in convenient batches. See the Study Manual for instructions concerning sample transfer.

Upon completion of the lead-in period, patients will begin Cycle 1 Day 1 (same visit as lead-in period Day 8) of study treatment using the assigned sitravatinib formulation and in combination with nivolumab (as described in the main study). On Cycle 1 Day 15 (± 2 days), rather than the single PK sample, a steady-state PK profile of sitravatinib administered with the described high-fat, high-calorie meal will be evaluated with sample collection over a 24-hour period (Table 25). Patient assessment and management will be as described in the main study.

Table 24: PK Sample Collection and Triplicate ECG Schedule During Lead-In Period

	PK Lead-In Period Following a Single Dose of Sitravatinib											
	Day 1								Day 2	Day 3	Day 4	Day 8 / C1D1
Collection Time and Allowable Window	**Pre-dose (-30 min)**	**30 min (± 10 min)**	**1 hour (±15 min)**	**2 hour (±15 min)**	**4 hour (±30 min)**	**6 hour (±30 min)**	**8 hour (±30 min)**	**12 hour [1] (±2 hours)**	**24 hour (±2 hours)**	**48 hour (±5 hours)**	**72 hour (±7 hours)**	**168 hour (±7 hours)**
PK Sample	X	X	X	X	X	X	X	X	X	X	X	X
Triplicate ECG [2]	X twice				X							

1 Sample collection at 12 hours after dosing is optional. While the sample collection at this timeframe is highly desirable to strengthen PK analysis, it is not mandatory in the event of logistical constraints.

2 ECGs should be taken in triplicate, each reading approximately 2 minutes apart. On Lead-in Day 1 only, two sets of triplicate ECGs should be done within 1 hour prior to dosing (e.g., at 30-minute intervals prior to dosing) to firmly establish the baseline for the patient. One set of triplicate ECGs is required at all other time points. In general, ECGs should be performed prior to the respective PK blood collection. An example of the schedule on Lead-in Day 1 would be triplicate ECG approximately -1.0 hr and again approximately -30 mins, followed by vital signs and PK sample approximately -15 min.

Table 25: PK Sample Collection and Triplicate ECG Schedule Cycle 1 Day 15 (± 2 Days)

	Cycle 1 Day 15								
Collection Time and Allowable Window	**Pre-dose (-30 min)**	**30 min (± 10 min)**	**1 hour (±15 min)**	**2 hour (±15 min)**	**4 hour (±30 min)**	**6 hour (±30 min)**	**8 hour (±30 min)**	**12 hour [1] (±2 hours)**	**24 hour (±2 hours)**
PK Sample	X	X	X	X	X	X	X	X	X
Triplicate ECG [2]	X								

1 Sample collection at 12 hours after dosing is optional. While the sample collection at this timeframe is highly desirable to strengthen PK analysis, it is not mandatory in the event of logistical constraints.

2 ECGs should be taken in triplicate, each reading approximately 2 minutes apart.

The PK evaluable population will consist of all patients who received treatment with sitravatinib and had sufficient concentration-time data to permit calculation of PK parameters for sitravatinib. For patients who were noncompliant with respect to administration of sitravatinib or prescribed food regimen, or for patients with incomplete data, a decision as to their inclusion in the analysis will be made on a case-by-case basis.

After completion of the food effect sub-study specific assessments and depending on the duration of treatment of individual patients and the long-term availability of various sitravatinib capsule formulations, patients may be transferred from the formulation assigned at the time of study entry to a different formulation to alleviate supply concerns. The need for any such transfers will be communicated to Investigators by the Sponsor in writing (to be retained with patient source documents).

PK concentration and parameter data will be descriptively derived and displayed. A descriptive comparison will be conducted using AUC_{0-t}, $AUC_{(0-\infty)}$, C_{max}, T_{max}, $t_{1/2}$, and steady state PK exposure parameters. The effect of food will be assessed based on the clinical relevance. Steady state exposure comparison will also be assessed and accounted for. Descriptive statistics will be used to summarize patient characteristics, treatment administration and safety variables between fed and fasted groups. Details of this analysis will be provided in the PKAP.