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: 10-January-2022

Statistical Analysis Plan

Sponsor:	Mirati Therapeutics, Inc
Protocol No:	MRTX-500
PRA Project Id:	MRTGSMN2-GSMNP2
Version Date:	11-Feb-2020
Version No.:	6.0

Title:	A Parallel Phase 2 Study of Glesatinib, Sitravatinib or Mocetinostat in Combination With Nivolumab in Advanced or Metastatic Non-Small Cell Lung Cancer
CRF Version No./Date:	4.0 / 07-Jan-2020
SAP No./Date	3.0 / 10-Jan-2022

1.0 Approvals

Sponsor	
Sponsor Name:	Mirati Therapeutics, Inc.
Representative / Title:	[redacted]
Signature / Date:	
Representative / Title:	
Signature / Date:	

PRA	
Biostatistician / Title (Owner):	[redacted]
Signature / Date:	

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2.0 Purpose

The statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Mirati Therapeutics, Inc. Protocol MRTX-500.

3.0 Scope

This plan is a living document that supplements the study protocol for statistical analysis-related aspects.

The SAP outlines the following:

- Study objectives and endpoints
- Study design
- Analysis populations
- Endpoint and variable definitions
- Data handling
- Data review
- Statistical methods

Deviations from the SAP will be described in the Clinical Study Report (CSR).

4.0 Introduction

This SAP describes the statistical methods to be used during the analysis and reporting of data collected under Mirati Therapeutics, Inc. Protocol MRTX-500.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the protocol v6.0 dated 11-Feb-2020 and CRF v4.0 dated 07-Jan-2020. Any further changes to the protocol or CRF may necessitate updates to the SAP.

The stable version of the SAP will be approved based on the current protocol and CRF, allowing programming to be initiated. A final version of the SAP will be issued for approval prior to database lock.

Each version of the SAP requires approval by the sponsor.

4.1 Changes from Protocol

4.1.1 Glesatinib

Enrollment into Glesatinib cohorts was discontinued in November 2017 as a result of Sponsor portfolio reprioritization. The analysis and reporting of this treatment arm is limited to the Lead-in phase only, and will be summarized for patient disposition, demographics, primary disease history, prior primary disease treatment, medical history, prior/concomitant medications and a single AE table only. Any other data will appear in listings only.

4.1.2 Mocetinostat

Enrollment into Mocetinostat cohorts was never initiated and therefore no analysis or reporting of this treatment arm is necessary. The reference to Mocetinostat will only remain in the SAP where text is copied verbatim from the protocol.

4.1.3 Analysis Populations

The modified Intent-to-Treat (mITT) population as defined in Section 9.3.1 of the protocol has been renamed as the Full Analysis Set (FAS).

Section 3.2 of the protocol described that for patients to be part of the Clinical Activity Evaluable (CAE) population they *"…must have at least one on-study disease assessment or discontinue from treatment for progressive disease (PD) prior to this assessment."* This definition was modified by Mirati to be as described in Section 7.3 of this SAP, where it includes *"patients with measurable disease (per RECIST 1.1) at baseline and have received at least one dose of both investigational study drug and Nivolumab, must have at least one on-study disease assessment or discontinue from treatment for PD."*

4.1.4 Clinical Benefit Rate (CBR)

Section 9.4.2 of the protocol states that *"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)."*

Amendments have been made to the later part of this definition to allow for at least one on-study assessment at least 42 days on study. This change is aligned with the definitions laid out in Section 8.2 in this SAP.

4.1.5 Sitravatinib Pharmacokinetic Sub-Studies

Two Sitravatinib sub-studies were added to protocol v4.0, however as per the project administrative letter, dated July 15th 2020;

- PK Formulations of capsules (Appendix 5 of protocol v6):

  This was intended to be an evaluation of Sitravatinib PK using three formulations of capsules. The objective of this sub-study was fulfilled in a healthy volunteer study (516-006) which demonstrated bioequivalence between the 100 mg Sitravatinib malate capsule formulation (test) and the 120 mg Sitravatinib free base capsule formulation (reference). Therefore, no additional data are needed.

- PK Food sub-study (Appendix 6 of protocol v6):

  This was intended to be an evaluation of PK when Sitravatinib capsules are administered orally in the fed state. Mirati Therapeutics has decided to conduct a separate study to evaluate the pharmacokinetics of Sitravatinib with and without food. Therefore, the Pharmacokinetic Food Effect Sub-Study (Appendix 6) will be closed.

As a result, the PK sub-study component of this study will be comprised of selected Demographic and Safety summaries, as described in Section 11.2. Patients from these PK sub-studies will be excluded from the main study summaries, their data will be listed separately.

4.2 Study Treatment Definitions

4.2.1 Study Drug

The investigational agents of primary interest (Glesatinib, Sitravatinib, Mocetinostat) are referred to in the protocol as both study drugs and study treatments. Within the context of this SAP these terms are used interchangeably.

4.2.2 Treatment Arm

The combination of Nivolumab and one of the investigational study treatments (including dose level) will be referred to as the "treatment arm".

5.0 Study Objectives and Endpoints

5.1 Objectives

5.1.1 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 non-small cell lung cancer (NSCLC).

5.1.2 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 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.

5.1.3 Exploratory Objectives

- [redacted]

5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint is the Objective Response Rate (ORR) as defined by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

5.2.2 Secondary Endpoints

- Safety characterized by type, incidence, severity, timing, seriousness and relationship to study treatment of adverse events (AEs), and laboratory abnormalities.
- Secondary efficacy endpoints

- Duration of Response (DoR)
- CBR
- Progression-Free Survival (PFS)
- 1-Year Survival Rate
- Overall Survival (OS)

- Blood plasma concentrations of the investigational agents.

5.2.3 Exploratory Endpoints

[redacted]

6.0 Study Design

Study MRTX-500 is an open-label, parallel Phase 2 evaluation of Nivolumab in combination with three 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 (checkpoint inhibitor therapy [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 Electrocardiogram (ECG) assessment time points are presented in Table 2, Table 3, and Table 4.

Specifics of two Sitravatinib sub-studies are presented in the protocol 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 three 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.

Table 1: Schedule of Assessments

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 Table 22, Table 23, Table 24, Table 25 from the protocol sub-study appendix 5 and appendix 6 for PK sub-studies							
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 in the protocol) 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. 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 protocol 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. rRR 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 (-0.5-0 hour)**		**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 protocol 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 protocol 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 protocol 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 (Study arm not initiated)

	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.

6.1 Lead-in Dose Escalation Evaluation

The study will begin with a lead-in phase 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. Table 5 lists the planned dose levels for each agent, with the starting dose for each agent shown as Dose Level 1.

Patients may be escalated to Dose Level 2 or de-escalated to Dose Level -1, depending on safety observations.

Table 5: Investigational Study Drug Starting Dose Levels for Cohorts of Patients in the Lead-In Phase 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 phase dose escalation evaluation, doses below those shown in Table 5 may be implemented in subsequent cohorts of patients after discussion among Investigators participating in the lead-in phase 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 the product labeling and replicated in Section 5.2 of the protocol.

6.1.1 Definition of Dose Limiting Toxicity (DLT)

The National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) v4.03 will be used for the evaluation of safety observations 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 drug 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.

6.1.2 Enrollment and Dose Escalation Plan

Patients meeting eligibility criteria as outlined in the protocol may enroll into the lead-in phase 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 drug will be observed for at least 1 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 1 full cycle and have received treatment with Nivolumab and at least 75% of scheduled investigational study drug 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 modified toxicity probability interval (mTPI) method (Dose-Finding Spreadsheet presented in Appendix 2 of the protocol). 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.

6.1.3 Definition of Maximum Tolerated Dose (MTD)

The Maximum Tolerated Dose (MTD) for each combination regimen is defined as the highest investigational study drug 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 of the protocol) using the experience of at least 6 patients during the first 28-day treatment cycle.

6.1.4 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 phase 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 drug and 100% dose intensity of Nivolumab; and
- no observed ≥Grade 3 or serious immune-related adverse events (irAEs) causally related to the combination regimen.

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

6.2 Phase 2 Study

Following completion of the lead-in phase 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 CR, PR or SD 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 1) in patients with prior treatment with a checkpoint inhibitor. Patients enrolled in the lead-in phase dose escalation evaluation and receiving the dose of investigational study drug 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 CIT (CIT-naïve), each investigational study treatment arm (i.e., Glesatinib and Sitravatinib) 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 1) in patients without prior treatment with a checkpoint inhibitor.

Disease response and progression as documented by the Investigator in the 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 conducted (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 (CI), as well as the DoR and PFS.

6.2.1 Sample Size Considerations

Approximately 24 patients may be enrolled into the lead-in phase of the study. A precise sample size cannot be defined as it is dependent on the number of dose escalations based on the mTPI (Ji 2013) method, and the number of patients enrolled in the expansion cohorts

6.2.1.1 Lead-In Phase

The mTPI method 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 DLT).

6.2.1.2 Phase 2 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-β) 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 CIT 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.

6.2.1.3 Phase 2 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% (p0); thus this rate is considered uninteresting. The target ORR using the investigational agents in combination with Nivolumab is 50% (p1).

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.

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% CI around the ORR point estimate. Protocol Amendment 3 (v4.0) eliminates enrollment expansion beyond Stage 2 except in the Sitravatinib segment of the study enrolling patients with CIT-experience.

6.2.1.4 Expansion Beyond Phase 2

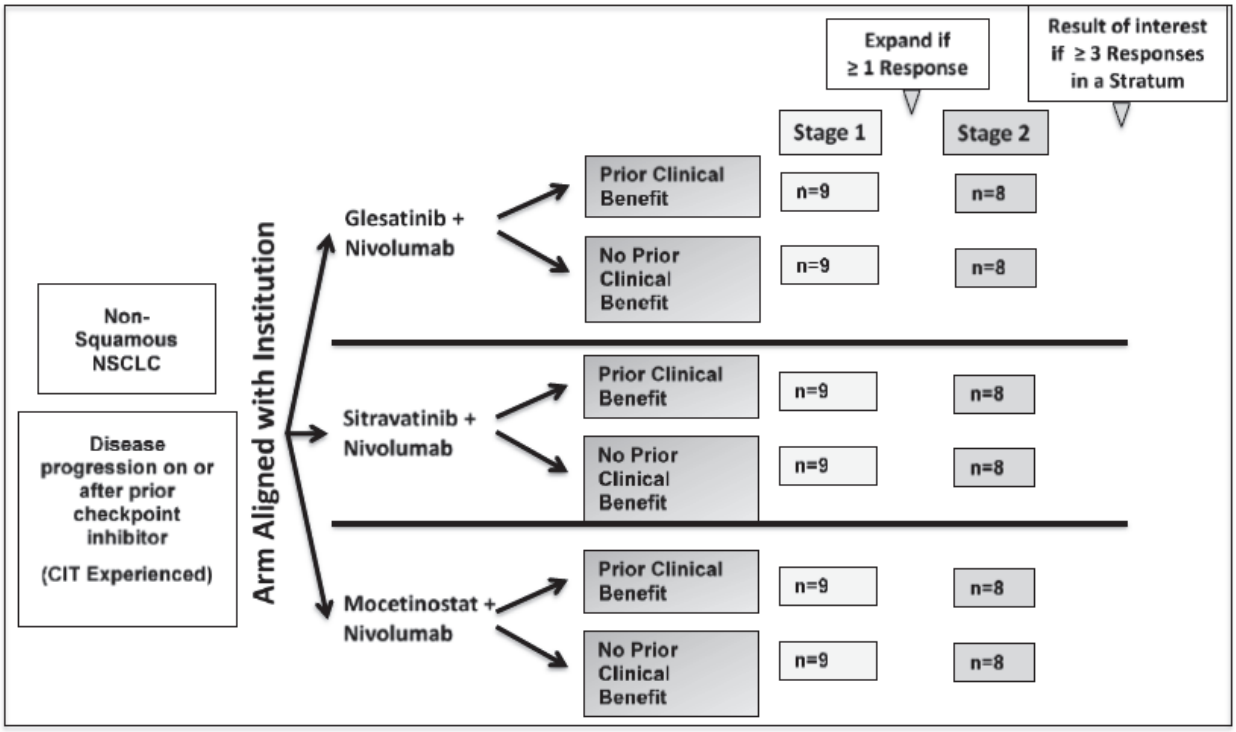
For the Sitravatinib segment of the study enrolling patients with CIT-experience, expansion of enrollment beyond Stage 2 will be managed as one cohort that includes all patients, regardless of prior clinical benefit during treatment with CIT. Based on preliminary clinical activity results as of June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

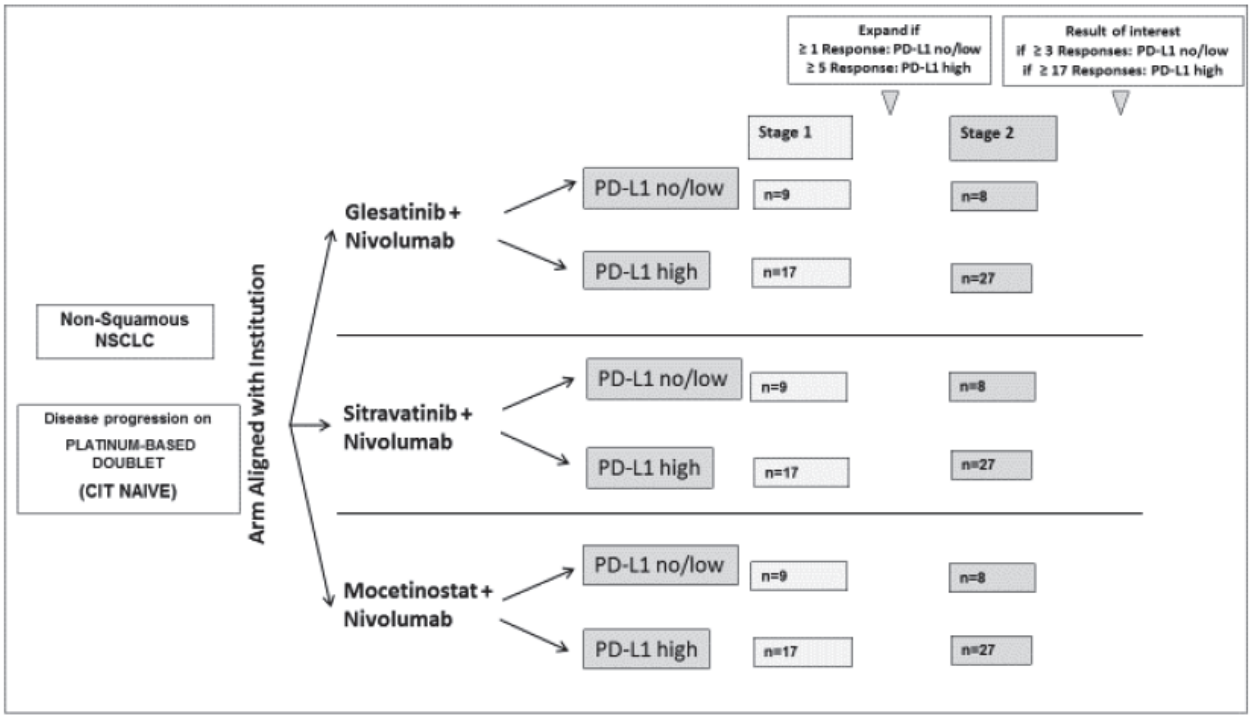
Expansion of Sitravatinib CIT-naïve cohorts beyond Stage 2 of enrollment is not anticipated.

6.3 Randomization

Random assignment to treatment arms is not being used in this study. Treatment arm assignment will be determined by the site where the patient is enrolled as described in Section 6.0.

Figure 1: Phase 2 Portion Study Diagram





7.0 Analysis Populations

Patients who consent to be part of the PK sub-studies will be excluded from all populations, with the exception of the enrolled population and the PK sub-study population.

7.1 Enrolled Population

The Enrolled Population is defined as all patients who sign an informed consent and are determined by the Investigator to meet all eligibility criteria during screening assessments. Percentages in the disposition summaries will be displayed using the Enrolled Population as the denominator.

7.2 Full Analysis Set (FAS)

The FAS is defined as all patients who receive at least one dose of both investigational study drug and Nivolumab. The analyses of the primary and secondary efficacy endpoints will be performed using the FAS.

7.3 Clinical Activity Evaluable (CAE) Population

The CAE Population is defined as all patients who have received at least one dose of both investigational study drug and Nivolumab, have evaluable baseline tumor assessment and at least one post-baseline tumor assessment. This population will be used for the supportive analysis of tumor responses.

7.4 Safety Population

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

7.5 DLT Evaluable Population

The DLT evaluable population is defined as any patient who is enrolled in a cohort in the lead-in phase of the study and who either has been on study for one full cycle and has received treatment with Nivolumab and at least 75% of scheduled investigational study treatment doses in Cycle 1 or who has experienced a DLT in Cycle 1.

7.6 PK Sub-Study Population

The PK sub-study population is defined as any patient consenting to be part of either the PK formulation or the PK food effect sub-studies. Consent will be identified programmatically from the Study Treatment Assignment page of the CRF.

8.0 Endpoint Definitions

8.1 Baseline Characteristics

8.1.1 Baseline

Baseline is defined as the last non-missing value prior to first dose. In most cases this will be Cycle 1 Day 1, however values from the Screening/Baseline visit may be used if Cycle 1 Day 1 is missing, or after first dose.

8.1.2 Age

Age (years) is calculated relative to the date of signing informed consent;

Age (years) = (Date of Informed Consent - Date of Birth) + 1 / 365.25.

8.1.3 Time Since Diagnosis

Time since diagnosis is calculated relative to the date of first dose of any study drug. Missing or partial dates of diagnosis will not be imputed.

Time Since Diagnosis (Years) = (Date of First Dose – Date of Diagnosis) +1/365.25.

8.2 Efficacy Variables

With regard to efficacy endpoints, the term “on-study” includes the period from the first dose of any study drug until the end of study. The term “baseline” will include screening and Cycle 1 Day 1 pre-dose assessment which would represent a 29-day window. Unscheduled visits assessments preceding Cycle 1 Day 1 will be also considered for baseline.

Disease assessments involving radiographic evaluations may be performed over the course of a few days. The date of response (CR, PR, SD, PD or Not Evaluable [NE]) will be recorded as the date of the last radiographic evaluation included in the series for that time point assessment. For the investigator assessment, the date will be determined using the latest Date of Assessment recorded among the radiologic modalities included for the applicable Time Point Assessment.

8.2.1 Objective Response Rate (ORR)

Objective disease response will be categorized in accordance with RECIST v1.1. ORR is defined as the proportion of patients documented to have a confirmed CR or PR. ORR as reported by the investigator will be used in decision making for study expansion (Predictive Probability Design).

Best Overall Response (BOR) is defined as the best response among all overall responses (in the order CR, PR, SD, PD then NE) recorded from the start of study drug until disease progression/recurrence or start of subsequent anti-cancer therapy, whichever comes first. The status of best response of CR or PR must be confirmed by repeat tumor assessment within no less than 4 weeks according to RECIST v1.1. If the status of CR or PR cannot be confirmed by repeat tumor assessment, the BOR of unconfirmed CR and PR will be SD or NE. The status of BOR of SD requires an on-study assessment after at least 42 days from first dose date of treatment.

Confirmed Response Based on Subsequent Assessments*;

First Time Point Response**	Second Time Point Response	Confirmed Response (Best Response)*
PD	No further evaluation	PD
NE	PD	PD
CR	PD	SD or PD (1)
PR	PD	SD or PD (1)
SD	PD	SD or PD (1)
CR	CR	CR
CR	NE **	SD or NE (2)
PR	CR	PR
PR	PR	PR
PR	SD (3)**	SD
PR	NE **	SD or NE (2)
SD	CR	SD
SD	PR	SD
SD	SD	SD
SD	NE	SD or NE (2)
NE	CR	SD
NE	PR	SD
NE	SD	SD
NE	NE	NE

* A Best Response of SD can only be made after the patient is on-study for a minimum of 42 days. If the patient is on-study less than 42 days, any tumor assessment indicating stable disease before this time period will have a Best Response of NE unless PD is identified.

** Subsequent documentation of CR may provide confirmation of a previously identified CR for patients where the second integrated response was NE. Subsequent documentation of PR may provide confirmation of a previously identified PR for patients where the second integrated response was NE or SD. If the third response confirms the CR (or PR) then the confirmed response will be CR (or PR).
For example: CR NE CR = CR; PR NE PR = PR.

Additionally, one SD is allowed between PRs (e.g., PR SD PR = PR).

(1) Best response will be SD if the first response is after 42 days on-treatment. Otherwise, the best response will be PD.
(2) Best response will be SD if the first response is after 42 days on-study. Otherwise, the best response will be NE.
(3) Response is SD if the increase from the first to the second assessment does not qualify for PD.

For patients with unconfirmed CR/PR that can't be confirmed due to dropping off study, the best overall response will be SD.

8.2.2 Duration of Response (DoR)

DoR is defined as the time in months from date of the first documentation of objective response (CR or PR) to the first documentation of objective PD or to death due to any cause in the absence of documented PD (i.e., min (PD date, death date) – date of the first observation of response +1). DoR will only be calculated for the subgroup of patients achieving a confirmed CR or PR.

DOR = (Min(PD Date, Death Date) – Date of the First Observation of Response +1)/30.4375

8.2.3 Clinical Benefit Rate (CBR)

CBR will be categorized in accordance with RECIST v1.1. CBR is defined as the proportion of patients documented to have a confirmed CR or PR, or SD.

8.2.4 Progression-Free Survival (PFS)

PFS is defined as the time from the first dose of study drug to the date of PD or death due to any cause in the absence of documented PD, whichever occurs first.

PFS (in months) = (First Event Date – First Dose Date +1)/30.4375.

8.2.5 Overall Survival (OS)

OS is defined as the time from first dose of study drug to the date of death due to any cause.

OS (in months) = (Date of Death − Date of First Dose of Study Drug +1)/30.4375.

8.3 Study Drug Exposure Variables

The term study drug in the exposure definitions below, refers to Glesatinib and Sitravatinib unless otherwise specified.

8.3.1 Study Treatment Duration

Study treatment duration will be summarized separately for each study drug and Nivolumab and is defined as;

- Study Treatment Duration (weeks) = (Last Dose Date – First Dose Date +1)/7.

8.3.2 Cumulative Dose Administered

Dose modifications should be accounted for in the cumulative dose administered calculations below;

- Cumulative dose received for Nivolumab (mg) is defined as the total amount of Nivolumab a patient receives during the study as recorded on the Nivolumab Administration CRF forms. Nivolumab is planned to be administered at a dose of 240 mg once every 2 weeks or 480 once every 4 weeks.
- Cumulative dose received for study drug (mg) is defined as the total amount of the study drug a patient receives during the study;

  The Sum of [(Last Dose Date – First Dose Date + 1) * Total Dose (mg per administration) * Dose Frequency] as recorded on the Study Drug Administration CRF forms.

8.3.3 Cycles Started

A patient is considered to have started a cycle if they received at least one dose of either study drug or Nivolumab in that cycle, per the Study Drug Administration CRF page.

8.3.4 Dose Intensity

- Relative dose intensity should apply to both Sitravatinib (Phase 2 only) and Nivolumab, from Cycle 1 Day 1,defined as:
    - For Sitravatinib, [cumulative dose received (mg) / cumulative planned dose (mg)] * 100, where cumulative planned dose is calculated as the starting daily dose multiplied by the study treatment duration in days.
    - For Nivolumab: [cumulative Nivolumab dose administered (mg)] / cumulative planned Nivolumab dose (mg)] * 100, where the cumulative planned total dose is:

      $$240mg\ x\ Round\left(\frac{Duration\ of\ Nivoumab\ (weeks)+X}{2}\right)$$

      Where X is 2 weeks for subjects who took 240mg as their last dose, and 4 weeks for subjects who took 480mg as their last dose.

8.3.5 Compliance

Compliance is only calculated for Sitravatinib (Phase 2 only), from Cycle 1 Day 1, defined as:

Compliance (%) = Cumulative Dose Received (mg) / Adjusted Cumulative Planned Dose (mg) * 100, where

Treatment Duration (Days) = Last Dose Date - First Dose Date +1, and

Adjusted Cumulative Planned Dose (mg) = Planned Dose * (Treatment Duration – Duration of Interruptions and/or Dose Reductions due to AE) + ∑(Each Planned Interruption and/or Dose Reduction (mg) * Duration of the given Planned Interruption/Reduction due to AE).

8.3.6 Days on Study Drug

Days on study drug is defined as the total number of days that a patient received treatment, after subtracting for interruptions or drug missed, that is:

- The [(Last Dose Date – First Dose Date captured on the Study Drug Administration CRF page) – number of days with 0 mg dose +1].

8.4 Safety Variables

With regard to safety summaries, the term “on-treatment” is the period from first dose until either last dose + 28 days or the start of anti-cancer therapy, whichever is earlier.

AEs, laboratory values and ECGs will be graded according to the NCI CTCAE v4.03 (see Section 13.0 for link to the criteria) , ECGs will also be graded according to International Conference on Harmonisation (ICH) E14.

8.4.1 Adverse Events

8.4.1.1 Treatment-Emergent AEs (TEAEs)

TEAEs are those that first occur or increase in severity after the first dose of study treatment and not more than 28 days after the last dose of study treatment and prior to the initiation of subsequent anti-cancer therapy. Any ongoing TEAE (or any baseline sign/symptom recorded as part of Medical History) that changes in attribution or increases in severity is captured as a new AE.

8.4.1.2 Serious Adverse Events (SAEs)

Serious adverse events (SAEs) are reported from the time that the patient provides informed consent (i.e., prior to undergoing any study-specific procedure or assessment) until at least 28 days after last administration of study treatment. All SAEs ongoing 28 days after the last dose should be followed until resolution, stabilization to a chronic condition or administration of alternative cancer treatment, whichever occurs first.

8.4.2 Immune-Related Adverse Event (irAE)

An irAE is defined as an AE that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. irAEs will be identified by the Investigator on the adverse events CRF page.

8.4.3 Adverse Events of Special Interest (AESI)

An AESI is defined as an AE 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. AESIs will be identified by the medical team based on coded terms.

8.4.4 Physical Examinations

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 are performed.

8.4.5 Vital Signs

Vital signs: systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, height and weight. Height will be recorded at screening only.

8.4.6 Clinical Laboratory Assessments

Clinical laboratory parameters to be collected routinely for hematology, chemistry, urinalysis and thyroid function are listed in Table 6 in Section 11.1.7.4 .

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.

8.4.7 Electrocardiograms

Single and triplicate 12-Lead ECG parameters will be collected as shown in Table 1-4. Assessments include rhythm, heart rate, PR, QRS, QT and RR, the QT interval will be corrected for heart rate using Fridericia's formula (QTcF). The Investigator's overall interpretation will also be collected.

The baseline to be used in the calculation of changes over time will be the mean of the 6 pre-dose values, i.e., the triplicate values at Cycle 1 Day 1 (-1 hour and -0.5 hours pre-dose). If any of the 6 values are missing, the mean will be calculated using the observed values.

8.4.8 Echocardiograms

Echocardiograms will be performed in the Sitravatinib treatment arm at screening, and thereafter as shown in Table 1. Additional assessments of left ventricular ejection fraction (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 will be performed until normalization as described in Section 5.1.3.4.1 of the protocol.

8.4.9 Prior and Concomitant Medications

Medications administered to study participants are captured on a log CRF page.

Medications are considered prior medications if they have a start date prior to the date of first dose of study medication or a partial start date which indicates the medication was begun prior to the first dose of study treatment. Medications with missing start dates will be considered both prior and concomitant medications, unless the end date is prior to first dose, in which case it would be considered prior only.

Medications with a missing start date but an observed end date after first dose of study treatment, will be considered as concomitant medication.

Concomitant medications are defined as medications administered to study participants on or after the first dose of study treatment, or a prior medication with an end date after the first dose of study treatment.

A medication can be considered both prior and concomitant.

8.5 Predetermined Covariates and Prognostic Factors

Enrollment into each treatment arm of the CIT-experienced patients will be stratified by prior outcome of treatment with a checkpoint inhibitor (prior clinical benefit, no prior clinical benefit). Each combination of treatment arm and prior clinical benefit stratum, including overall, will be analyzed separately.

Enrollment into each treatment arm of the CIT-naïve patients will be stratified according to the patient's PD-L1 status (No/Low, High). Each combination of treatment arm and PD-L1 status, including overall, will be analyzed separately.

9.0 Data Handling

9.1 Missing Dates

9.1.1 Imputation of Partial Adverse Event or Medication Dates

The rules to impute missing start and stop dates will be applied as follows;

Start Date

If the start date is completely missing (i.e., the day, month, and year are all unknown) the start date will not be imputed.

Missing Day Only

- If the month and year of the incomplete date are the same as the month and year of the first dose date, then the day of the first dose date will be assigned to the missing day.
- If either the year is before the year of the first dose date or if years are the same but the month is before the month of the first dose date, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the first dose date or if both years are the same but the month is after the month of the first dose date, then the first day of the month will be assigned to the missing day.

Missing Month Only

- The day will be treated as also missing and both month and day will be replaced according to the below procedure.

Missing Day and Month

- If the year of the incomplete date is the same as the year of the first dose date, then the day and month of the first dose date will be assigned to the missing fields.
- If the year of the incomplete date is not the same as the year of the first dose date, then January 1 will be assigned to the missing fields.

- If the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date.

Stop Date

Missing Day Only

- If the month and year of the incomplete date are the same as the month and year of the last visit date, then the day of the last visit date will be assigned to the missing day.
- If either the year is before the year of the last visit date or if both years are the same but the month is before the month of the last visit date, then the last day of the month will be assigned to the missing day.
- If either the year is after the year of the last visit date or if both years are the same but the month is after the month of the last visit date, then the first day of the month will be assigned to the missing day.

Missing Month Only

- The day will be treated as missing and both month and day will be replaced according to the below procedure.

Missing Day and Month

- If the year of the incomplete date is the same as the year of the last visit date, then the day and month of the last visit date will be assigned to the missing fields.
- If the year of the incomplete date is before the year of the last visit date, then December 31 will be assigned to the missing fields.
- If the year of the incomplete date is after the year of the last visit date, then January 01 will be assigned to the missing fields.

9.1.2 Imputation of Partial Subsequent Anti-Cancer Therapy Dates

The following rules will be applied to impute missing subsequent anti-cancer therapy dates.

Missing Day Only

- If the month and year of the incomplete date are the same as the month and year of the last dose date, then the last dose date + 1 will be assigned to the missing day.
- If the month and year of the incomplete date are after the month and year of the last dose date, then the first day of the month will be assigned to the missing day.

Missing Month Only

- The day will be set as missing and treated as missing Day and Month.

Missing Day and Month

- If the year of the incomplete date is the same as the year of the last dose date, then the last dose date + 1 will be assigned to the missing day and month.
- If the year of the incomplete date is after the year of the last dose date, then January 01 will be assigned to the missing fields.

9.2 Laboratory Values Beyond the Limits of Quantification

Laboratory values of the form of "< x" (i.e., below the lower limit of quantification) or "> x" (i.e., above the upper limit of quantification) will be imputed as "x" for the purpose of calculating summary statistics and comparing to normal ranges. These values will remain as "< x" or "> x" in the listings.

9.3 Important Protocol Deviations

Potential planned or unplanned protocol deviations noted during clinical monitoring will be documented by category (i.e., inclusion criteria, exclusion criteria, study drug, safety assessment, efficacy assessment, visit window, informed consent, prohibited medication, and other). All deviations will be reviewed, categorized, designated important or not important, and finalized prior to database lock. Important protocol deviations will be defined as those potentially impacting safety or efficacy assessments. Additional details of what will be considered important can be found in the Protocol Deviation Guidance document.

10.0 Interim Analyses

There are no formal interim analyses in the study. Tumor responses will be reviewed for the CAE population to make decisions per the Predictive Probability Design on whether a cohort should be stopped for lack of tumor response as detailed in Section 6.2.

11.0 Planned Analysis

PK sub-study patients will be excluded from any main study summaries and will be presented in PK sub-study specific summaries only. Screen Failures will be summarized in a Screen Failure table, but otherwise excluded from all tables and listings. Listings will include all relevant derived variables.

All data collected during this study will be displayed in data listings, unless otherwise specified. Data listings will be presented separately for enrolled patients in the main study and those in the PK sub-studies.

Descriptive statistics (mean, median, standard deviations [STD] or standard error, first quartile [Q1], third quartile [Q3], minimum and maximum values) for continuous variables will be presented. Mean and median will be presented to 1 decimal more than original data. STD will be presented to 2 decimals more than original data. Minimum and maximum values will match the decimal points in the original data. For categorical variables, summary measures will include the frequency and percentage (with 1 decimal place) of patients in each category.

Safety summaries will be presented for assessments on-treatment (as defined in Section 8.4) and will include patients from both the safety lead-in and phase 2 parts of the study. Efficacy summaries will be presented for assessments on-study (defined in Section 8.2) and will include patients receiving the recommended phase 2 dose (120mg QD) only. All tables will be presented by treatment arm and strata.

Unless otherwise noted, missing data will not be imputed or carried forward.

All data summaries and tabulations will be prepared with SAS® v9.4 or higher.

11.1 Analysis for Main Study (non PK sub-studies)

11.1.1 Patient Disposition

The number and percentage of patients in each analysis population will be presented, along with the patients who withdrew from the study, discontinued Nivolumab or the investigational study drug, with the breakdown of corresponding withdrawal/discontinuation reasons. The number and percentage of deaths, including cause of death and the duration on treatment (time from first dose date to end of treatment, in months) will also be presented.

The number of patients enrolled by site and overall will be presented.

Disposition will be summarized descriptively by treatment arm and strata.

11.1.2 Important Protocol Deviations

Important protocol deviations (see definition in Section 9.3) for patients in the Enrolled Population will be listed only. A listing of patients who enroll with inclusion or exclusion criteria exceptions will also be provided.

11.1.3 Demographic and Baseline Characteristics

Demographic and baseline data will be summarized descriptively using the Safety population.

Demographic variables to be summarized include sex, reproductive status for female, race, ethnicity, age (years), baseline weight (kg), baseline height (m), baseline Eastern Cooperative Oncology Group (ECOG) status, and smoking history.

Primary disease history will summarize Histology (Adenocarcinoma, Large Cell Carcinoma, and Other), Current Stage (Locally Advanced, Metastatic), the time since diagnosis and the time since metastatic diagnosis.

Prior primary disease treatment (systemic therapies including platinum therapies and checkpoint inhibitors, radiotherapy, and surgery) will summarize the following:

- Prior Systemic Therapy - Platinum Agent Received (Cisplatin, Carboplatin, Other)
- Prior Checkpoint Inhibitor - (Nivolumab, Pembrolizumab, Durvalumab, Atezolizumab, Avelumab, Other)
- Best Response to Prior Checkpoint Inhibitor
- Prior Regimens (Number of Regimens and Type)
- Prior Radiotherapy - Type (Adjuvant, Palliative)
- Prior Surgery - Location (Lung, Liver, Lymph Node, Adrenal, Brain, Other)

Demographic, primary disease history, and prior primary disease treatment data will also be listed by patient.

11.1.4 Prior and Concomitant Medications and Procedures

Concomitant medications will be coded using World Health Organization (WHO) Drug Enhanced (Version: March 2016).

Prior and concomitant medications will be tabulated separately for the Safety Population by Anatomical Therapeutic Chemical (ATC) Classification (2nd Level) and preferred drug name using counts and percentages. The number and percentage of patients using at least one medication will be summarized.

Prior and concomitant medications along with concomitant procedures will be listed.

11.1.5 Medical History

Medical history will be tabulated using the Safety Population by system organ class (SOC) and preferred term (PT). Medical history will also be listed by patient.

Signs and symptoms of the patient's cancer diagnosis and/or comorbidities present prior to Day 1 of study treatment dosing are recorded in the CRF as medical history.

11.1.6 Efficacy Analyses

All efficacy analyses will be presented by planned treatment arm and strata, as described in Section 8.5.

The 120mg dose of Sitravatinib was given to patients in both the lead-in phase and in phase 2, hence the efficacy results will be presented for all subjects receiving this dose combined across phases.

If a treatment arm includes patients only in the lead-in phase and not in phase 2, then only listings will be presented for this treatment arm. If a treatment arm was not initiated, then no efficacy results will be presented.

11.1.6.1 Primary Variable

Descriptive statistics for ORR and BOR (CR, PR, SD, PD and NE) based on the response assessments by the Investigator will be presented by treatment arm and strata. Exact 95% Clopper-Pearson CIs for ORR will also be presented.

An exact test for single proportion (one-sided α=0.025) will be performed to test H_0: ORR ≤5% against H_1: ORR >5% for CIT-experienced and PD-L1 no/low or CIT naïve for each treatment arm which proceeds to Phase 2 and test H_0: ORR ≤27% against H_1: ORR >27% for PD-L1 high of CIT naïve.

Patients who cannot be assessed for response will be counted as non-responders.

The primary analysis will be conducted using the FAS with supportive analyses presented using the CAE population.

11.1.6.2 Secondary Variables

DoR, CBR, and PFS will be based on the response assessments by the Investigator. Secondary analyses will be conducted using either the CAE population or the FAS as described within each variable section below.

11.1.6.2.1 Clinical Benefit Rate (CBR)

Descriptive statistics for CBR, confirmed CR, PR or SD based on the response assessments by the Investigator will be presented by strata and treatment arm using both the FAS and the CAE population. Exact 95% Clopper-Pearson CIs for CBR will also be presented.

11.1.6.2.2 Duration of Response (DoR)

DoR will be summarized descriptively using a subset of the CAE population (patients who have confirmed CR or PR), presenting Kaplan-Meier (KM) estimates for the median, 25th and 75th percentiles and their two sided 95% CIs (Brookmeyer and Crowley, 1982) where appropriate. In addition, minimum and maximum values will also be displayed.

DoR will be listed and KM plots will also be provided.

Censoring Rules for DoR

- Patients without documented PD will be censored at the date of the last evaluable tumor assessment prior to the start of the new therapy (if received any), unless they die within 122 days of last evaluable tumor assessment, in which case they will be assessed as having an event on the date of death.

11.1.6.2.3 Progression-Free Survival (PFS)

PFS will be summarized in the same manner as DoR, though conducted using the FAS. In addition, the PFS rate at 3, 6 and 9 months will be analyzed using KM methodology (Greenwood's formula, Kalbfleisch and Prentice, 1980).

Censoring Rules for PFS

- Event time will be censored on the date of first dose with duration of 1 day for;
    - No Disease Assessments Performed On-Study

      i.e. Patients lacking evaluation of disease after first study treatment, unless they die within 2 tumor assessments of baseline (on or prior to week 16, i.e. Cycle 5 Day 1 plus the 10 day window, which is Study Day 122]), then they will be treated as experiencing an event with date of death as the event date.
    - Patients with baseline or post-baseline assessments inadequate to apply RECIST v1.1 criteria.
- Patients without documented PD will be censored at the date of the last evaluable tumor assessment prior to the start of the new therapy (if received any), unless they die within 122 days of last evaluable tumor assessment, in which case they will be assessed as having an event on the date of death.

11.1.6.2.4 Overall Survival (OS)

OS will be summarized similarly to PFS. Additionally, the 1-year OS rate (proportion and 95% CI) will be analyzed using KM methodology (Greenwood's formula, Kalbfleisch and Prentice, 1980).

Censoring Rules for OS

For patients who are continuing the study at the time of an analysis, lost to follow-up, or who withdrew consent, the OS endpoint will be censored on the last date that patients were known to be alive. The date last known to be alive is derived from the CRF and may include but not limited to the latest visit date for patients ongoing in the study or the latest Date of Contact on the Long-Term Follow-up/Survival Status page, whichever occurs latest. For patients with no follow-up after the first dose of study drug, OS will be censored at the date of first dose.

11.1.6.2.5 Extent of Follow-Up

The median extent of follow-up with 95% CI will be calculated and presented in a dedicated table using a reverse KM approach (reversing the OS censoring).

11.1.7 Safety Analyses

All safety analyses will be summarized by actual treatment arm.

DLTs will be presented using the DLT Evaluable Population, all other safety parameters will be presented using the Safety Population.

11.1.7.1 Extent of Study Drug Exposure

Descriptive statistics will be provided separately for each study drug, for the duration of exposure (weeks) and the total number of cycles started. The number of doses administered, cumulative dose administered (mg), relative dose intensity and overall compliance will be presented for Sitravatinib only.

For Glesatinib and Sitravatinib, the number and percentage of patients will also be presented for patients with at least one dose reduced from the previous dose, and at least one dose interrupted, along with all associated reasons.

For Nivolumab the number and percentage of patients will also be presented for patients with at least one dose interrupted or delayed from the previous, and at least one infusion interrupted along with all associated reasons.

Information regarding patients' dosing regimens will be listed separately for each investigational study drug.

11.1.7.2 Treatment Emergent Adverse Events (TEAEs)

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) v19.0 dictionary by SOC, PT, and severity grade using NCI CTCAE v4.03.

An overall summary of TEAEs will be presented, with supporting tables summarizing TEAEs by SOC and PT, as well as PT only. Counts will be presented by patient rather than event and those experiencing multiple instances of the same event will be counted only once within each SOC or PT.

The following summaries will be presented by SOC and PT for the Sitravatinib plus Nivolumab treatment arm, using the Safety Population, unless otherwise specified.

- Any TEAEs
- Any DLTs (DLT Evaluable Population)
- Any Treatment-Related TEAEs
- Any Nivolumab-Related TEAEs
- Any Sitravatinib-Related TEAEs
- Any TEAE leading to dose reduction or interruption of either study drug
- Any Treatment-Related TEAE leading to dose reduction or interruption of either study drug
- Any TEAE leading to drug discontinuation of either study drug
- Any TEAE leading to Nivolumab discontinuation
- Any TEAE leading to Sitravatinib discontinuation
- Any Treatment-Related TEAE leading to drug discontinuation of either study drug
- Any Nivolumab-Related TEAE leading to Nivolumab discontinuation
- Any Sitravatinib-Related TEAE leading to Sitravatinib discontinuation
- Any TEAE leading to study discontinuation
- Any TEAEs by Maximum CTCAE Grade
- Any Treatment-Related TEAEs by Maximum CTCAE Grade
- Any Nivolumab-Related TEAEs by Maximum CTCAE Grade
- Any Sitravatiib-Related TEAEs by Maximum CTCAE Grade
- Any irAEs

- Any AESIs (if at least one AESI is identified)

For the Glesatinib and Nivolumab treatment arm, a single summary table by SOC and PT will be presented.

- Any Glesatinib-Related TEAEs

In addition to the SOC and PT summaries, the following summaries will also be presented by PT only for the Sitravatinib plus Nivolumab treatment arm

- Any TEAEs
- Any TEAEs by Maximum CTCAE Grade (Any Grade, Grade 3, Grade 4, Grade 5)
- Any Treatment-Related TEAEs by Maximum CTCAE Grade (Any Grade, Grade 3, Grade 4, Grade 5)
- Any Nivolumab-Related TEAEs by Maximum CTCAE Grade (Any Grade, Grade 3, Grade 4, Grade 5)
- Any Sitravatinib-Related TEAEs by Maximum CTCAE Grade (Any Grade, Grade 3, Grade 4, Grade 5)

All TEAEs will be listed, separate listings for irAEs and TEAEs leading to study drug discontinuation (TEAEs and related TEAEs) will also be presented.

11.1.7.3 Serious Adverse Events (SAEs) and Deaths

The following summaries of treatment emergent SAEs, including TEAEs that lead to death, will be presented by SOC and PT for the Sitravatinib plus Nivolumab treatment arm, using the Safety Population:

- Any Treatment-Emergent SAEs
- Any Treatment-Related Treatment-Emergent SAEs
- Any Nivolumab-Related Treatment-Emergent SAEs
- Any Sitravatinib-Related Treatment-Emergent SAEs
- Any TEAE with an outcome of death

In addition to the SOC and PT summaries, the following summaries will also be presented by PT only for the Sitravatinib plus Nivolumab treatment arm

- Any Treatment-Emergent SAEs
- Any Treatment-Related Treatment-Emergent SAEs

All treatment emergent SAEs and TEAEs with an outcome of death will be listed.

11.1.7.4 Laboratory Data

Laboratory data will be presented for hematology, chemistry, urinalysis and thyroid function tests (see Table 6 for a list of specific parameters under each category), by scheduled visit using the Safety Population for patients with at least 1 measurement for each parameter, regardless of whether or not a baseline assessment is present. Unscheduled visits will be included in any presentation of minimum, maximum or worst case summaries across all cycles.

All laboratory data will be summarized in International System (SI) units, with selected chemistry parameters repeated using British imperial units commonly used in the United States. The conversion factors from conventional units to SI units are documented in the Lab Loader Specification (v1.0 October 13th 2020) for this study.

Descriptive statistics will be provided for each parameter result and associated changes from baseline by cycle. Multiple measurements taken during a given visit for a patient will be represented by the most severe value for each parameter. Criteria for selecting the most severe value in these cases are described in the category specific sections below.

Shift tables for selected parameters will present shifts in CTCAE grades from baseline to each post-baseline scheduled visit, to the maximum post-baseline grade (including unscheduled visits), and to the last assessment.

All clinical laboratory results will be listed, with any laboratory values meeting NCI CTCAE Grade 3 or 4 criteria being listed separately.

CTCAE Coding of Laboratory Data

Grades are applied based only on the numeric SI value of the parameter assessed; clinical signs and symptoms are not considered. For example, Grade 4 hyperglycemia will be assigned based solely on the value of the glucose measurement, and acidosis will not be considered. Where categories are only distinguished by clinical signs or symptoms, the lowest of the possible grades will be assigned.

NCI CTCAE grades will be applied for the following lab parameters:

- Hematology: hemoglobin, WBC, lymphocyte, neutrophils, and platelets.
- Chemistry: ALT, albumin, alkaline phosphatase, AST, total bilirubin, calcium, creatinine, magnesium, potassium, sodium, uric acid.

Laboratory measurements that are within their institutional limits of normal and are not graded as 1-4, per the CTCAE, will be summarized as “Grade 0,” which is defined as normal.

Table 6:

Hematology Panel
• Hemoglobin [High or Low]
• Platelet Count
• White Blood Cell (WBC) Count
• Neutrophil Count
• Lymphocyte Count [High or Low]
• International Normalized Ratio (INR)
• Partial Thromboplastin Time (PTT)

Urinalysis (Dip Stick)
• Blood
• Protein

Thyroid Function Test
• Thyroid Stimulating Hormone (TSH)
• Free-T4

Chemistry Panel
• Alkaline Phosphatase
• ALT
• AST
• Total Bilirubin [IU]
• Direct Bilirubin [IU]
• Indirect Bilirubin [IU]
• Lipase
• Amylase
• Creatinine [IU]
• Blood Urea Nitrogen (BUN) [IU]
• Chloride [Low]
• Bicarbonate [CO^2] [Low]
• Sodium [High or Low]
• Potassium [High or Low]
• Glucose (Non-Fasted) [High or Low]
• Albumin [Low]
• Calcium [High or Low / IU]
• Magnesium
• Uric Acid

IU: Indicates Chemistry parameter that will be summarized twice, once in SI units and once in Imperial units.
Low: Indicates Chemistry parameter where most severe values are low.
High or Low Indicates parameter where most severe values can be in either direction.

11.1.7.4.1 Hematology

If a patient has multiple measurements taken during a given visit the most severe value for each hematology parameter. The most severe value will be determined using the following criteria;

Severity in One Direction (Either Low or High);

- If the values are all within the normal range, select the value closest to the upper or lower limit of the normal (dependent on which direction is considered severe)
- If at least one value is outside of the normal range, select the value furthest from the upper or lower limit will be selected (dependent on which direction is considered severe).
- In the event that this algorithm does not allow for determining the most severe (e.g. a tie), select the first chronological value.

Severity in Both Directions (Both Low and High);

- If the values are all within the normal range, select the value closest to the normal limit (in either direction)
- If at least one value is outside the normal range, select the value most distant from the normal limit (in either direction)

In the event that this algorithm does not allow for determining the most severe (e.g. a tie), select the first chronological value.

Low values are considered the most severe for all hematology parameters, unless otherwise noted in Section 8.4.6 and the notation $^{\text{High or Low}}$ within Table 6.

Shift tables will present shifts in CTCAE grades from baseline for the following hematology parameters;

- Hemoglobin (Anemia and Hemoglobin Increased),
- Neutrophils (Neutrophil Count Decreased),
- Platelets (Platelet Count Decreased)
- Lymphocyte Count (Lymphocyte Count Decreased and Lymphocyte Count Increased)

Patients who develop a ≥ Grade 3 toxicity will be also listed separately.

11.1.7.4.2 Chemistry

Selected chemistry parameters will be repeated using British imperial units commonly used in the US, refer to Section 8.4.6 and the notation $^{\text{IU}}$ within Table 6.

If a patient has multiple measurements taken during the visit for a patient will be represented by the most severe value for each chemistry parameter. The most severe value will be determined using the following criteria;

High values are considered the most severe for all chemistry parameters, unless otherwise noted in Section 8.4.6 and the notation $^{\text{Low}}$ or $^{\text{High or Low}}$ within Table 6. The most severe value will be determined using the same criteria described for Hematology parameters,

Shift tables will present shifts in CTCAE grades from baseline for the following selected chemistry parameters;

- AST (AST Increased),
- ALT (ALT Increased),
- Creatinine (Creatinine Increased),
- Sodium (both Hyponatremia and Hypernatremia),
- Potassium (both Hypokalemia and Hyperkalemia),
- Phosphate (Hypophosphatemia),
- Uric Acid (Hyperuricemia).

For parameters where separate grading criteria exists, all low values will be included in the Grade 0 group when summarizing high values as being most severe and vice versa (all high values will be included in the Grade 0 group when summarizing low values as being most severe).

Patients who develop a Grade ≥3 toxicity will be also listed separately.

11.1.7.4.3 Hy's Law

Hepatic function abnormality defined by an increase in AST and/or ALT to ≥ 3x ULN concurrent with an increase in total bilirubin to ≥ 2x ULN but without increase in alkaline phosphatase (i.e., alkaline phosphatase < 2x 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 is identified.

A set of evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) figures displaying patients who reach 3xULN for ALT or AST, plus 2x ULN for Total Bilirubin and thus, are at risk for a drug induced liver injury according to Hy's law will be presented for all patients. A listing of patients at risk will also be presented.

11.1.7.4.4 Urinalysis

Urinalysis results for the parameters blood and protein will be listed only.

11.1.7.4.5 Thyroid

Results for TSH and Free-T4 will be listed only.

11.1.7.5 Vital Signs

The following vital signs will be summarized: pulse rate (bpm), systolic blood pressure (SBP; mmHg), diastolic blood pressure (DBP; mmHg), respiration rate (breaths/min), body temperature (C), and weight (kg).

Vital signs and change from baseline will be summarized descriptively. All vital signs and change from baseline through the last Cycle will be summarized. In these tables, baseline will generally be the Cycle 1 Day 1 measurement for all comparisons. This will include a summary of the minimum and maximum values observed while the patient was on treatment and change from baseline to that observed value.

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.

Potentially clinically important (PCI) values will also be summarized based on the thresholds detail in the table below.

Vital Signs Parameter	PCI Thresholds
SBP	• ≥ 160 mmHg • ≥ 180 mmHg • ≥ 200 mmHg
DBP	• ≥ 100 mmHg • ≥ 120 mmHg
Weight	• ≥ 5% increase from baseline • ≥ 10% decrease from baseline

All vital signs including baseline ECOG performance status will be listed.

11.1.7.6 Physical Examinations, ECGs, and Other Observations Related to Safety

Physical Examination

Complete physical examinations will be conducted during screening and at the End of Treatment visit. Abbreviated physical examinations will be performed on Day 1 and Day 15 of all cycles. Any new abnormal physical exam findings will be collected as AEs. Physical Examination data will be listed for the Safety population.

Electrocardiogram

A summary of ECG parameters including heart rate (beats/min), QT interval (msec), QTcF (msec), PR (msec), QRS (msec) and RR interval (msec) and change from baseline will be presented for each planned visit as well as the minimum, maximum and last observation on treatment.

Where triplicates of ECG parameters are collected, the values will be averaged before use in any analysis.

In addition, listings and summaries will be generated for patients by Maximum ICH E14 Category for absolute value (<450 msec, ≥450 to ≤480, >480 to ≤500 msec and >500 msec) and change from baseline (≤30 msec, >30 to ≤60 msec and >60 msec). Patients with PR value >220 msec and change from baseline >25%, as well as patients with QRS >110 msec and change from baseline >25%, will also be summarized and presented in listings.

QTcF will be graded per CTCAE (v4.03). The grades are as follows:

- Grade 0: QTcF <450 msec
- Grade 1: QTcF 450 to 480 msec
- Grade 2: QTcF >480 to 500 msec
- Grade 3: QTcF >500 or increase from baseline >60 msec

A shift from baseline to worst CTCAE grade summary will also be presented.

A separate listing of the ECG results along with the overall interpretation will be presented.

Echocardiogram

Descriptive statistics of the observed values and changes from baseline will be presented for LVEF data from the echocardiogram or multigated acquisition (MUGA) scan at Screening, Cycle 3 Day 1 and end of treatment.

Additionally, patients who have at least one on-treatment decrease will be summarized using the following categories:

- decrease from baseline of ≥10% and absolute on-treatment value ≥40%,
- decrease from baseline of ≥10% and absolute on-treatment value <40%,
- decrease from baseline of ≥20% and absolute on-treatment value ≥40%,
- decrease from baseline of ≥20% and absolute on-treatment value <40%,

  where on-treatment is defined as the period of time after the first dose of study treatment and not more than 28 days after the last dose of study treatment and prior to the initiation of subsequent systemic anti-cancer therapy.

All echocardiogram results will be listed.

Pregnancy Test

For patients of childbearing potential, a serum or urine pregnancy test will be performed 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. Pregnancy testing data will be listed for the Safety Population.

Long Term Follow-up and Death

Long term follow-up, inclusive of survival status, follow-up anti-cancer therapies and causes of death will be presented in separate listings.

Biomarkers

[redacted]

11.2 Analysis for PK Sub-Studies

The two sub studies described in Appendix 5 and Appendix 6 (Food Effect Study) of the protocol were closed early, refer to Section 4.1.5 for details on this change from the protocol. The sub-study component of the CSR will now consist of only selected demographic and safety summaries, with a standalone PK analysis plan covering the details of any analysis and reporting of PK parameters and related concentration summaries.

All PK sub-study summaries falling within the scope of this SAP will be based on the PK sub-study population. Each summary table will be presented by strata and then by cohort, with 3 cohorts for the formulation study (one for each formulation type), one cohort for the food effect study (fed state) and an overall total across all 4 cohorts presented side by side.

The following selected analysis will be presented separately for each sub-study (formulation and food effect):

- Demographic Characteristics
- TEAEs by SOC and PT
- Treatment Related TEAEs by SOC and PT
- TEAEs by SOC, PT and Maximum CTCAE Grade
- Treatment Emergent SAEs by SOC and PT

All main study safety listings will be repeated for the PK sub-study patients.

12.0 Validation

PRA seeks to ensure the quality of the results provided for the study in the form of tables, figures and listings (TFLs), and the derived datasets used in their creation, through the following processes:

The entire set of TFLs will be checked for completeness and consistency prior to its delivery to the client by the lead analysis programmer, the lead statistician, and a senior level statistician, or above, who is not a member of the project team.

The PRA validation process will be repeated any time TFLs are redelivered using different data. Execution of this validation process will be documented through the study Table of Programs that will be provided to Mirati at study conclusion.

13.0 References

1. Ji 2013: Ji Y, Wang S-J. Modified Toxicity Probability Interval Design: A Safer and More Reliable Method than the 3 + 3 Design for Practical Phase I Trials. J Clin Oncol. 2013;31(14):1785-1791. doi:10.1200/JCO.2012.45.7903.

2. Lee 2008: Lee JJ, Liu DD. A predictive probability design for phase II cancer clinical trials. Clinical Trials 2008; 5: 93–106.

3. Brookmeyer, R and Crowley, J. A confidence interval for mean survival time. Biometrics, 1982, 38, 29-41.

4. Kalbfleisch, JD and Prentice, RL. The statistical analysis of time failure data. 1980, New York: John Wiley.

5. NCI Common Terminology Criteria for Adverse Events (CTCAE) data files:

   http://evs.nci.nih.gov/ftp1/CTCAE/About.html

6. U.S. Department of Health and Human Services, FDA 2005: Guidance for Industry E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

Appendix: Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BOR	Best Overall Response
BUN	Blood Urea Nitrogen
CAE	Clinical Activity Evaluable
CBR	Clinical Benefit Rate
CI	Confidence Interval
CIT	Checkpoint Inhibitor Therapy
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Toxicity Criteria for Adverse Events
ctDNA	Circulating Tumor Deoxyribonucleic Acid
DBP	Diastolic Blood Pressure
DLT	Dose Limiting Toxicity
DoR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eDISH	Evaluation of Drug-Induced Serious Hepatotoxicity
ICH	International Conference on Harmonisation
irAE	Immune-related Adverse Event
INR	International Normalized Ratio
KM	Kaplan-Meier
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MTD	Maximum Tolerated Dose
mTPI	Modified Toxicity Probability Interval
MUGA	Multigated Acquisition
NCI	National Cancer Institute

NE	Not Evaluable
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PCI	Potentially Clinically Important
PD	Progressive Disease
PD-L1	Programmed Cell Death Ligand 1
PFS	Progression-Free Survival
PK	Pharmacokinetic
PR	Partial Response
PT	Preferred Term
PTT	Partial Thromboplastin Time
Q1	First Quartile
Q3	Third Quartile
QTcF	Fridericia's corrected QT Interval
QxW	Every x Weeks
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Stable Disease
SI	International System
SOC	System Organ Class
STD	Standard Deviation
TEAE	Treatment-emergent Adverse Event
TFL	Tables, Figures, and Listings
TSH	Thyroid-stimulating Hormone
WBC	White Blood Cell
WHO	World Health Organization