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Statistical Analysis Plan

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1. Approvals

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2. 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 516-002.

3. 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 statistical analysis plan will be described in the Clinical Study Report (CSR).

4. Introduction

This SAP describes the statistical methods to be used during the analysis and reporting of data collected under Mirati Therapeutics, Inc. Protocol 516-002.

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 dated 16 May 2018 and CRF version 1.0 dated 29 August 2018. Any further changes to the protocol or CRF may necessitate updates to the SAP.

The SAP will be developed in two stages. An initial SAP will be finalized based on the current protocol and CRF, so that programming may be created. Changes following approval of the SAP will be tracked in the SAP Change Log. A final version of the SAP, known as the amended SAP, will be issued prior to database lock.

Each version of the SAP requires approval by the project manager and the sponsor.

5. Study Objectives and Endpoints

5.1. Objectives

5.1.1. Primary Objective

- To evaluate the preoperative clinical activity of the combination of sitravatinib and nivolumab in patients with locally-advanced clear-cell renal cell carcinoma (ccRCC) undergoing nephrectomy.

5.1.2. Secondary Objectives

- To evaluate the safety and tolerability of the combination regimen in the selected population.
- To characterize the baseline tumor-related immune profile in patients with RCC.
- To determine the immune effects of sitravatinib and the combination regimen in patients with ccRCC.
- To evaluate the pharmacokinetics (PK) of sitravatinib administered alone and in combination with nivolumab in patients with ccRCC.

- To characterize the time to surgery.
- To evaluate secondary efficacy endpoints with the combination regimen in the selected population.

5.1.3. Exploratory Objectives

- To evaluate changes in gene expression and the T-cell repertoire in response to therapy in patients with ccRCC.

5.2. Endpoints

5.2.1. Primary Endpoint

Percentage of patients achieving a point in time objective response (either CR or PR) prior to surgery.

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.
- Descriptive characterization of immune cell populations in the tumor and/or peripheral blood at baseline.
- Temporal changes in PD-L1 expression, selected cytokines and immune cell populations in the tumor and/or peripheral blood (including myeloid-derived suppressor cells [MDSCs], regulatory T-cells [Tregs], CD4+ [helper] and CD8+ [cytotoxic] T-cells, and the ratio of Type1:Type 2 tumor-associated macrophages).
- Blood plasma concentration of sitravatinib.
- Time-to-surgery.
- Disease free-survival (DFS).

5.2.3. Exploratory Endpoints

- Gene expression and T-cell receptor sequencing.

6. Study Design

Study 516-002 is an open-label, non-randomized, preoperative window of opportunity Phase 2 study of sitravatinib and nivolumab in the neoadjuvant setting for the treatment of patients with locally-advanced clear cell renal cell carcinoma (ccRCC) undergoing nephrectomy. The study will enroll approximately 25 subjects with imaging results consistent with a clinical diagnosis of locally-advanced renal cancer in order to identify and treat with the study drug treatment 18 clinical activity evaluable patients with ccRCC. Study drug treatment will be conducted in 2 sequential preoperative treatment segments. During the first segment, patients will receive single-agent sitravatinib for 2 weeks, followed by a renal biopsy. Patients will then begin the second segment, consisting of combination treatment with sitravatinib and nivolumab for at least 4 weeks (and up to a maximum of 6 weeks to allow for flexibility with the scheduling of the planned nephrectomy). This segment will be followed by planned surgical resection by way of standard-of-care partial or radical nephrectomy. Patients will be followed for survival.

The primary objective is to evaluate the clinical activity of the combination regimen using percentage of patients with ccRCC achieving a point in time objective response (either CR or PR) prior to surgery with the combination treatment of sitravatinib and nivolumab. Objective responses will be assessed in accordance with RECIST 1.1. Secondary objectives include evaluation of safety and determination of

immune effects of the combination treatment, along with pharmacokinetics (PK) of sitravatinib. The Schedule of Assessments to be performed in the study is presented in Table 1. The schedule for collection of PK/Pharmacodynamics and ECG assessment time points are presented in Table 2.

Further detail on sample collection and analyses are presented in Section 7.3 of the protocol and the Study Laboratory Manual. The study will collect blood and tumor tissue collections as described in the Schedule of Assessments (Table 1) depicted and the study schema in Figure 1. Protocol guidance of special interest is listed below.

- Freshly biopsied tumor tissue collection at pre-treatment is required for study drug treatment. Similarly, the on-treatment mid-study tumor biopsy on D14 is highly desirable for all treated patients. Archival samples cannot be submitted in lieu of pre-treatment samples. All attempts should be made to biopsy the same lesion on the mid-study biopsy as the initial biopsy.
- Tumor gene expression in freshly biopsied tumor samples will be determined using next generation sequencing performed by a central laboratory. For patients in whom tumor tissue has previously been tested using next generation sequencing, presence of specific tumor gene mutations and estimation of total mutation burden will be collected in the case report form (CRF).

Table 1: Schedule of Assessments

Study Assessments	Screening	Initial Biopsy[1]	Neoadjuvant Tx (6-8[2] wks)					Preop Rebaseline	Surgery	EOS/ Withdrawal[4]	Long-term Follow-Up
	D-28 to Initial Biopsy	D-4 (±3)	D1	D14[3] (±1)	D15 (± 2)	D29 (±2)	D43[2] (±2)	≤3 dys of Surgery			
Informed Consent[5]	X										
Collection of Tumor Tissue[6]		X		X					X		
Medical History, Disease History, Prior Therapy	X										
Physical Exam[7] including Vital Signs & ECOG PS	X									X	
Abbreviated Physical Exam[8] including Vital Signs			X		X	X	(X)	X			
Hematology and Serum Chemistry[9,10]	X	X	X		X	X	(X)	X		X	
Coagulation and Urinalysis[9,10]	X		As clinically indicated					Coagulation only	As clinically indicated		
Thyroid Function Test[9,10]	X							X		X	
Pharmacokinetic, Pharmacodynamic, and Baseline ctDNA Blood Samples, and Triplicate 12-Lead ECG[11]	See Table 2		See Table 2								
Single 12-Lead ECG[11]	X	As clinically indicated								X	
Echocardiogram	X					X		X			
Disease Assessment[12]	X							X			
Pregnancy Test[13]	X	As clinically indicated									

Table 1: Schedule of Assessments (Continued)

Study Assessments	Screening	Initial Biopsy[1]	Neoadjuvant Tx (6-8[2] wks)					Preop Rebaseline	Surgery	EOS/ Withdrawal[4]	Long-term Follow-Up
	D-28 to Initial Biopsy	D-4 (±3)	D1	D14[3] (±1)	D15 (± 2)	D29 (±2)	D43[2] (±2)	≤3 dys of Surgery			
Sitravatinib Dispensing and/or Reconciliation			X			X		Preop hold for 2 dys from Surgery[16]	Surgery Hold		
Nivolumab Administration					X	X	(X)				
AEs[14] and Concomitant Medications	SAEs only	Throughout									
Long-Term Follow-Up[15]											X

1. On the Initial Biopsy Visit, laboratory blood assessments completed in the previous week do not need to be repeated. The Initial Biopsy will preferably be scheduled for D-4 (±3); however, to allow flexibility for logistical reasons, this period can include up to 2 weeks from D1 (including D-14).
2. Neoadjuvant therapy will be administered for at least 6 weeks (unless treatment discontinuation is warranted), and up to a maximum of 8 weeks, to allow for flexibility with the scheduling of the nephrectomy (surgery). Consequently, nivolumab will be administered as neoadjuvant therapy for at least 2 injections, and up to a maximum of 3 injections. The third injection will only be administered if the subject's planned day of Surgery is at least one week after D43 and further treatment is not contraindicated [e.g., interruptions for adverse events (AEs)].
3. D14 visit (±1), which has for purpose the mid-study biopsy, must occur prior to first nivolumab injection on D15 (±2).
4. End of Study (EOS)/Withdrawal: Laboratory blood assessments completed in the previous 4 weeks do not need to be repeated. EOS visit must occur at least 28 days after last dose of study drug or surgery, whichever occurs last.
5. Informed Consent: May be performed within 28 days prior to the first dose of sitravatinib therapy on D1 and must be completed prior to initiation of any study specific assessments.
6. Collection of Tumor Tissue: Tumor tissue will be collected from initial and mid-study biopsies and surgical sample. Fresh tumor biopsies are to be collected on study; archival tissue will not be accepted as an alternative. The tumor biopsy collected on the Initial Biopsy Visit will confirm the histology of the renal cancer. Tumor tissue will be collected and used to assess immune effects through tissue biomarkers prior to and during and following treatment. Parameters may include, but are not limited to, quantification of tissue immune cell populations by flow cytometry including T-cell subpopulations (CD8+, CD8+/Ki67+ and regulatory T-cells [Tregs]), natural killer (NK) cells, myeloid-derived suppressor cells (MDSCs) and macrophages; immunohistochemistry and/or immunofluorescence for assessment of PD L1 status and characterization of immune cell populations; tumor gene expression analysis; and DNA sequencing to assess T-cell clonality. In addition, next generation sequencing (NGS) analyses for tumor mutations and tumor mutation burden may be assessed using tissue from the surgical sample.
7. Physical Examinations: A complete physical examination required at Screening and EOS/Withdrawal only. Height will be recorded at screening only. All other evaluations will be symptom-directed, abbreviated evaluations. Vital signs include weight, temperature, blood pressure, and pulse rate to be assessed prior to dosing as indicated.
8. Abbreviated Physical Exam includes vital signs (weight, temperature, blood pressure, and pulse rate to be assessed prior to dosing as indicated) and symptom-directed evaluation.

9. Selected D1 Assessments: Repeat assessment not required if screening assessment performed within 7 days before the first dose.
10. Safety Laboratory Assessments: Hematology, coagulation, chemistry, thyroid function and urinalysis evaluations will be performed by local laboratories.
11. Pharmacokinetic (PK) Blood Samples: Blood samples for PK measurements will be collected as outlined in Table 2.
    Pharmacodynamic Blood Samples: Blood samples will be collected for the assessment of immune effects through circulating biomarkers prior to and during and following treatment as outlined in Table 2. Parameters may include, but are not limited to, quantification of circulating immune cell populations by flow cytometry including T-cell subpopulations (CD4+, CD4+/Ki67+, CD8+, CD8+/Ki67+ and Tregs), NK cells, and MDSCs; blood levels of selected cytokines and chemokines including IFN-γ, IL-1ß, IL-6, IL-8, IL-12, IL-18 and CXCL10 (IP-10); and DNA sequencing to assess T-cell clonality.
    Baseline ctDNA Blood Samples: NGS analyses for tumor mutations and tumor mutation burden may be assessed at baseline using ctDNA as outlined in Table 2.
    12-Lead ECGs: Triplicate ECGs will accompany PK sampling as described in Table 2. In addition, single ECGs are to be performed as clinically indicated. Assessments will include an evaluation of RR, QT, and QTc intervals. In case RR interval cannot be machine-read, ventricular heart rate should be reported instead.
12. Disease Assessments will occur at the following times:
    a) during screening (within 28 days of D1),
    b) preoperatively (within 1 week prior to the surgery).
    At screening/baseline, assessments are to include evaluation of any superficial lesions, Computed Tomography Scan (CT) with contrast or X-ray (radiography) of the chest, Magnetic Resonance Imaging (MRI) with and without gadolinium or CT abdomen, as well as, if clinically indicated, MRI of the brain and a chest x-ray. The subsequent disease assessment should include all sites of disease identified at baseline or suspected to have developed. More detailed guidance on exceptional circumstances is provided in the protocol.
13. Pregnancy Test: If the patient is a woman of childbearing potential, negative serum or urine pregnancy test performed by the local laboratory at screening will be required. The informed consent process must include discussion of the risks associated with pregnancy and adequate contraception methods. Additional pregnancy testing may be necessary if required by local practices or regulations, or if potential pregnancy is suspected.
14. Adverse Events: SAEs (serious adverse events) will be reported from the time of informed consent until at least 28 days after the last administration of sitravatinib or nivolumab. Ongoing SAEs should be followed until resolution or stabilization to a chronic condition. AEs will be reported from the day of the initial biopsy until at least 28 days after last dose of study drug.
15. Long Term Follow-up: Survival status will be collected by review of medical records or telephone contact with the patient or treating healthcare professional approximately every 6 months from EOS visit for up to 3 years or more until death, disease recurrence or loss to follow-up. Disease recurrence will be based on imaging assessments performed off study per standard of care after nephrectomy.
16. 2-day preoperative hold such that the last dose of any drug is administered a minimum of 72 hours prior to surgery.

Table 2: Schedule of Pharmacokinetic, Pharmacodynamic, Baseline ctDNA, and Triplicate ECG Assessments

	Screening	Neoadjuvant Tx						Preop Rebaseline
	D-28 to Initial Biopsy	D1			D15 (± 2)	D29 (± 2)	D43 (± 2)	≤ 3 dys of Surgery
Collection Time and Allowable Window		**Pre-dose (-0.5-0 hour)**	**30 min (± 10 min)**	**4 hour (2-6 hour)**	**Pre-dose (-2-0 hour)**	**Pre-dose (-2-0 hour)**	**Pre-dose (-2-0 hour)**	
PK Blood Samples[1,2,3]		X	X	X	X		X (whichever visit occurs first)	
Flow Cytometry Blood Samples[3,4]	X >2 dys from D1	X			X	X	X (whichever visit occurs first)	
Protein and Cytokine Biomarkers Blood Samples[3,4]		X			X	X	X (whichever visit occurs first)	
TCR Sequencing Blood Samples[3,4]		X						X
Baseline ctDNA Blood Samples[4,5]	X							
Triplicate ECG[6]		X	X		X			

1. 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 sitravatinib.
2. Scheduled vital signs and triplicate ECGs precede PK sample collection in all cases. Sitravatinib dosing and sampling should precede nivolumab infusion.
3. Pharmacokinetic, pharmacodynamic, and baseline ctDNA blood samples should be collected as detailed in the study Lab Manual and in the study kit.
4. Blood for Pharmacodynamics: Immune effects will be evaluated through circulating prior to and during and following treatment. Blood samples will be collected for the assessment of parameters that may include, but are not limited to, quantification of circulating immune cell populations by flow cytometry including T-cell subpopulations (CD4+, CD4+/Ki67+, CD8+, CD8+/Ki67+ and Tregs), NK cells, and MDSCs; blood levels of selected cytokines and chemokines including IFN-γ, IL-1ß, IL-6, IL-8, IL-12, IL-18 and CXCL10 (IP-10); and DNA sequencing to assess T-cell clonality.
5. Baseline ctDNA Blood Samples: NGS analyses for tumor mutations and tumor mutation burden may be assessed at baseline using ctDNA.
6. ECGs should be taken in triplicate, each reading approximately 2 minutes apart. On D1 only, two sets of triplicate ECGs should be done within 1 hour prior to dosing (e.g., at 30-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.
   - Example for D1 pre-dose ECG/PK assessments: ~ -1.0 hour (Triplicate ECGs); ~ -30 minutes (Triplicate ECGs); ~ -15 minutes (Vitals/PK).
   - Example for all other pre-dose ECG/PK assessments: ~ -30 minutes (Triplicate ECGs); ~ -15 minutes (Vitals/PK).

Assessments will include evaluation of RR, QT and QTc intervals. In case RR interval cannot be machine-read, ventricular heart rate should be reported instead.

6.1. Prior to Start of Treatment

All enrolled patients will have met all entry criteria and have completed baseline procedures including disease assessments and blood collection for baseline immune characteristics and scheduled to undergo an initial diagnostic tumor biopsy of their renal lesion. Patients with a histology other than ccRCC will proceed to their End of Study (EOS) visit following the histology results, with no treatment with study drugs. Subjects with a clear cell histology will proceed to the study drug treatment which will be conducted in 2 sequential preoperative treatment segments as described in the following sections.

6.2. Segment 1

The first segment of treatment period will consist of a 2-week treatment with single-agent sitravatinib. Sitravatinib will be administered at a dose of 120 mg orally QD, on a continuous daily dosing regimen. After completion of the 2-week dosing period, patients will undergo a renal biopsy.

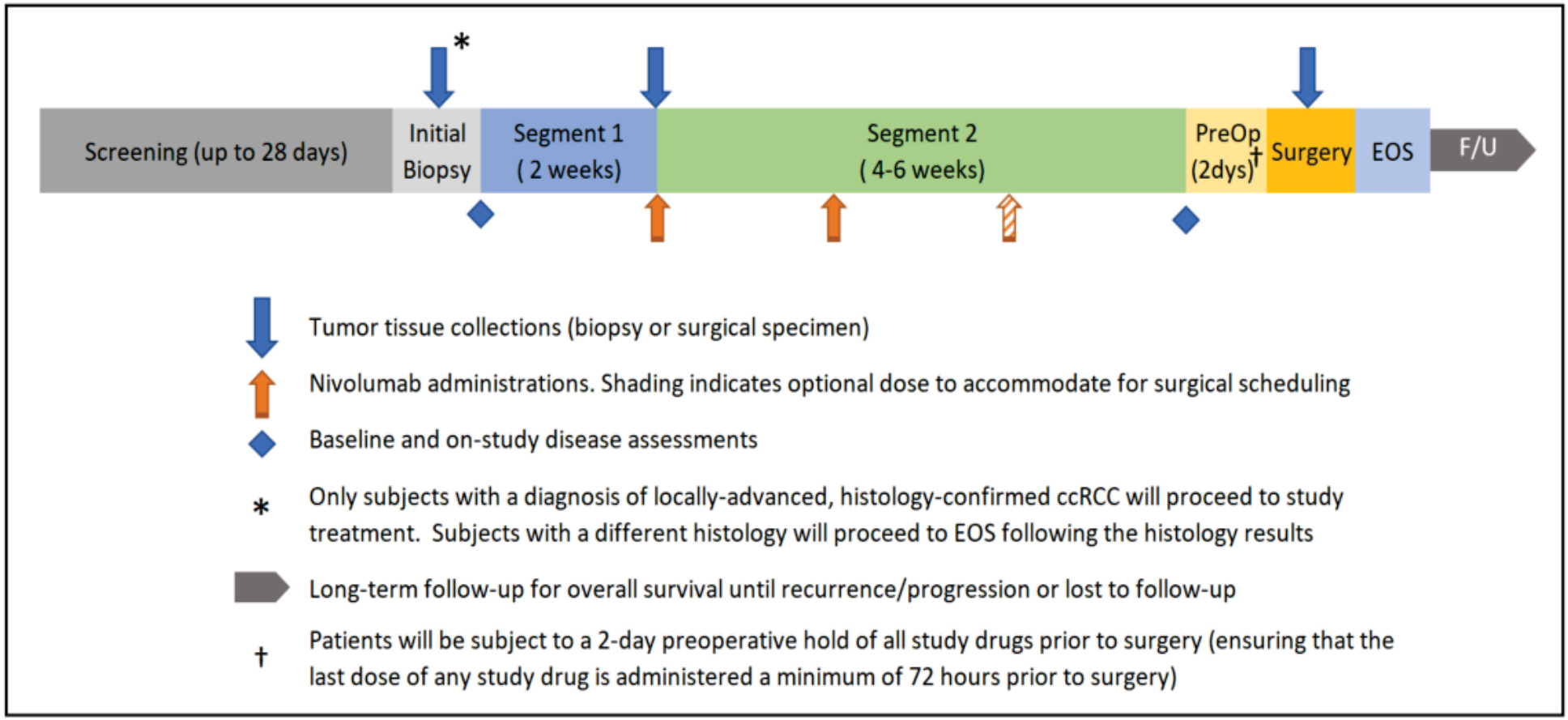
6.3. Segment 2

The second segment of treatment period will consist of a combination treatment with sitravatinib and nivolumab for at least 4 weeks (and up to a maximum of 6 weeks to allow for flexibility with the scheduling of the nephrectomy). Sitravatinib will be administered at a dose of 120 mg orally daily, on a continuous daily dosing regimen for this entire segment. Nivolumab will be administered, in accordance with approved labeling, by IV infusion, 240 mg every Q2W (namely, on D15, D29, and potentially D43). Patients will receive the nivolumab injection on D43 only if their surgery is expected to occur more than a week from that date. Patients will be subject to a 2-day preoperative hold of all study drugs prior to surgery (such that the last dose of any drug is administered a minimum of 72 hours prior to surgery).

6.4. Surgery, EOS and Follow-up

After completion of neoadjuvant therapy, patients will undergo planned nephrectomy. Patients will have their EOS visit following surgery, with no further study drug administration. Patients will be followed for disease-free survival for up to 3 years or more until either death, disease recurrence or loss to follow-up.

Figure 1: Study Schema



6.5. Sitravatinib Dose De-escalation

Based on available safety and pharmacokinetic data from an ongoing Phase 1b trial in patients with various solid tumors and an ongoing Phase 2 trial in combination with nivolumab in patients with NSCLC, the starting dose and regimen recommended is 120 mg sitravatinib administered daily. If unacceptable toxicity is observed, the starting dose may be decreased during the study. Starting doses in the event of dose de-escalation will be clarified in the amended SAP as necessary.

The Modified Toxicity Probability Interval (mTPI) method (Ji-2010) will be used to set rules on a dose de-escalation plan to monitor and limit toxicity of the combination regimen in the neoadjuvant setting. The first assessment will occur after the first 6 patients have completed 3 weeks on therapy, or earlier if 2 or more patients with toxicity are suspected. Subsequent assessments will occur at intervals that include up to 6 additional patients completing the observation period. Assuming a maximum toxicity level of no more than 20% at the tolerated dose, the dose will be decreased if more than 2 patients with toxicities are observed in the first 6 patients (Refer to Appendix 4 of the protocol for the dose de-escalation table). For the purposes of decision making for dose de-escalation, patients with the following treatment-related adverse events will be used to determine the number of patients having toxicity:

1. Non-hematologic Grade 4 adverse event.
2. Non-hematologic Grade 3 adverse event with the following exceptions:
    a. Grade 3 nausea, vomiting or diarrhea that is manageable with supportive care and persists for ≤ 72 hours;
    b. Grade 3 electrolyte abnormality that is not clinically complicated and resolves spontaneously or with conventional medical treatment within 72 hours;
    c. Grade 3 fatigue that persists for ≤ 8 days;
    d. Grade 3 amylase or lipase elevation that is not associated with symptoms or clinical manifestations of pancreatitis.
3. Surgical delay of greater than 2 weeks and due to toxicity.

Study drug toxicities and dose de-escalations that occur during the study will be recorded and documented by the sponsor. In the proposed plan, there is no dose escalation, and surgical delay will be assessed only for those patients who have already undergone surgery.

6.6. Hypothesis and Sample Size Considerations

With currently available treatments, the percentage of patients with a point in time objective response prior to surgery is assumed to be 5% (p0); thus, this rate is considered uninteresting. The target percentage of patients with a point in time objective response prior to surgery using sitravatinib and nivolumab in this study is assumed to be 30% (p1). Controlling for a Type 1 error (α) of 0.05, and using an exact test (two-sided), with 18 clinical activity evaluable patients, we have 80% power to rule out a percentage of patients with a point in time objective response prior to surgery of 5% assuming percentage of patients with a point in time objective response prior to surgery of 30%.

Assuming a non-evaluable rate between 25%-30% from enrolled patients to clinical activity evaluable patients, the study will enroll approximately 25 patients in order to get 18 clinical activity evaluable patients. Additional subjects may be enrolled for a total of 12 subjects with complete tumor tissue collection (collected from initial and mid-study biopsies and surgical sample).

6.7. Randomization

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

7. Analysis Populations

7.1. Screened Population

The Screened population is defined as all patients who sign an informed consent for the study. Screen failure patients and disposition summaries will be displayed using the Screened Population. .

7.2. Enrolled Population

The Enrolled population is defined as all patients who sign an informed consent and meet inclusion and exclusion criteria. Percentages in the disposition summaries will use the Enrolled Population as the denominator.

7.3. Clinical Activity Evaluable Population

The Clinical Activity Evaluable population will include patients who 1) have measurable disease (per RECIST 1.1) at baseline, 2) receive at least one dose of both sitravatinib and nivolumab, 3) have their on-study disease assessment prior to surgery, and 4) undergo surgery and are deemed disease-free (i.e. non-metastatic) after surgery.

This population will be used to present tumor responses.

7.4. Safety Population

The Safety population is defined as all patients who received at least 1 dose of either sitravatinib or nivolumab. The Safety population will be used for all safety analyses including serious adverse events (SAE) summaries.

7.5. Pharmacokinetic Evaluable Population

The Pharmacokinetic Evaluable population will consist of all patients who received treatment with sitravatinib and have sufficient concentration-time data to permit calculation of PK parameters for sitravatinib. For patients who are 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. Details of this analysis will be provided in the PKAP.

7.6. Pharmacodynamic Evaluable Population

The Pharmacodynamic Evaluable population will consist of all patients who receive at least 1 dose of either sitravatinib or nivolumab for whom sufficient pharmacodynamic data are available. Details of this analysis will be provided in the PDAP.

8. Endpoint Definitions

The term “baseline” is defined as the last pre-dose assessment, (includes screening and Study Day 1 pre-dose assessment which would represent a 29-day window). Unscheduled visits assessments will be considered for baseline. If assessment time is missing and there is no way to determine if the assessment occurred before or after study drug administration, Study Day 1 assessments will be considered for baseline.

8.1. Efficacy Variables

With regard to efficacy endpoints, the term “on-study” includes the period from signing of the informed consent until End of Study evaluation.

For the investigator assessment, the date of response or progression will be determined using the latest Date of Assessment recorded among the radiologic modalities included for the applicable Time Point Assessment.

8.1.1. Percentage of Patients Achieving a Point-in-time Objective Response Prior to Surgery

- Single point in time objective response to treatment at the Preoperative Rebaseline visit will be categorized in accordance with RECIST 1.1. The primary endpoint of this study is percentage of patients with ccRCC achieving a point in time objective response (either CR or PR) prior to surgery with the combination treatment of sitravatinib and nivolumab.
- Additionally, information regarding pathologic complete response (pCR) will be collected in the CRF and will be descriptively summarized. The determination of pCR to detect residual disease in kidney and regional lymph nodes will be based on the pathology examination of the surgical sample. pCR is defined as the absence of residual invasive disease on evaluation of the complete resected renal specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy.

8.1.2. Disease-Free Survival (DFS)

DFS is defined as the time from date of surgery to disease recurrence or death whichever occurs first. Disease recurrence will be based on imaging assessments performed off study per standard of care after nephrectomy. After sufficient data for the primary endpoint is collected in this study, the electronic study database may be locked, and the collection of the long-term survival status may be recorded through a different mechanism (rather than using the electronic database) at the site.

DFS (in months) will be calculated as (first event date – surgery date +1)/30.4375.

In cases of staggered surgeries, the surgery date should reflect the latest surgical date in the clinical database.

8.1.3. Time-to-Surgery

Time-to-surgery is defined as the number of calendar days between study Day 1 and the planned nephrectomy. Only subjects who complete treatment and undergo on-study surgery will be included in this analysis.

In cases of staggered surgeries, the surgery date should reflect the earliest surgical date in the clinical database.

In addition, delays in days between planned surgery date (at time of study treatment initiation) and actual surgery date will be described using descriptive statistics.

8.2. Study Drug Exposure Variables

8.2.1. Study Treatment Duration

Study treatment duration (weeks) is defined as [(the last dose date – the first dose date +1) / 7].

8.2.2. Total Number of Injections of Nivolumab Received

Total number of injections of nivolumab 240 mg received is defined as the cumulative number of injections of nivolumab received at the 240 mg dose.

8.2.3. Days on sitravatinib

Days on study drug is defined as the total number of days patient received sitravatinib, after subtracting for interruptions or drug missed, that is, the [(latest Stop Date - the earliest Start Date captured on the Sitravatinib Administration CRF page) – number of days with 0 mg dose + 1] for sitravatinib.

8.2.4. Cumulative Dose Received

- Cumulative dose received for nivolumab (mg) is defined as the total amount of the study drug a patient receives during the study as recorded on the Nivolumab Administration CRF forms. Nivolumab is planned to be administered as a 240 mg intravenous infusion over 30 minutes every 2 weeks only in Segment 2 (starting from Day 15 [±2]). Dose modifications should be accounted for in the cumulative dose received calculations.
- Cumulative dose received for sitravatinib (mg) is defined as the total amount of the study drug a patient receives during the study, that is, Sum of [(Stop date – Start date + 1) * Total Dose (mg per administration) * Dose Frequency] as recorded on the Sitravatinib Administration CRF forms. Dose modifications should be accounted for in the cumulative dose received calculations.

8.2.5. Dose Intensity

- Absolute dose intensity (mg/day) is calculated as cumulative dose received (mg) / Treatment duration (days), including dose decreases and interruptions as per physician's decision. Absolute dose intensity should only apply to sitravatinib.
- Relative dose intensity should apply to both sitravatinib and nivolumab and is 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, which does not take into account dose reduction or interruption.
    - For nivolumab: [total dose administered (mg)] / [rounded, planned total dose (mg)] * 100, where the rounded, planned total dose is:
        - 240 mg times (last nivolumab dose date - first nivolumab dose date + 14) divided by 14. Then round the number to the nearest multiple of 240.
          For example, if the first dose date is 2019-01-01 and last dose date is 2019-01-17, the planned total dose is 240 mg * (16+14) / 14 = 514.29 mg. And the rounded, planned total dose is 480 mg.
- Compliance is calculated as cumulative dose received (mg) / cumulative planned dose (mg, including dose reduction and interruptions due to AE). Compliance should only apply to sitravatinib.

8.3. Safety Variables

Adverse events (AEs) and laboratory values will be graded according to the NCI CTCAE Version 5.0.

With regards to adverse events, the term "on-study" includes the period from the first dose of study treatment until at least 28 days after the last dose of study treatment or surgery, whichever occurs last. AEs and laboratory values will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

8.3.1. Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 21.0 or higher). Non-serious AEs will be reported from the day of first dose of study treatment until at least 28 days after last administration of study dug treatment or surgery, whichever occurs last. 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 or surgery, whichever occurs last.

8.3.1.1. Baseline Signs and Symptoms

- 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.

8.3.1.2. Treatment-Emergent AEs (TEAEs)

- TEAEs are AEs that begin on or after Day 1 of study treatment and prior to 28 days after last dose of study drug or surgery, whichever occurs last, and prior to the initiation of subsequent systemic anti-cancer therapy. Baseline signs and symptoms that change attribution or severity during the on-study period are TEAEs. Any ongoing TEAEs that changes in attribution or severity is captured as a new AE. All AEs will be coded according to the MedDRA Version 21.0 dictionary by SOC, PT, and severity grade using NCI CTCAE Version 5.0.

8.3.1.3. 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. Preferred terms (PTs) of AESI will be identified by sponsor's medical director from potential Standardised MedDRA Queries (SMQs).

8.3.1.4. 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 on the adverse events CRF page.

8.3.2. Physical Examinations

A physical examination including all major body systems is mandated at Screening and End of Study (EOS) Visits only. During study treatment, symptom-directed physical examinations are performed.

8.3.3. Vital Signs

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

8.3.4. Clinical Laboratory Assessments

Clinical laboratory parameters to be collected routinely on-study (i.e. from signing of the informed consent until End of Study evaluation) are listed in Table 6 below.

Table 6: 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
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	Albumin
	Total calcium
Thyroid Function Test	Magnesium
Thyroid stimulating hormone (TSH)	Phosphate
	Uric acid

Pregnancy Testing: 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.

8.3.5. Electrocardiograms

Single and triplicate 12-Lead electrocardiogram (ECG) parameters will be collected as shown in Table 1 and Table 2: rhythm, heart rate, QT, RR, and the overall impression. QT interval corrected for heart rate by the Fridericia's formula (QTcF) will be manually calculated in the database.

For each planned visit for which a triplicate ECG is obtained, the average the 3 values will be calculated and reported. 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 -1 hour and -0.5 hour predose.

8.3.6. Echocardiograms

Echocardiograms will be performed at screening, and thereafter as shown in Table 1.

8.3.7. Prior and Concomitant Medications

Medications administered to study participants during the on-study period 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 prior medications. Concomitant medications are defined as medications administered to study participants on or after the first dose of study treatment and prior to 28 days after the last dose of study treatment or surgery, whichever occurs last. Medications start 29 days after the last dose of study treatment or surgery, whichever occurs last, will be considered as post-study meds and will not be summarized or listed. If medication with missing start dates but the end date is after first dose of study treatment, it will be

considered as concomitant medication as well. A medication can be considered both prior and concomitant. Collected prior and concomitant medications will be coded using the World Health Organization (WHO) medical dictionary.

8.4. Other Endpoints

- Pharmacokinetic evaluations of sitravatinib.
- Pharmacodynamic evaluation in tumor tissue.
- Pharmacodynamic evaluation in the blood.
- Circulating tumor DNA.

9. Data Handling

9.1. Missing Dates

The following rules will be applied to impute missing start and stop dates in appropriate data types (e.g., AEs or concomitant medications). Imputations of missing dates will only apply to summary tables (and not listings).

Start Date

If the start date is completely missing (i.e., the day, month, and year are all unknown) the start date will be set to the date of first dose of study medication.

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 both 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 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 before the year of the **first dose date**, then January 1 will be assigned to the missing fields.
- If the year of the incomplete date is after the year of the **first dose date**, then January 01 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 January 01 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.

9.2. 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 administration, study procedures/assessments, study visit schedule, informed consent, 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. Interim Analyses

No interim statistical analysis is planned during this study.

11. Statistical Methods

All data collected during this study will be displayed in data listings, unless otherwise specified. Data listings will be sorted by patient identifier for safety and efficacy listings. Screen failures will be excluded from all tables and listings, except for SAE listings (which includes all patients that provides informed consent). In addition, listings will include all relevant derived variables.

Descriptive statistics (mean, median, standard deviations [STD], 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 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.

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

All data summaries and tabulations will be prepared with SAS® Version 9.4 or higher.

11.1. Patient Disposition

The number and percentage of patients enrolled and treated in the study will be presented. The number and percentage of patients and each population to which they belong will be presented as well as the number and percentage of patients who withdrew from the study and a breakdown of the corresponding reasons for withdrawal and the number and percentage of patients who discontinued nivolumab or sitravatinib with the corresponding reasons. Summaries will be reported for all screened patients. Disposition will be summarized descriptively for all screened patients.

11.2. Important Protocol Deviations

Important protocol deviations for patients in the Enrolled Population will be reported by category. Important protocol deviations will be listed.

11.3. Treatments

11.3.1. Prior and Concomitant Medications

Concomitant medications will be coded using World Health Organization (WHO) Drug Enhanced (version: March 2018).

Prior medications will be tabulated separately for the Safety population and Enrolled population by Anatomical Therapeutic Chemical Classification level 2, level 4, and preferred drug name using counts and percentages. Concomitant medications will be summarized separately for the Safety population and Enrolled population and by sitravatinib starting dose and by segment. Concomitant medications in segment 1 are defined as the medications started between the first dose and the last dose of sitravatinib in segment 1. Concomitant medications in segment 2 are defined as the medications started between the first dose of nivolumab and the last dose of sitravatinib or nivolumab in segment 2.

Prior and concomitant medications will be included in a patient data listing.

11.4. Demographic and Baseline Characteristics

Demographic and baseline data will be summarized descriptively for the Safety population. For continuous variables, descriptive statistics will include the mean, STD (or standard error), median, range, and interquartile range. For categorical variables, descriptive statistics will include the number and percent.

Demographic variables to be summarized include gender, reproductive status for female, race, ethnicity, age (years), baseline weight (kg), baseline height (cm), baseline Eastern Cooperative Oncology Group (ECOG) status, and smoking history. Age is calculated from date of informed consent and date of birth.

Primary disease history will be tabulated for the Safety population and will include the summary statistics (count and percentage) for primary tumor stage (TX, T0, T1, T1a, T1b, T2, T2a, T2b, T3, T3a, T3b, T3c, T4), regional lymph node stage (NX, N0, N1), and distant metastasis stage (M0, M1).

Prior primary disease treatment (systemic therapies; radiotherapy, and surgery) will be tabulated for the Safety population and include the summary statistics (count and percentage).

Medical history will be tabulated by system organ class (SOC) and preferred term (PT) using counts and percentages for the Safety population.

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

11.5. Medical History

Medical history will be tabulated by system organ class (SOC) and preferred (PT) using counts and percentages for the Safety population. Medical history will be listed by patient.

11.6. Efficacy Analyses

11.6.1. Primary Variable

Descriptive statistics (frequency and percentage) for point in time objective response (either CR or PR) prior to surgery and pCR based on the response assessments by the Investigator and the exact 95% Clopper-Pearson confidence interval of the response rate will be presented. Summaries will be presented in the Clinical Activity Evaluable Population and Safety Population. An exact test for single proportion (two-sided α=5%) will be performed to test H_0: percentage of patients with ccRCC achieving a point in time objective response (either CR or PR) prior to surgery ≤5% against H_1: percentage of patients with ccRCC achieving a point in time objective response prior to surgery >5%. Descriptive statistics (frequency and percentage) for point in time objective response will be presented; In addition, exact binomial 95% CIs for the percentage will be displayed.

11.6.2. Secondary Variables

11.6.2.1. Time to Surgery:

Time-to-surgery will be summarized descriptively using the Kaplan-Meier estimate. The median, 25th percentile, and 75th percentile of time-to-surgery and their two sided 95% CIs (Brookmeyer and Crowley, 1982) will be calculated where appropriate. In addition, minimum and maximum will also be displayed. Kaplan-Meier plots will be provided for time-to-surgery. Delays in Surgery will be presented using descriptive statistics.

Censoring Rules

No censoring rules will apply to this variable.

11.6.2.2. DFS:

DFS will be summarized descriptively using the Kaplan-Meier estimate. The median, 25th percentile, and 75th percentile of time-to-surgery, and DFS and their two sided 95% CIs (Brookmeyer and Crowley, 1982) will be calculated where appropriate. Kaplan-Meier plots will be provided for DFS.

Censoring Rules

The following censoring rules will be applied to DFS:

- Event time will be censored on the date of surgery, or date of last follow-up assessment documenting absence of recurrence or Death, whichever occurs later for patients within the follow-up period and disease-free at the time of an analysis.

For staggered surgeries, date of surgery should reflect the latest of the surgery dates in the clinical database.

All secondary analyses will be conducted in the Clinical Activity Evaluable population.

11.7. Safety Analyses

All safety analyses will be summarized in the Safety population.

11.7.1. Extent of Study Drug Exposure

Descriptive statistics will be provided separately for each study drug, for the duration of exposure (days), number of doses received, cumulative dose received (mg) and absolute and relative dose intensities as well as compliance.

Number and percentage of patients with at least 1 dose reduced and reasons for reduction (only for sitravatinib), at least 1 injection (for nivolumab) or dose (for sitravatinib) interrupted and reasons for injection/dose interruption will be presented. For sitravatinib dose interruption, include a minimum of 3 days of consecutive interruption as the threshold for what counts as treatment interrupted.

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

11.7.2. Adverse Events

All adverse event summary tables will be based on the Safety Population and presented by segment and in total. An overall summary of TEAEs by segment will be presented. TEAEs in segment 1 are defined as TEAEs started between the first dose and the last dose of sitravatinib in segment 1. TEAEs in segment 2 are defined as TEAEs started between the first dose of nivolumab and the last dose of sitravatinib or nivolumab in segment 2.

A breakdown of the number and percentage of patients reporting each adverse event categorized by SOC and PT will be presented. Note that counting will be by patient not event and patients are only counted once within each SOC or PT. The following summaries will be presented:

- Treatment-emergent adverse events
- Treatment-related treatment-emergent adverse events
- Sitravatinib-related treatment-emergent adverse events
- Nivolumab-related treatment-emergent adverse events
- CTCAE Severity Grade 3 or greater treatment-emergent adverse events
- CTCAE Severity Grade 3 or greater treatment-related treatment emergent adverse events
- CTCAE Severity Grade 3 or greater Sitravatinib-related treatment-emergent adverse events
- CTCAE Severity Grade 3 or greater Nivolumab-related treatment-emergent adverse events
- Treatment-emergent adverse events leading to dose reduction or interruption of either study drug
- Treatment-related treatment-emergent adverse events leading to dose reduction or interruption of either study drug
- Treatment-emergent adverse events leading to drug discontinuation of either study drug
- Treatment-related treatment-emergent adverse events leading to drug discontinuation of either study drug.

TEAEs will be presented by PT in descending order of frequency.

AESIs and irAEs will be summarized separately by SOC and PT. Separate listings will be provided for AESIs and irAEs.

The following summaries will be presented by SOC, PT, and maximum CTCAE grade:

- Treatment-emergent adverse events
- Treatment-related treatment-emergent adverse events
- Sitravatinib-related treatment-emergent adverse events
- Nivolumab-related treatment-emergent adverse events.

The following summaries will be presented by PT and maximum CTCAE grouped grade:

- Treatment-emergent adverse events
- Treatment-related treatment-emergent adverse events

- Sitravatinib-related treatment-emergent adverse events
- Nivolumab-related treatment-emergent adverse events.

All AEs (including non-treatment-emergent events) recorded on the CRF will be listed using the Enrolled Population.

11.7.3. Deaths and Serious Adverse Events

TEAEs that lead to death and SAEs will be summarized by SOC and PT. The following summaries will be presented:

- Serious treatment-emergent adverse events
- Serious treatment-related treatment-emergent adverse events
- Serious Sitravatinib-related treatment-emergent adverse events
- Serious Nivolumab-related treatment-emergent adverse events
- Treatment-emergent adverse events leading to death
- Treatment-related treatment-emergent adverse events leading to death
- Sitravatinib-related treatment-emergent adverse events leading to death
- Nivolumab-related treatment-emergent adverse events leading to death

A listing of AEs leading to death will be presented. A listing of patients who experience a SAE (including those occurring during screening) will also be presented.

11.7.4. Laboratory Data

All laboratory data will be summarized in International System (SI) units. The conversion factors from conventional to SI units will be documented in the Local Lab Conventions document for this study. In general, laboratory data will be presented by visit. Values at unscheduled visits will be included in the summary of maximum for all study visits and minimum for all study visits, which will present the largest and smallest values observed for each patient post-baseline for each test.

Selected parameters will be presented in shift tables of baseline against worst grade test result. The shift from baseline to worst post baseline (including unscheduled visit) NCI CTCAE Version 5.0 grade will be presented for albumin (albumin increased), AST (AST increased), ALT (ALT increased), bilirubin (bilirubin increased), creatinine (creatinine increased), hemoglobin (anemia), neutrophils (neutrophil count decreased), platelets (platelet count decreased), sodium (hyponatremia and hypernatremia), potassium (hypokalemia and hyperkalemia), calcium (hypocalcemia and hypercalcemia), phosphate (hypophosphatemia), and uric acid (hyperuricemia).

For sodium, potassium, and calcium, separate grading criteria exist depending whether the analyte is high or low. For the purpose of shift tables, all low values will be included in the Grade 0 group in the shift tables for high values, and vice versa (all high values should be included in the Grade 0 group in the shift tables for low values.

Patients with at least 1 on-study (i.e. from signing of the informed consent until End of Study evaluation) measurement for each laboratory parameter will be included, regardless of whether or not a baseline assessment is present.

Clinical laboratory results will be listed by subject. Laboratory values that meet Grade 3 or 4 criteria according to NCI CTCAE Version 5.0 will also be listed separately.

11.7.4.1. Hematology

Hematology parameters include hemoglobin, platelet count, WBC count, lymphocytes, and neutrophils. The coagulation parameters include partial thromboplastin time (PTT), and international normalized ratio (INR).

Descriptive statistics will be provided for each test result and for change from baseline by visit and by sitravatinib starting dose (120mg and 80mg). Multiple measurements taken during the visit for a patient will be represented by the most severe value for each hematology test. The most severe value will be determined first by the value closest to the upper or lower limit of the normal limits (dependent on which direction is considered severe) if the value is within the normal limits. If the value is outside the normal limits, 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, etc.) the first chronological value will be selected. Low values are considered the most severe for all hematology parameters. Shift tables (for hemoglobin (anemia), neutrophils (neutrophil count decreased), platelets (platelet count decreased)), summarizing the shift from baseline grade to each post-baseline visit, maximum post-baseline CTCAE grade including unscheduled visits, and last assessment on study will be presented. Patients who develop a ≥ Grade 3 toxicity will be listed.

11.7.4.2. Chemistry

Serum chemistry parameters include ALT, AST, alkaline phosphatase, total bilirubin, lipase, amylase, creatinine, uric acid, BUN, albumin, sodium, potassium, chloride, magnesium, phosphate, calcium and bicarbonate.

Descriptive statistics will be provided for each test result and for change from baseline by visit and by sitravatinib starting dose (120mg and 80mg). Multiple measurements taken during the visit for a patient will be represented by the most severe value as noted in Section 11.7.4.1. For all chemistry analytes, the most severe value is the highest value, with the exception of albumin, chloride, and bicarbonate. The most severe could be in either direction for glucose, potassium, sodium, and calcium. For these analytes, if within the normal limits, then the value closest to the normal limit (either direction) will be selected. If outside the normal limits, then the value most distant from the normal limit (either direction) will be used. Shift tables (for AST (AST increased), ALT (ALT increased), creatinine (creatinine increased), sodium (hyponatremia and hypernatremia), potassium (hypokalemia and hyperkalemia), phosphate (hypophosphatemia), and uric acid (hyperuricemia), summarizing the shift from baseline grade to each post-baseline visit, maximum post-baseline CTCAE grade including unscheduled visits, and last assessment on study will be presented. Patients who develop a ≥ Grade 3 toxicity will be listed.

11.7.4.3. Urinalysis

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

11.7.4.4. Thyroid

Results will be listed for TSH.

11.7.4.5. CTCAE Coding of Laboratory Data

Where laboratory values are categorized into NCI CTCAE v5.0 grades, the categories are defined according to the criteria available on the following website: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Note that grades are applied based only on the numeric SI value of the parameter assessed; clinical signs and symptoms are not 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, phosphate, 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.

11.7.4.6. 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 is identified.

A figure displaying patients who are at risk for a drug induced liver injury according to Hy’s law will be presented. A listing of patients at risk will also be presented.

11.7.5. Vital Signs

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. The following vital signs will be summarized: pulse rate (beats/min), systolic blood pressure (SBP; mmHg), diastolic blood pressure (DBP; mmHg), body temperature (C), Height (cm) and weight (kg). Height will be recorded at screening only.

All vital signs and change from baseline through the last study visit will be summarized. This will include a summary of the maximum and minimum values observed while the patient was on treatment and change from baseline to that observed value.

All vital signs including all baseline and post-baseline ECOG will be listed.

11.7.6. Physical Examinations, ECGs, and Other Observations Related to Safety

11.7.6.1. Physical Examination

Complete physical examinations will be conducted during screening and EOS/Withdrawal visits only. Abbreviated physical examinations will be performed on Day 1, Day 15, Day 29, and Day 43 (if patient has Day 43 visit). Any new abnormal physical exam findings will be collected as AEs. Physical Examination data will be listed for the Safety population.

11.7.6.2. Electrocardiogram

A summary of ECG parameters including heart rate (beats/min), QT interval (msec), QTcF (msec), rhythm, 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. In addition, a summary will be generated for patients with QTcF increased to value >450 and ≤480 msec, , >480 and ≤500 msec, and value >500 msec, and patients with change-from-baseline QTcF increased by ≤30, 30 to ≤60 msec, and by >60 msec. A shift from baseline to worst CTCAE grade summary will also be presented.

A listing of the ECG results along with the overall interpretation will be presented. For assessments where triplicate ECGs are taken, the individual values will be displayed.

11.7.6.3. Echocardiogram

LVEF data from the echocardiogram will be summarized for the Screening, Day 29 and Preop Rebaseline results only in the safety population. Additionally, patients who have at least one post-baseline decrease in value will be summarized using the following categories: decrease from baseline of 10-<20% decrease from baseline and value ≥40%, 10-<20% decrease from baseline and value <40%, ≥20% drop from baseline and value ≥40%, and ≥20% drop from baseline and value <40%.

LVEF will be graded per CTCAE v5.0. The grades are as follows:

- Grade 1: n/a
- Grade 2: Resting ejection fraction (EF) 50–40%; 10-19% drop from baseline
- Grade 3: Resting EF 39-20%; ≥20% drop from baseline
- Grade 4: Resting EF <20%
- Grade 5: n/a

Shift in LVEF results from baseline to worst post-baseline by CTCAE Grade will be presented.

Echocardiogram results will be listed for the screened population.

11.7.6.4. Pregnancy Test

Pregnancy testing data will be listed for the Safety population.

11.7.6.5. Long Term Follow-up

Long term follow-up/survival data will be listed for the safety population. Additionally, all follow-up disease recurrence will be listed.

11.7.6.6. Death Report

Death report data will be summarized and listed for the Enrolled Population.

12. Validation

PRA seeks to ensure the quality of the results provided for the study in the form of 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 statistical 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. References

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

Ji Y, Liu P, Li Y, et al. A modified toxicity probability interval method for dose-finding trials. Clin Trials. 2010 Dec;7(6):653-63.

Appendix 1 Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
C	Celsius
ccRCC	Clear Cell Renal Cell Carcinoma
CI	Confidence Interval
CO^2	Carbon Dioxide
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computed Tomography Scan
CTCAE	Common Toxicity Criteria for Adverse Events
ctDNA	Circulating Tumor Deoxyribonucleic Acid
DBP	Diastolic Blood Pressure
DFS	Disease-Free Survival
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOS	End of Study
INR	Internal Normalized Ratio
irAE	Immune-related Adverse Event
IV	Intravenous
MDSC	Myeloid-Derived Suppressor Cell
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
mTPI	Modified Toxicity Probability Interval
NCI	National Cancer Institute
NGS	Next Generation Sequencing
NK	Natural Killer
NSCLC	Non-small Cell Lung Cancer

pCR	Pathological Complete Response
PD	Progressive Disease
PD-L1	Programmed Cell Death Ligand 1
PK	Pharmacokinetic
PR	Partial Response
PT	Preferred Term
PTT	Partial Thromboplastin Time
QD	Once Daily
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SI	International System
SMQs	Standardised MedDRA Queries
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