Protocol Number: 516-003

Official Title: A Phase 2 Study of Sitravatinib in Combination with PD-(L)1 Checkpoint Inhibitor Regimens in Patients with Advanced or Metastatic Urothelial Carcinoma

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Statistical Analysis Plan

Sponsor:	Mirati Therapeutics, Inc
Protocol No:	516-003
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1.0 Approvals

Sponsor	
Sponsor Name:	Mirati Therapeutics, Inc.
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PRA	
Biostatistician/Title (Owner):	[redacted]/Senior Principal Biostatistician
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2.0 Change History

Version/Date	Change Log
1.0/04Jun2021	Created as new
2.0/09Dec2021	Incorporate the client's comments to SAP v1.0 and finalize the SAP
3.0/15Mar2022	Add rule for the imputation of completely missing anti-cancer therapy dates. Add a definition for extent of follow-up. Revise the censoring rules for DoR and PFS as such: • add the derivation of last evaluable assessment, • add cohort-specific details to rule for patients lacking evaluation of disease after first study treatment, • add rule for patients that start a new anti-cancer therapy prior to PD or death. Add a definition of "on-treatment" to the Safety Analysis Section. Add definition of last evaluable assessment Remove repeated block of text from the irAE Section. Revise the definition of TEAEs to coincide with the MRT51605 study. Correct WHO Drug Dictionary Version to: 2018MAR01 DDE+HD B3 Added cut for end date of defining concomitant medications Remove Cis from BOR

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3.0 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 516-003.

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

5.0 Introduction

This SAP describes the statistical methods to be used during the analysis and reporting of data collected under Mirati Therapeutics, Inc. Protocol 516-003.

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 version 4.0 dated 22 June 2020 and CRF version 5.0 dated 29 Oct 2020. 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, known as the 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 and an amended SAP will be finalized prior to database lock.

6.0 Study Objectives and Endpoints

6.1 Objectives

6.1.1 Primary Objective

- To evaluate the clinical activity of sitravatinib in combination with PD-(L)1 checkpoint inhibitor regimens in patients with advanced or metastatic urothelial carcinoma.

6.1.2 Secondary Objectives

- To evaluate the safety and tolerability of the combination regimen in the selected population.
- To evaluate secondary efficacy endpoints of the combination regimen in the selected population.
- To evaluate the pharmacokinetics (PK) of sitravatinib administered in combination regimens.
- To evaluate the PK of sitravatinib in patients with renal impairment, to be implemented in selected study sites contingent upon early results in the study or sitravatinib program.
- Cohort 9 only: To identify recommended Phase 2 combinatorial doses (RP2Ds) of sitravatinib, pembrolizumab and enfortumab combination treatment.

6.1.3 Exploratory Objectives

- To assess the effect of the combination regimen on circulating PD-L1, immune cell populations and cytokines.
- To assess the effect of the combination regimen on tumor cell PD-L1 expression, tumor infiltrating immune cell populations and gene expression signatures.
- To assess the correlation of tumor PD-L1 protein expression and gene alterations in circulation and in tumor tissue with treatment outcome.

6.2 Endpoints

6.2.1 Primary Endpoint

The primary endpoint is the Objective Response Rate (ORR) as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) as per local Physicians in all other Cohorts.

6.2.2 Secondary Endpoints

- Safety characterized by type, incidence, severity, timing, seriousness and relationship to study treatment of adverse events, and laboratory abnormalities.
- Secondary efficacy endpoints
  - Duration of Response (DOR)
  - Clinical Benefit Rate (CBR)
  - Progression-Free Survival (PFS)
  - 1-Year Survival Rate
  - Overall Survival (OS)
- Blood plasma concentrations of sitravatinib.
- Lead-in dose escalation portion of Cohort 9 only: Dose-limiting toxicities (DLTs).

6.2.3 Exploratory Endpoints

- Circulating PD-L1 concentration
- Circulating immune cell populations
- Circulating cytokine concentrations
- Circulating tumor deoxyribonucleic acid (ctDNA)
- T-Cell Receptor sequencing
- Tumor PD-L1 expression
- Immune cell populations in the tumor
- Gene expression signatures in the tumor
- Tumor gene alterations

7.0 Study Design

Study 516-003 is an open-label, Phase 2 evaluation of the investigational agent sitravatinib in combination with PD-(L)1 checkpoint inhibitor regimens in patients with locally advanced or metastatic urothelial carcinoma. The study will evaluate sitravatinib in combination with the PD-1 checkpoint inhibitor nivolumab, and sitravatinib in combination with the PD-1 checkpoint inhibitor pembrolizumab and

the antibody-drug conjugate (ADC) enfortumab. An initial lead-in dose escalation evaluation may be initiated followed by further evaluation of clinical activity in 2 populations if a tolerable dose regimen for this combination is identified.

The primary objective is to evaluate the clinical activity of the combination regimens using ORR in accordance with RECIST 1.1. Secondary objectives include evaluation of safety, secondary efficacy endpoints, PK of sitravatinib, and (for lead-in dose escalation portion of Cohort 9 (35mg, 70mg, and 100mg) DLTs for Cohort 9. The Schedule of Assessments to be performed in the study are presented in Table 1 and

. The schedule for collection of pharmacokinetic and pharmacodynamic samples and ECG assessment time points are presented in Table 2 and Table 4.

7.1 Initial and Contingent Study Cohorts

Initial cohorts will be used to refer to the first two cohorts (cohort 1 and cohort 2) in which patients with documented disease progression on or after checkpoint inhibitor therapy as the most recent treatment will be enrolled.

Contingent cohorts will be used to refer to one or more cohorts (cohort 3, 4 and up to cohort 9) that may be added to the study on a contingent basis. Cohorts 3 and 4 will enroll patients previously receiving treatment with selected immunotherapies, including anti-CTLA-4, anti-OX40 or anti–CD137 therapy. Cohorts 5 and 6 will enroll patients who have not previously received checkpoint inhibitor therapy (CIT-naïve). Cohort 7 will enroll patients with documented disease progression on or after a previous anti-PD-(L)1 and ADC (in combination or separately, and in any order), and who were previously treated with a platinum-based chemotherapy. Cohort 8 will enroll patients with documented disease progression on or after a previous anti-PD-(L)1 and ADC (in combination or separately, and in any order), and considered ineligible for platinum-based chemotherapy. Cohort 9 (including lead-in dose escalation) will enroll patients who have previously received a PD-(L)1 checkpoint inhibitor and a platinum-based chemotherapy.

7.1.1 Initial Study Cohorts

The initial study population will include patients with documented disease progression on or after a PD-(L)1 checkpoint inhibitor therapy as the most recent treatment [anti-PD-(L)1 refractory cohorts], stratified into 2 cohorts based on whether patients were previously treated with or ineligible for platinum-based chemotherapy, as depicted in Figure 1.

- Cohort 1: Patients with documented disease progression on or after previous anti-PD-(L)1 as most recent treatment, and who were previously treated with a platinum-based chemotherapy.
- Cohort 2: Patients with documented disease progression on or after previous anti-PD-(L)1 as most recent treatment, and considered ineligible for platinum-based chemotherapy.

Enrollment will occur in 3 stages. Stage 1 of enrollment will include a minimum of 9 evaluable patients in each cohort. Patients included in the evaluable population will have received treatment with both sitravatinib and nivolumab and have at least one on-study disease assessment prior to discontinuation. The exact stopping rules will be calculated based on the Predictive Probability Design (Lee-2008), once the exact number of patients evaluable at Stage 1 is known. 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 cohort, for a total sample size of 17 evaluable patients. If at least 3 Objective Responses are observed in a treatment cohort, further investigation may be warranted. If Stage 2 results in a cohort are of high interest for efficacy (in terms of examining the risk benefit ratio and not only in terms of ORR), enrollment may be expanded to as many as 40 patients in total in that cohort to narrow the 95% Confidence Interval (CI) around the ORR point estimate and to further characterize the durability of disease control.

7.1.2 Contingent Study Cohorts

In the event that results in the initial cohorts are of high interest for efficacy, contingency plans are described in Appendix 5, Appendix 6, Appendix 8 and Appendix 9 of the Protocol to add one or more study cohorts. Decisions for implementation of additional cohorts in the study will be made in collaboration with the Investigators and documented for Regulators and Institutional Review Boards by an Administrative Letter to Investigators.

Appendix 5 of the Protocol describes addition of contingent Cohort 3 and Cohort 4 (other prior selected immunotherapy cohorts, including anti-CTLA-4, anti-OX40 or anti-CD137). The statistical design for these cohorts will be the same as applied to Cohorts 1 and 2. These contingent cohorts described below were implemented by Administrative Letter, as depicted in Figure 1.

- Cohort 3: Patients with documented disease progression on or after a previous anti-PD-(L)1 as most recent treatment, who previously received (in combination or separately) other selected immunotherapies, and who were previously treated with a platinum-based chemotherapy.

- Cohort 4: Patients with documented disease progression on or after a previous anti-PD-(L)1 as most recent treatment, who previously received (in combination or separately) other selected immunotherapies, and considered ineligible for platinum-based chemotherapy.

Appendix 6 of Protocol describes addition of contingent Cohort 5 and Cohort 6 [anti-PD-(L)1 naïve cohorts]. The statistical design for these cohorts is described in the next section. These contingent cohorts described below were implemented by Administrative Letter and still enrolling, as depicted in Figure 1.

- Cohort 5: Patients who have not previously received an anti-PD-(L)1, and who were previously treated with a platinum-based chemotherapy.

- Cohort 6: Patients who have not previously received an anti-PD-(L)1, and considered ineligible for platinum-based chemotherapy.

Appendix 8 of Protocol describes addition of contingent Cohort 7 and Cohort 8 [post-ADC (antibody-drug conjugate) cohorts]. The statistical design for these new cohorts is described in the next section. These contingent cohorts described below were implemented by Administrative Letter.

- Cohort 7: Patients with documented disease progression on or after a previous anti-PD-(L)1 and ADC (in combination or separately, and in any order), and who were previously treated with a platinum-based chemotherapy.

- Cohort 8: Patients with documented disease progression on or after a previous anti-PD-(L)1 and ADC (in combination or separately, and in any order), and considered ineligible for platinum-based chemotherapy.

Appendix 9 of the Protocol describes addition of Cohort 9 to evaluate sitravatinib in combination with pembrolizumab and enfortumab. The next section describes the initial lead-in dose escalation followed by further evaluation of clinical activity in 2 populations if a tolerable dose regimen is identified. Cohort 9 is introduced and implemented with this protocol Version 4.0.

- Cohort 9 (including lead-in dose escalation): Patients who have previously received a PD-(L)1 checkpoint inhibitor and a platinum-based chemotherapy.

Table 1 Schedule of Assessments: Cohorts 1 through 8

Assessments	Screen/Baseline	Cycles 1, 2, and 3		≥ Cycle 4		End of Treatment	
	Within 28 days	Day 1 (± 2 days for Cycles 2 & 3)	Day 15 (± 2 days)	Day 1 (± 2 days)	Day 15 (± 2 days)	End of Treatment/ Withdrawal[14]	Post Treatment Follow Up
Study Participation Informed Consent[1]	Before study specific assessments						
Tumor Tissue Collection for PD-L1 Expression, Immune Cell Populations and Tumor Gene Alterations[2]	X[2]		X (Cycle 2 only) Optional[2]				
Medical History, Disease History, Prior Therapy	X						
ECOG Performance Status	X						
Physical Exam[3]	X					X	
Abbreviated Physical Exam[3]		X	X	X	X if nivolumab Q2W		
Vital Signs[4]	X	X	X	X	X if nivolumab Q2W	X	
Pregnancy Test[5]	X	As clinically indicated					
Hematology[6, 7]	X	X	X	X		X	
Coagulation[6, 7]	X	As clinically indicated					
Urinalysis[6, 7]	X	As clinically indicated					
Serum Chemistry[6, 7]	X	X	X	X		X	
Thyroid Function Test[6, 7]	X	X		X		X	
Blood for Sitravatinib Pharmacokinetics[8]		See Table 2					

Assessments	Screen/Baseline	Cycles 1, 2, and 3		≥ Cycle 4		End of Treatment	
	Within 28 days	Day 1 (± 2 days for Cycles 2 & 3)	Day 15 (± 2 days)	Day 1 (± 2 days)	Day 15 (± 2 days)	End of Treatment/ Withdrawal[14]	Post Treatment Follow Up
ctDNA blood sample[9]	X	At assessment for confirmation of disease response (PR or CR)				X	
Single 12-Lead ECG[10]	X	As clinically indicated				X	
Triplicate 12-Lead ECG[10]		See Table 2					
Echocardiogram or MUGA	X (Within 35 days)	Cycle 3 only (± 7 days)		As clinically indicated after C3		X	
Disease Evaluation[11]	X	Every 8 weeks (± 10 days) for ~12 months and then every 16 weeks					
Sitravatinib Dispensing and/or Reconciliation		X		X			
Nivolumab Administration		Throughout as directed in protocol					
Adverse Events[12] and Concomitant Medications	SAEs only	Throughout					
Long Term Follow-up[13]							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, Tumor Immune Cell Populations, and Tumor Gene Alterations: Fresh, pre-treatment tumor tissue biopsies are preferred, when possible. Archival tumor tissue is allowed. Biopsy may precede informed consent if performed as Standard of Care (SOC) or to assess eligibility for a different clinical trial. Prior PD-L1 test results including % tumor and/or immune cell staining and, when available, previously reported tumor gene mutation profile and total mutation burden estimates from next generation sequencing data will be collected. An optional tumor tissue collection after and as close as possible to C2D15 is desirable for all patients and is not dependent on the type of tumor tissue submitted at screening. A urinalysis should be performed prior to any study-related biopsy involving the genitourinary tract. If the results are consistent with a urinary tract infection, tumor lesions in other anatomical areas should be selected, if present.

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 (Table 8) 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.

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

10 12-Lead ECGs: Triplicate ECGs will accompany PK sampling as described in Table 2. In addition, ECGs are to be performed as clinically indicated. Assessments will include an evaluation of heart rate, QT, and QTc intervals. RR interval should be recorded during each ECG assessment in order to calculate QTcF.

11 Disease Evaluations: To be performed at screening (28-day window allowed) and every 8 weeks from Cycle 1 Day 1(± 10-day window for all other assessments except screening) until week 49 (~12 months) 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, CT or MRI of the abdomen and pelvis, as well as brain Magnetic Resonance Imaging (MRI) with and without gadolinium or CT with contrast, a whole-body bone scan (or PET or PET/CT if local standard for clinical trials) 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. Patients who discontinued the study for reasons other than objective disease progression will continue to have disease assessments at the same frequency until patient has radiologically confirmed progression, initiates a new anticancer therapy, or death.

12 Adverse Events: Serious Adverse Events (SAEs) will be reported from the time of informed consent until at least 28 days after the last administration of a study treatment. 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 adverse events and/or ongoing SAEs.

13 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 or email.

14 End of Treatment: Perform within 7-14 days of decision to permanently discontinue all 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).

Table 2 Sitravatinib Schedule of PK, Biomarker Samples and Triplicate ECG Assessments: Cohorts 1 through 8

	Screen/ Baseline	Cycle 1 Day 1				Cycle 1 Day 15 (± 2 days)		Cycle 2, 3, 5 Day 1 only	Cycle 2 Day 15 only
Collection Time and Allowable Window	**Within 28 days**	**Pre-dose (-0.5-0 hour)**		**30 min (± 10 min)**	**7 hour[5] (5-9 hour)**	**Pre-dose (-0.5-0 hour)**	**7 hour[5] (5-9 hour)**	**Pre-dose (-0.5-0 hour)**	**Pre-dose (-0.5-0 hour)**
PK Sample[1,2]		X		X	X	X	X	X	
TCR Sequencing[3]		X				X			
Flow Cytometry[3]	X	X				X			X
Protein and Cytokine Biomarkers[3]		X				X			X
Triplicate ECG[4]		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. Post-dose PK sample collections are not required for visits where sitravatinib dose is held but should be subsequently collected at the next visit following at least 7 days of sitravatinib intake. Alternatively, both pre-dose and post-dose PK collections are not required for visits preceded by more than 4 days of sitravatinib hold but should be subsequently collected at the next visit following at least 7 days of sitravatinib intake.

2 In addition to the scheduled samples, an unscheduled PK blood sample should be drawn before a daily sitravatinib dose (trough sample) in the event of any of the following events: 1) as soon as possible after an SAE, 2) at a clinic visit at least one week following a dose modification of the investigational agent, and 3) as soon as possible after renal function declines by one Stage as defined in Appendix 2 of the Protocol, if the patient continues study treatment.

3 The Day 1 blood samples for TCR sequencing, flow cytometry, protein and cytokine 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.

4 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 timepoints. 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)

5 Timepoints changed in Version 3.0 of protocol to 7 hours (5-9 hours). In preceding versions, these timepoints were 4 hours (2-6 hours).

Table 3 Schedule of Assessments: Cohort 9

The Schedule of Assessments provides an overview of the protocol visits and procedures. Refer to Sections 6 and 7 for detailed information on each assessment. Additional, unplanned assessments should be performed as clinically indicated, including for the purpose of fully evaluating adverse events.

Assessments	Screen/ Baseline	Cycles 1, 2, and 3			≥Cycle 4		End of Treatment	
	Within 28 days	Day 1 (± 2 days for Cycles 2 & 3)	Day 8 (± 2 days)	Day 15 (± 2 days) Only Lead-in Dose Escalation of Cohort 9	Day 1 (± 2 days)	Day 8 (± 2 days)	End of Treatment/ Withdrawal[14]	Post Treatment Follow Up
Study Participation Informed Consent[1]	Before study specific assessments							
Tumor Tissue Collection for PD-L1 Expression, Immune Cell Populations and Tumor Gene Alterations[2]	X[2]	X (Cycle 3 only) Optional[2]						
Medical History, Disease History, Prior Therapy	X							
ECOG Performance Status	X							
Physical Exam[3]	X						X	
Eye Exam[15]	X (Within ≤ 3 months)	As clinically indicated					X	
Abbreviated Physical Exam[3]		X	X	X	X	X		
Vital Signs[4]	X	X	X	X	X	X	X	

Assessments	Screen/ Baseline	Cycles 1, 2, and 3			≥Cycle 4		End of Treatment	
	Within 28 days	Day 1 (± 2 days for Cycles 2 & 3)	Day 8 (± 2 days)	Day 15 (± 2 days) Only Lead-in Dose Escalation of Cohort 9	Day 1 (± 2 days)	Day 8 (± 2 days)	End of Treatment/ Withdrawal[14]	Post Treatment Follow Up
Pregnancy Test[5]	X	As clinically indicated						
Hemoglobin A1c[7]	X							
Hematology[6, 7]	X	X	X	X	X	X	X	
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	
Blood for Sitravatinib PK[8]		See Table 4						
ctDNA blood sample[9]	X	At assessment for confirmation of disease response (PR or CR)					X	
Single 12-Lead ECG[10]	X	As clinically indicated					X	
Triplicate 12-Lead ECG[10]		See Table 4						
Echocardiogram or MUGA	X (Within 35 days)		Cycle 3 only (± 7 days)		As clinically indicated after C3		X	
Disease Evaluation[11]	X	Every 9 weeks (± 10 days) for ~12 months and then every 18 weeks						
Sitravatinib Dispensing and/or Reconciliation		X			X			

Assessments	Screen/ Baseline	Cycles 1, 2, and 3			≥Cycle 4		End of Treatment	
	Within 28 days	Day 1 (± 2 days for Cycles 2 & 3)	Day 8 (± 2 days)	Day 15 (± 2 days) Only Lead-in Dose Escalation of Cohort 9	Day 1 (± 2 days)	Day 8 (± 2 days)	End of Treatment/ Withdrawal[14]	Post Treatment Follow Up
Enfortumab and Pembrolizumab Administration		Throughout as directed in protocol (Note: pembrolizumab should be administered after sitravatinib, and enfortumab should be administered at least 30 minutes after pembrolizumab)						
Adverse Events[12] and Concomitant Medications	SAEs only	Throughout						
Long Term Follow-up[13]								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, Tumor Immune Cell Populations, and Tumor Gene Alterations: Fresh, pre-treatment tumor tissue biopsies are preferred, when possible. Archival tumor tissue is allowed. Biopsy may precede informed consent if performed as Standard of Care (SOC) or to assess eligibility for a different clinical trial. Prior PD-L1 test results including % tumor and/or immune cell staining and, when available, previously reported tumor gene mutation profile and total mutation burden estimates from next generation sequencing data will be collected. An optional tumor tissue collection after and as close as possible to C3D1 is desirable for all patients and is not dependent on the type of tumor tissue submitted at screening. A urinalysis should be performed prior to any study-related biopsy involving the genitourinary tract. If the results are consistent with a urinary tract infection, tumor lesions in other anatomical areas should be selected, if present. Nectin-4 testing by immunohistochemistry may be evaluated.

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 11 of Protocol) will be performed by local laboratories. If HbA1c is elevated (≥ 6.5 %), refer patient to appropriate provider during Cycle 1 for glucose management.

8 Pharmacokinetic Samples: Blood samples to be collected following ECGs and assessment of vital signs as scheduled in Table 4 of Protocol.

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

10 12-Lead ECGs: Triplicate ECGs will accompany PK sampling as described in Table 4 of the Protocol. In addition, ECGs are to be performed as clinically indicated. Assessments will include an evaluation of heart rate, QT, and QTc intervals. RR interval should be recorded during each ECG assessment in order to calculate QTcF.

11 Disease Evaluations: To be performed at screening (28-day window allowed) and every 9 weeks from Cycle 1 Day 1 (± 10-day window for all other assessments except screening) until week 49 (~12 months) and then every 18 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, CT or MRI of the abdomen and pelvis, as well as brain Magnetic Resonance Imaging (MRI) with and without gadolinium or CT with contrast, a whole-body bone scan (or PET or PET/CT if local standard for clinical trials) 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 18 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. Patients who discontinued the study for reasons other than objective disease progression will continue to have disease assessments at the same frequency until patient has radiologically confirmed progression, initiates a new anticancer therapy, or death.

12 Adverse Events: Serious Adverse Events (SAEs) will be reported from the time of informed consent until at least 28 days after the last administration of a study treatment. 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 adverse events and/or ongoing SAEs.

13 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 or email.

14 End of Treatment: Perform within 7-14 days of decision to permanently discontinue all 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).

15 Eye exam: Patients with recent ocular complaints (within ≤ 3 months of screening) must have a complete eye examination at Screening Visit performed by a qualified ophthalmologist or optometrist, including but not limited to: uncorrected, corrected and best corrected visual acuity, slit lamp, tonometry examination, and dilated fundus examination. Prior ophthalmologic exam done within 3 months of screening is acceptable provided there are no new symptoms since that exam. End of Treatment Visit slit lamp examinations are required for all patients who experience corneal adverse events during the study and must be performed ≥ 28 days from last dose of enfortumab. Additional eye examinations are to be conducted as clinically indicated.

Table 4 Sitravatinib Schedule of PK, Biomarker Samples and Triplicate ECG Assessments: Cohort 9

	Screen/ Baseline	Cycle 1 Day 1				Cycle 2 Day 1 (± 2 days)		Cycle 2, 3, 6 Day 8 only	Cycle 3 Day 1 only
Collection Time and Allowable Window	**Within 28 days**	**Pre-dose (-0.5-0 hour)**		**30 min (± 10 min)**	**7 hour[5] (5-9 hour)**	**Pre-dose (-0.5-0 hour)**	**7 hour[5] (5-9 hour)**	**Pre-dose (-0.5-0 hour)**	**Pre-dose (-0.5-0 hour)**
PK Sample[1,2]		X		X	X	X	X	X	
TCR Sequencing[3]		X				X			
Flow Cytometry[3]	X	X				X			X
Protein and Cytokine Biomarkers[3]		X				X			X
Triplicate ECG[4]		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. Post-dose PK sample collections are not required for visits where sitravatinib dose is held but should be subsequently collected at the next visit following at least 7 days of sitravatinib intake. Alternatively, both pre-dose and post-dose PK collections are not required for visits preceded by more than 4 days or sitravatinib hold but should be subsequently collected at the next visit following at least 7 days of sitravatinib intake.

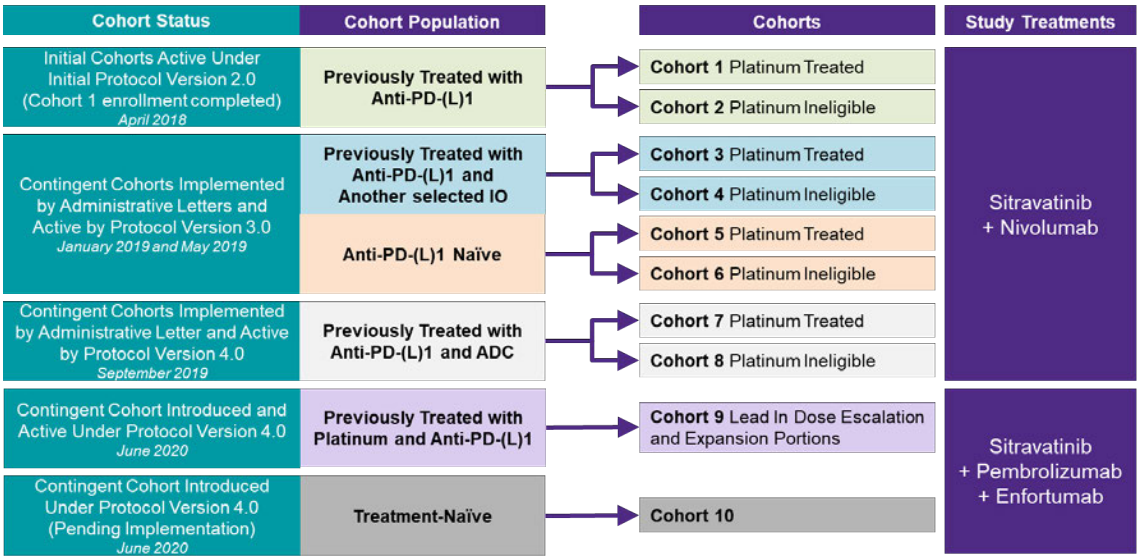
2 In addition to the scheduled samples, an unscheduled PK blood sample should be drawn before a daily sitravatinib dose (trough sample) in the event of any of the following events: 1) as soon as possible after an SAE, 2) at a clinic visit at least one week following a dose modification of the investigational agent, and 3) as soon as possible after renal function declines by one Stage, if the patient continues study treatment.

3 The Day 1 blood samples for TCR sequencing, flow cytometry, protein and cytokine 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.

4 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 timepoints. 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)

5 Timepoints changed in Version 3.0 of protocol to 7 hours (5-9 hours). In preceding versions, these timepoints were 4 hours (2-6 hours).

Figure 1 Study Schema (Note that Cohort 9 Expansion and Cohort 10 will not be opened)



7.1.3 Study Treatments

Throughout the study, nivolumab, pembrolizumab and enfortumab (where applicable) will be administered in accordance with approved labeling. Nivolumab is to be administered by intravenous infusion, 240 mg Q2W or 480 mg Q4W. Guidance for adverse event management and associated nivolumab treatment modifications are provided in product labeling. Pembrolizumab is to be administered by intravenous infusion, 200 mg Q3W. Guidance for adverse event management and associated pembrolizumab treatment modifications are provided in product labeling. Enfortumab is to be administered by intravenous infusion, with a starting dose of 1.25mg/kg on days 1 and 8 of Q3W (a lower dose may be used if necessary; see **Error! Reference source not found.** of the protocol). In addition, a dose de-escalation step for enfortumab may be undertaken as appropriate. Guidance for adverse event management and associated enfortumab treatment modifications are provided in product labeling. Note: nivolumab (for Cohorts 1 through 8) or pembrolizumab (for Cohort 9) should be administered after sitravatinib (and specifically after the 30 minute PK sampling on applicable study visits), whereas enfortumab (for Cohort 9) should be administered at least 30 minutes after pembrolizumab.

Sitravatinib capsules will be administered orally. A starting dose of 120 mg QD of the free base capsule formulation (in 28-day cycles) was used for the sitravatinib and nivolumab combination cohorts under previous versions of this protocol. Newly enrolled patients under Cohorts 1 through 6 will continue to receive the free base formulation with the starting dose of 120 mg QD. For Cohorts 7 and 8, transition to use of an alternative formulation, sitravatinib malate capsule formulation, is being implemented with this protocol Version 4.0. Newly enrolled patients in Cohorts 7 and 8 under this protocol Version 4.0 will receive a starting dose of 100 mg QD of the malate capsule formulation (an equivalent dose to 120 mg QD of the free base capsule formulation), based on the results of Study 516-006 described in Section **Error! Reference source not found.** of the protocol. Patients who began treatment with the free base capsule formulation will remain on the free base capsule formulation throughout the duration of the study. A lead-in dose escalation will determine the starting dose of sitravatinib using the malate capsule formulation (21-day cycles) for sitravatinib combination with pembrolizumab and enfortumab Cohort 9. Guidelines for sitravatinib administration and dose reduction in the event of toxicity are provided in Section **Error! Reference source not found.** of the protocol.

Detailed descriptions of the study treatments are presented in Section 5 of the protocol.

7.1.4 Contingent PK Evaluation in Patients with Renal Impairment

In the event results in initial patient cohorts enrolled in this study or results emerging from other ongoing clinical trials of sitravatinib are of high interest for efficacy, the evaluation of the pharmacokinetics of sitravatinib in patients with mild or moderate renal impairment may be implemented. Appendix 7 of the protocol describes the plan for this assessment. Upon implementation of this study appendix, the evaluation of the PK of sitravatinib in at least 6 patients each having mild or moderate renal impairment at enrollment will be undertaken. Details of this analysis will be provided in the PKAP.

7.1.5 Hypothesis and Sample Size Considerations

This Phase 2 study will use Predictive Probability Designs (Lee-2008) for initial cohort 1 and 2. In summary, Cohorts 3 and 4 will also use Predictive Probability Designs with the same assumptions as the initial cohorts (Section 6.1), Cohorts 5 and 6 will use Predictive Probability Designs with revised assumptions, Cohorts 7 and 8 will use confidence interval method with the revised assumptions, the lead-in dose escalation portion of Cohort 9 will use the mTPI-2 design (Guo-2017; Appendix 2).

In creating the statistical designs, the Type 1 error (α) is constrained to <0.05 and Power ($1-\beta$) is constrained to ≥ 0.90.

7.1.5.1 Cohort 1 and 2:

ORR in accordance with RECIST v1.1 is the primary endpoint. The ORR using nivolumab in the population of advanced/metastatic urothelial carcinoma who experienced disease progression on or after treatment with a checkpoint inhibitor is assumed to be 5% (p0); thus, this rate is considered uninteresting. The target ORR using sitravatinib in combination with nivolumab in this study population is 30% (p1). Stage 1 of enrollment will include a minimum of 9 evaluable patients in each cohort. Patients included in the evaluable population will have at least one on-study disease assessment prior to discontinuation; patients who discontinue treatment due to adverse events or withdrawal of consent prior to the first on-study disease assessment will not be included in the evaluable population. 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 cohort, for a total sample size of 17 evaluable patients. If at least 3 Objective Responses are observed in a treatment cohort, 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.

The exact stopping rules for futility for each cohort 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 include a minimum of 9 evaluable patients at Stage 1. If Stage 2 results in a cohort are of high interest for efficacy (in terms of examining the risk benefit ratio and not only in terms of ORR), enrollment may be expanded to as many as 40 patients total in that cohort to narrow the 95% CI around the ORR point estimate and to further characterize the durability of disease control.

Table 5 presents estimates of the 95% CI around the observed ORR for several potential outcomes using the sample size of 40 patients, and the Clopper-Pearson method.

Table 5 Estimates of 95% CI Using Clopper-Pearson in After Enrollment of 40 Patients

Number of Observed Responses Among 40 Patients	ORR	95% CI
10	25%	(12.7%, 41.2%)
12	30%	(16.6%, 46.5%)
14	35%	(20.6%, 51.7%)
16	40%	(24.9%, 56.7%)
20	50%	(33.8%, 66.2%)

7.1.5.2 Cohort 3 and 4:

In the event that results in the initial study cohorts are of high interest for efficacy, one or more cohorts in patients with documented disease progression on or after a PD-(L)1 checkpoint inhibitor therapy as the most recent treatment, and who previously received (in combination or separately) treatment with selected immunotherapies, including but not limited to anti-CTLA-4, anti-OX40 or anti–CD137 therapy, may be added to the study. Decisions for implementation of additional cohorts in the study will be made in collaboration with the Investigators and documented for Regulators and Institutional Review Boards by an Administrative Letter to Investigators.

Based on the evolving treatment landscape of urothelial carcinoma including regimens combining selected immunotherapies with checkpoint inhibitors, and in consult with Investigators, both Cohort 3 and Cohort 4 described in this appendix were implemented by an Administrative Letter dated January 2019.

The statistical design is the same as cohort 1 and 2.

7.1.5.3 Cohort 5 and 6:

In the event that results in the initial study cohorts are of high interest for efficacy, one or more cohorts in patients who have not previously received checkpoint inhibitor therapy (CIT-naïve) may be added to the study. Decisions for implementation of additional cohorts in the study will be made in collaboration with the Investigators and documented for Regulators and Institutional Review Boards by an Administrative Letter to Investigators.

Based on the evolving treatment landscape of urothelial carcinoma and early efficacy and safety results from active study cohorts, and in consult with Investigators, both Cohort 5 and Cohort 6 described in this section were implemented by an Administrative Letter dated May 2019.

The ORR using nivolumab in the population of advanced/metastatic urothelial carcinoma who have not previously received treatment with a checkpoint inhibitor therapy is assumed to be 20% (p0); thus, this rate is considered uninteresting. The target ORR using sitravatinib in combination with nivolumab in this study population is 40% (p1). Stage 1 of enrollment will include approximately 24 evaluable patients in each cohort. Patients included in the evaluable population will have received treatment with both sitravatinib and nivolumab and will have at least one on-study disease assessment prior to discontinuation; patients who discontinue treatment due to adverse events or withdrawal of consent prior to the first on-study disease assessment will not be included in the evaluable population. With exactly 24 evaluable patients at Stage 1, if at least 6 patients have Objective Responses, enrollment of 21 additional evaluable patients is needed in the treatment cohort, for a total sample size of 45 evaluable patients. If at least 14 Objective Responses are observed in a treatment cohort, further investigation may be warranted. If the true ORR is 20% (null hypothesis), the probability of early termination during the study is 0.66; the Type 1 error is equal to 0.0483 and the power is equal to 0.9001.

The exact stopping rules for futility for both 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 include approximately 24 evaluable patients at Stage 1. The Sponsor retains the option to take more than one look at the data when making decisions based on the PPD method to expand cohorts.

7.1.5.4 Cohort 7 and 8:

In the event that results in the initial study cohorts are of high interest for efficacy, one or more cohorts in patients with documented disease progression on or after a PD-(L)1 checkpoint inhibitor therapy and an antibody-drug conjugate (ADC; e.g. enfortumab vedotin, sacituzumab govitecan), in any order or in combination together. Decisions for implementation of additional cohorts in the study will be made in collaboration with the Investigators and documented for Regulators and Institutional Review Boards by an Administrative Letter to Investigators.

Based on the evolving treatment landscape of urothelial carcinoma in particular with the clinical activity of ADCs, and early efficacy and safety results from active study cohorts, and in consult with Investigators, both Cohort 7 and Cohort 8 described in this section were implemented by an Administrative Letter dated September 2019.

The ORR using taxanes in the population of advanced/metastatic urothelial carcinoma who have previously received treatment with a checkpoint inhibitor therapy and ADC is assumed to be 10%; thus, this rate is considered uninteresting. The design for Cohort 7 and Cohort 8 will utilize a 95% confidence interval to exclude an ORR of 10%. Assuming sitravatinib in combination with nivolumab treatment will result in an ORR of at least 25% in this treatment setting, a sample size of approximately 55 evaluable patients would be sufficient for the lower bound of a 2-sided 95% confidence interval (Clopper-Pearson method) to exclude an ORR of 10%.

The design will include a non-binding stopping rule for futility derived using East® software v6.5 to control the Type 2 error rate of 0.117. The Type 2 error spending function is based on the Rho family with parameter 2.0. The futility analysis will be conducted when approximately 17 evaluable patients (approximately 30% of the total number of patients) are available for the response assessment. The futility bound will be 1 or fewer observed responses among the first 17 patients.

7.1.5.5 Cohort 9:

In the event that results in the initial study cohorts are of high interest for efficacy, one or more cohorts in patients for treatment with sitravatinib in combination with pembrolizumab and enfortumab may be added to the study. Decisions for implementation of additional cohorts in the study will be made in collaboration with the Investigators and documented for Regulators and Institutional Review Boards by an Administrative Letter to Investigators.

Based on the evolving treatment landscape of urothelial carcinoma in particular with the clinical activity of ADCs, and early efficacy and safety results from active study cohorts, and in consult with Investigators, Cohort 9 described in this appendix is considered implemented of this protocol Version 4.0.

Study Design – Design details specific to Cohort 9 (including lead-in dose escalation) are described below including description of the populations to be enrolled into these contingent cohorts evaluating the triple combination of sitravatinib, pembrolizumab and enfortumab, the study design and dose-limiting toxicities (DLTs) as applicable.

Initially, the lead-in dose escalation portion of Cohort 9 will evaluate sitravatinib administered in combination with pembrolizumab and enfortumab in patients who have previously received a PD-(L)1 checkpoint inhibitor and a platinum-based chemotherapy. If a tolerable dose is identified for sitravatinib in combination with pembrolizumab and enfortumab, the recommended dose regimen of sitravatinib in combination with pembrolizumab and enfortumab may be further evaluated in as many as 2 populations including in patients who have previously received a PD-(L)1 checkpoint inhibitor. Depending on the results in previous cohorts, only one or more of Cohort 9 may be implemented. Description of the populations to be enrolled into Cohort 9 evaluating the triple combination of sitravatinib, pembrolizumab and enfortumab are described below.

Lead-In Dose Escalation Portion of Cohort 9 Evaluating Sitravatinib in Combination with Pembrolizumab and Enfortumab

This portion of the study will begin with the lead-in dose escalation portion of Cohort 9 of up to three dose levels of sitravatinib in combination with up to two dose levels of pembrolizumab and enfortumab combination regimen, in patients who have previously received a PD-(L)1 checkpoint inhibitor and a platinum-based chemotherapy. Sitravatinib starting dose levels using the malate formulation are shown in Table 6, whereas the starting doses for pembrolizumab and enfortumab are shown in Table 7. Dosing will begin at 35 mg QD of sitravatinib in combination with the recommended doses of pembrolizumab and

enfortumab combination regimen. This starting dose for sitravatinib represents three dose levels below the dose administered as a single agent and in combination (with nivolumab) Phase 2 and 3 trials. Dose Level 3 in Table 6 is the dose used in single agent and combination Phase 2 and 3 trials. The starting doses for pembrolizumab and enfortumab (labeled as Dose Level 1 in Table 7) represent the recommended doses from the EV-103 Phase 2 trial and the EV-302 Phase 3 trial of pembrolizumab and enfortumab used in combination (Rosenberg-2020; Hoimes-2019). It is of note that the EV-302 Phase 3 trial also uses these recommended doses of pembrolizumab and enfortumab in the triple combination investigation arm combining pembrolizumab and enfortumab with the platinum-chemotherapy agents cisplatin or carboplatin. In addition, a dose de-escalation step for enfortumab may be undertaken as appropriate (labeled as Dose Level -1 in Table 7). Throughout the study, pembrolizumab and enfortumab will be administered in accordance with approved labeling. Guidance for adverse event management and associated pembrolizumab treatment modifications are provided in product labeling.

Table 6 Sitravatinib Starting Dose Levels for Lead-In Dose Escalation Cohort 9 (Malate Formulation)

Sitravatinib Dose Level	Sitravatinib Daily Dose
1	35 mg PO QD
-2[1]	50 mg PO QD
2	70 mg PO QD
3	100 mg PO QD

Abbreviations: PO = orally; QD = once daily.

1 The 50 mg dose level will be enrolled only if de-escalation is needed after assessment of the next higher dose level (70 mg).

Table 7 Pembrolizumab and Enfortumab Dose Levels

Combination Regimen Dose Level	Pembrolizumab[1]	Enfortumab[1]
-1[2]	200 mg IV Q3W	1 mg/kg IV on days 1 and 8 of Q3W
1	200 mg IV Q3W	1.25 mg/kg IV on days 1 and 8 of Q3W

Abbreviations: IV = intravenous; Q3W = every 3 weeks.

1 Pembrolizumab and enfortumab should be administered according to USPI and standard care.

2 The 1 mg/kg dose level of enfortumab will be enrolled only if de-escalation is needed after assessment of the next higher dose level (1.25 mg/kg).

Dose-Limiting Toxicities (DLTs) in Cycle 1 for the Lead-In Dose Escalation Portion of Cohort 9

DLTs are only defined for patients in the lead-in dose escalation portion of Cohort 9. 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 sitravatinib in combination with pembrolizumab and enfortumab that occurs from Cycle 1 Day 1 through pre-dose Cycle 2 Day 1:

Hematological DLTs:

- Grade 4 neutropenia, if it lasts more than 7 days.
- ≥ Grade 3 febrile neutropenia.

- ≥ Grade 3 neutropenia with significant clinical sequelae.
- Grade 4 thrombocytopenia.
- Grade 3 thrombocytopenia associated with clinically significant bleeding.
- Any requirement for a platelet transfusion.
- Grade 4 anemia unexplained by underlying disease.

Non-hematological DLTs:

- ≥ Grade 4 infusion related reaction.
- Grade 3 infusion related reaction that does not resolve within 24 hours.
- Any ≥ Grade 4 non-hematological toxicity.
- Grade 3 hypertension that cannot be controlled with medical therapy, including:
    - Severe hypertension with systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥120 mmHg, on more than one occasion.
    - Sustained uncontrolled hypertension, with systolic blood pressure ≥160 mmHg (but <180 mmHg) or diastolic blood pressure ≥100 mmHg (but <120 mmHg) lasting for ≥14 days or causing treatment delay for ≥4 days.
- Other Grade 3 non-hematologic toxicity lasting for >3 days despite optimal supportive care, with the following exceptions:
    - Endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that can be effectively managed with hormone replacement therapy.
    - Fatigue that persists for ≤7 days.
    - Rash that resolves to Grade ≤1 within 3 weeks.
    - Tumor flare (defined as local pain, irritation, or rash localized at sites of known or suspected tumor).
- 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.
- ≥ Grade 3 non-hematological laboratory abnormalities with clinical consequences that do not resolve within 24 hours.
- ALT > 3 x ULN with bilirubin > 2 x ULN.
- Any other related toxic effect during the first 3 weeks may be assessed as a DLT if, upon review by the Investigators and Sponsor, it is agreed that the toxicity was of sufficient severity to be considered dose limiting.
- Any toxicity that requires suspension of sitravatinib for more than 1 week.

- A patient did not receive at least 1 dose of pembrolizumab and at least 2 doses of enfortumab up to and including Cycle 2 Day 1 due to tolerability issues (i.e., other related AEs not attributed as DLTs).

Patients from the lead-in dose escalation portion of Cohort 9 are considered DLT evaluable if they experience a DLT during the first cycle of treatment or if they clear the DLT period. Patients who received prohibited therapy during Cycle 1 (refer to Section **Error! Reference source not found.**), or who did not take at least 80% of the planned dose of sitravatinib, the 1 planned dose of pembrolizumab and 2 planned doses of enfortumab in Cycle 1 will be ineligible for DLT evaluation and will be replaced unless they experience a DLT event. Initially, at least 3 patients will be enrolled at each new dose level. The first patient to be treated at each new dose level will be observed for at least one week prior to enrollment of subsequent patients at that dose level. Decision making for dose escalation or de-escalation will be in accordance with the mTPI-2 method (Dose-Finding Spreadsheet presented in Appendix 2), and will be made in collaboration with the Investigators and documented for Regulators and Institutional Review Boards by an Administrative Letter to Investigators.

For the lead-in dose escalation evaluation, no dose reductions of any investigational product are allowed during Cycle 1.

Hypothesis and Sample Size

Lead-In Dose Escalation Evaluation for Sitravatinib in Combination with Pembrolizumab and Enfortumab (Cohort 9)

Up to 30 patients may be enrolled into the lead-in dose escalation portion of Cohort 9.

The mTPI-2 design (Guo-2017) will be employed in decision making of dose escalation within each regimen investigated. The mTPI-2 design is based on the following assumptions:

- the maximum tolerated dose (MTD) is the dose associated with probability of dose limiting toxicity in 30% of patients during the first treatment cycle; and

- the acceptable variance around the MTD is - 0.05 to + 0.03 (i.e., the region of the MTD is 25% to 33% incidence of dose limiting toxicity).

Refer to 02 of the protocol for the dose escalation decision table using the mTPI-2 method.

7.2 Randomization

Random assignment to treatment arm is not being used in this study. Enrollment decisions will be determined by the site where the patient is enrolled as described in Section 6.1 of the protocol.

7.3 COVID-19 Pandemic Changes to Study Conduct

Table 8 below summarizes temporary changes to specific protocol assessments and procedures that are allowable during the COVID-19 pandemic (FDA-2020); these changes will not be recorded as protocol deviations unless otherwise specified. This appendix should be considered in effect until notification from Mirati is provided via Administrative Letter. Upon such notification, this appendix will no longer be applicable, and study conduct in accordance with the language in the body of the protocol will resume.

Patients should not be enrolled into the lead-in dose escalation portion of Cohort 9 unless they are able to meet the protocol defined assessments and procedures including adhering visit windows.

Table 8 COVID-19 Pandemic Changes to Study Conduct

Assessment/Procedure	Change During COVID-19 Pandemic
Visit Window	• Visit widows of up to +/- 5 days are allowed for Day 1 (beyond Cycle 1) and Day 15 clinic visits.
Clinic Visits	• Clinic visits may be conducted remotely by telephone/video conference; any missed assessments or procedures (e.g., tumor assessment, laboratory assessments, vital signs, study drug administration, etc.) should be documented as Protocol Deviations. • Clinic visits may be conducted at the patient's residence by qualified home health care professionals; any missed assessments or procedures (e.g., laboratory assessments, vital signs, study drug administration, etc.) should be documented as Protocol Deviations.
Safety Laboratory Assessments	Safety laboratory assessments may be performed at the patients nearest CAP or CLIA certified local laboratory if a remote visit is being conducted, whenever feasible.
Nivolumab Dosing (for Cohorts 1 through 8)	In order to reduce the need for Day 15 visits, Investigators should: • Consider switching all patients who are on the Q2 week 240 mg nivolumab regimen to the Q4 week 480 mg regimen instead, as possible. • Start all newly enrolled patients on the Q4 week 480 mg regimen.
Day 15 Sample Collection for PK and Other Exploratory Tests (for Cohorts 1 through 8)	In order to eliminate the Day 15 clinic visit (for Cohorts 1 through 8): • C1D15 PK samples, PD samples (TCR sequencing, flow cytometry, protein and cytokine biomarkers), and triplicate ECG may be collected at C2D1 instead. • C2D15 PD samples (flow cytometry, protein and cytokine biomarkers) may be collected at C3D1 instead.
PK Sample Collections	For Cohorts 1 through 8: • The PK collection required post-dose at 7 hours (5-9 hours) on C1D1 and C1D15 may not be collected in order to reduce the time that patients need to remain in the clinic for the blood draw and ECGs.
PK sub-study for patients with renal impairment (for Cohorts 1 through 8)	Temporarily suspended for new patients to reduce the time patients need to remain in the clinic or hospital for blood draws.

Action and Reporting in the Event of Documented or Suspected COVID-19 Infection

Study Treatment

- Patients in Screening for Study Entry – Patients who exhibit symptoms consistent with COVID-19 infection or have recent COVID-19 test results consistent with active viral replication should delay

study entry and start of study treatment until resolution of symptoms and evaluation by the Investigator. Questions should be directed to the Sponsor's Medical Monitor.

- Patients in Study Treatment – For patients on study treatment exhibiting symptoms consistent with COVID-19 infection, contact the Sponsor's Medical Monitor as soon as feasible.

8.0 Analysis Populations

8.1 Screened Population

The Screened Population is defined as all patients who sign an informed consent for the study.

8.2 Enrolled Population

The enrolled population is defined as all patients who sign an informed consent form for the study and are determined by the investigator to meet all eligibility criteria during screening assessments. This population will be used to describe disposition and may include patients who have not received study treatment.

8.3 Full Analysis Set (FAS)

The full analysis set will include patients who receive at least one dose of each study treatment drug (i.e. at least one dose of both sitravatinib and nivolumab for Cohorts 1 through 8, or at least one dose each of sitravatinib, pembrolizumab and enfortumab for Cohort 9).
This population will be used to present OS and PFS analyses and will also be the population set used for tumor assessment, tumor response and time to event listings.

8.4 Clinical Activity Evaluable Population

Patients included in the clinical activity evaluable population are patients who receive at least one dose of each study treatment drug and have an evaluable baseline tumor assessment and at least one-post-baseline tumor assessment.

This population will be used to summarize tumor responses as well as to make decisions throughout the first two stages of the study on the Predictive Probability Design for Cohorts 1 through 6.

8.5 Safety Population

The safety population is defined as all patients who received at least 1 dose of any study treatment (sitravatinib, nivolumab, pembrolizumab or enfortumab). The Safety population will be used for all safety analyses.

8.6 Molecular Marker Evaluable Population

The molecular marker evaluable population will consist of all patients who receive at least one dose of any study treatment (sitravatinib, nivolumab, pembrolizumab or enfortumab) and for whom PD-L1 expression or circulating PD-L1 results are available.

8.7 Pharmacokinetic Evaluable Population

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

8.8 Pharmacodynamic Evaluable Population

The pharmacodynamic evaluable population will consist of all patients who receive at least one dose of any study treatment (sitravatinib, nivolumab, pembrolizumab or enfortumab) and for whom PD results are available.

8.9 DLT Evaluable Population (only applicable to lead-in dose escalation portion of Cohort 9)

The DLT evaluable population is defined as patients enrolled in the lead-in dose escalation portion of Cohort 9, who experienced a DLT or who cleared the DLT period. Patients who received prohibited therapy during Cycle 1 (refer to Section **Error! Reference source not found.**), or who did not take at least 80% of the planned dose of sitravatinib, and 1 planned dose of pembrolizumab and 2 planned doses of enfortumab in Cycle 1 will be ineligible for DLT evaluation and will be replaced unless they experience a DLT event. The DLT evaluable population will be used for dose escalation decisions during the lead-in dose escalation evaluation.

9.0 Data Handling

Listings of all patient data will be prepared. Data summaries will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

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

9.1 Imputation of AEs or Concomitant Medications

Start Date

If the start date of AE 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. No imputation will be performed for medications with completely missing start dates.

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 Jan 1 will be assigned to the missing fields.

9.2 Imputation of Alternative Cancer Treatment Start Date

If the start date is completely missing, given that the patient did receive the anti-cancer therapy. the start date will be set to last dose date + 1.

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 Jan 1 will be assigned to the missing day and month.

9.3 Imputation of Laboratory Values with Character Symbol

Missing laboratory data will not be imputed. However, 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 calculation of summary statistics and comparing to normal ranges. These values will still be displayed as "< x" or "> x" in the listings.

9.4 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

No interim statistical analysis is planned during this study. As detailed in Protocol Section 9.1, per the Predictive Probability Design, tumor responses in the clinical activity evaluable population will be reviewed and enrollment decisions will be documented.

11.0 Statistical Methods

All data collected during this study will be displayed in data listings, unless otherwise specified. Data listings will be sorted by cohort and patient identifier for safety and efficacy listings. In addition, listings will include all relevant derived variables.

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

The summary tables will be presented by cohort (including initial and contingent cohorts) and for all cohorts combined.

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, sitravatinib, pembrolizumab, or enfortumab with the corresponding reasons. Summaries will be reported by cohort. The number of patients enrolled by site and across sites will be presented. Disposition will be summarized descriptively by cohort and for all cohorts combined.

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 Demographic and Baseline Characteristics

Demographic and baseline data will be summarized descriptively by cohort and all cohorts combined for the initial and contingent cohorts for the Safety population. For continuous variables, descriptive statistics will include the mean, STD, median, Q1, Q3, and range. For categorical variables, descriptive statistics will include the number and percent.

The term “baseline” is defined as the last pre-dose assessment, (includes screening and Cycle 1 Day 1 pre-dose assessment which would represent a 29-day window), unless otherwise specified. Unscheduled visits assessments preceding C1D1 will be also 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, Cycle 1 Day 1 assessments will be considered for baseline.

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

Primary disease history will be tabulated for the Safety population and will include the summary statistics (count and percentage) for Disease Location (Renal Pelvis, Ureter, Bladder, or Urethra), disease stage (Unresectable Locally-Advanced or Metastatic), and Clinical Stage (III, IIIA, IIIB, IV, IVA, IVB, Stage unknown).

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

Prior primary disease treatment (systemic therapies including platinum therapies and checkpoint inhibitors; radiotherapy, and surgery) will be tabulated for the Safety population and include the summary statistics (count and percentage) for the following:

- Prior platinum therapy - Platinum agent received (Cisplatin, Carboplatin, Other); Setting (Metastatic, Peri-operative); Disease Progression (Yes, No); Ineligible for platinum-based chemotherapy (Yes, No);
- Prior systemic therapy - Type (Neo-adjuvant or Adjuvant, Advanced Disease Treatment Regimen, Other);
- Prior checkpoint inhibitor – (Nivolumab, Pembrolizumab, Durvalumab, Atezolizumab, Avelumab, Other); Best Overall Response to prior Checkpoint inhibitor (CR, PR, SD, PD);
- Prior antibody drug conjugate – antibody drug conjugate received (Enfortumab Vedotin, Sacituzumab Govitecan);
- Prior radiotherapy – Type (Adjuvant, Palliative);
- Prior surgery – Location (Renal Pelvis, Ureter, Bladder, Urethra, Lung, Liver, Bone, Lymph Node, Other).

11.3.1 Baseline Bellmunt Score

The Bellmunt prognostic risk factor score is a tool that is often used to predict treatment outcomes before initiating a secondline treatment regimen. Baseline Bellmunt Score will be computed as number or risk factor (0,1,2,or 3) out of the following:

- ECOG PS ≥ 1
- Hemoglobin concentration < 10 g/dL
- Liver metasteses present

11.4 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. 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. Concomitant medications are defined as medications administered to study participants on or after the first dose of study treatment and before the last dose of study treatment. A medication can be considered both prior and concomitant. Collected prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Enhanced (version: 2018MAR01 DDE+HD B3 medical dictionary.

Prior and concomitant medications will be tabulated separately for the Safety population by Anatomical Therapeutic Chemical Classification and preferred drug name using counts and percentages. Summaries will be presented by cohort (including initial and contingent cohorts) and all cohorts combined. Prior and concomitant medications will be included in a patient data listing.

11.5 Medical History

Medical history will be tabulated by system organ class (SOC) and preferred term (PT) using counts and percentages for the Safety population. Medical history will be coded according to Medical Dictionary for Regulatory Activities (MedDRA, Version 21.0). Medical history will be listed by patient.

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 primary disease history.

11.6 Efficacy Analyses and Efficacy Variables

11.6.1 Objective Response Rate (ORR)

Disease assessments involving radiographic evaluations may be performed over the course of a few days. The date of response (Complete Response, CR; Partial Response, PR; Stable Disease, SD; or Not Evaluable, NE) will be recorded as the date of the last radiographic evaluation included in the series for that time point assessment. The date of progression (PD) will be recorded as the date of the first radiographic evaluation included in the series for that time point assessment to identify progression.

ORR will be categorized in accordance with RECIST v1.1. (Appendix 3) Objective Response Rate (ORR) is defined as the percent of patients documented to have a confirmed CR or PR as defined in Table 9.

Descriptive statistics (frequency and percentage) for ORR, CR, and PR will be presented. The 95% exact Clopper-Pearson CI of these response rates will be calculated. An exact test for single proportion (two-sided $\alpha = 5\%$) will be performed to test H_0: ORR $\leq$ 5% against H_1: ORR > 5%.
Best overall response (BOR) is defined as the best response among all overall responses (in the order CR, PR, SD, PD, and indeterminate NE) recorded from the start of study drug until disease progression/ recurrence, or start of 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 version 1.1. If the status of CR or PR cannot be confirmed by repeat tumor assessment, the BOR of unconfirmed CR and PR will be determined per RECIST 1.1. The status of BOR of SD requires an on-study assessment after at least 42 days on treatment. Patients without a valid clinical response assessment will be assigned a best overall response of NE. No response will be counted after PD.

Table 9 lists out the different scenarios of confirmed response based on subsequent assessment. The status of SD requires an on-study assessment at least 42 days on study. Patients without a valid clinical response assessment will be assigned a best overall response of NE.

Table 9 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)
First Time Point Response**	**Second Time Point Response**	**Confirmed Response (Best Response)***
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 six (6) weeks (42 days).If the patient is on-study less than six (6) weeks (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 Time Point Response (TPR) confirms the CR (or PR) then the Confirmed Response will be CR (or PR). For this study, only one (1) intervening NE is allowed between CRs/PRs. For example: CR NE CR = CR; PR NE PR = PR. Additionally, one (1) SD is allowed between PRs (e.g., PR SD PR = PR).

(1) Best response will be SD if the first TPR is after at least six (6) weeks (42 days) on-treatment. Otherwise, the best response will be PD.

(2) Best response will be SD if the first TPR is after six (6) weeks (42 days) on-study. Otherwise, the best response will be NE.
(3) TPR is SD if the increase from the first to the second assessment does not qualify for PD.

For patients with unconfirmed CR/PR and who subsequently drop off the study, the best overall response will be SD.

Descriptive statistics (frequency, percentagefor best overall response (CR, PR, SD, PD, NE) based on response assessments by the investigator will be presented.

The primary analysis will be conducted in the Full Analysis Population and supportive analysis will be presented in the Clinical Activity Evaluable population.

11.6.2 Duration of Response (DOR)

Duration of response (DOR) in months is defined as the time from date of the first documentation of confirmed 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)/30.4375. Duration of response will only be calculated for the subgroup of patients achieving a confirmed CR or PR.

DOR will be summarized descriptively using the Kaplan-Meier estimate. The median, 25th percentile, and 75th percentile of DOR and their two-sided 95% CI (Brookmeyer & Crowley, 1982) will be calculated where appropriate. In addition, minimum and maximum will also be displayed. Kaplan-Meier plots will be provided for DOR.

DOR will be based on response assessments by Investigator. DOR will be conducted in the CAE population who have confirmed CR or PR.

11.6.3 Overall Survival (OS)

Overall survival (OS) is defined as the time from first dose of study drug to the date of death due to any cause. OS (in months) is calculated as (date of death − date of first dose of study drug +1)/30.4375.

OS will be summarized descriptively using the Kaplan-Meier estimate. The median, 25th percentile, and 75th percentile of OS and their two-sided 95% CI (Brookmeyer & Crowley, 1982) will be calculated where appropriate. In addition, minimum and maximum will also be displayed. Kaplan-Meier plots will be provided.

The 1-year OS rate (proportion and 95% CI) will be analyzed using Kaplan-Meier methodology (Greenwood's formula, (Kalbfleisch & Prentice, 1980)).

Analysis will be performed on the FAS.

Censoring Rules

For patients who are continuing study at the time of analysis, lost to follow-up or who withdraw 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 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 first dose of study drug, OS will be censored at the date of first dose (Day 1).

11.6.4 Extent of Follow-up

The extent of follow-up is defined as the time from the date of the first dose to the last known date that the patient was alive (for patients who are alive) or death date (for patients who died).
The median extent of follow-up with 95% CI will be calculated and presented using a reverse KM approach.
Analysis will be performed on the FAS.

11.6.5 Progression-Free Survival (PFS)

Progression-free survival (PFS) is defined as the time from the first dose of study drug to the date of PD or death due to any cause, whichever occurs first in the absence of documented PD. PFS (in months) will be calculated as (first event date – first dose date + 1)/30.4375.

PFS will be summarized descriptively using the Kaplan-Meier estimate. The median, 25th percentile, and 75th percentile of PFS and their two-sided 95% CI (Brookmeyer & Crowley, 1982) will be calculated where appropriate. In addition, minimum and maximum will also be displayed. Kaplan-Meier plots will be provided for PFS.

Analysis will be performed on the FAS.

Censoring Rules for DoR and PFS

The following censoring rules will apply to event dates for time-to-event endpoints that are based on radiographic evaluations, i.e., DOR and PFS:

- Endpoints will be censored on the date of first dose (or randomization) with duration of 1 day under the following scenarios, unless patients die within 2 consecutive tumor assessments of first dose (on or prior to week 16, i.e. Cycle 5 Day 1 plus the 10 day window, which is Study Day 122 for Cohorts 1-8 or Day 136 for Cohort 9), , in which case they will be assessed as having an event on the date of death (apply to PFS only):
    - baseline disease assessment inadequate to apply RECIST1.1;
    - no disease assessments are performed during study treatment; or
    - all disease assessments performed during study treatment result in the conclusion of NE.
- Endpoints will be censored on the date of the last evaluable disease assessment prior to the start of subsequent anti-cancer therapy under the following scenarios (apply to PFS and DOR). Last evaluable assessment date is defined as the last response assessment date on or after treatment start date with a response of CR, PR, or SD.
    - PD or death occur after ≥2 consecutive tumor assessments (i.e., ≥ 122 days of last evaluable tumor assessment for Cohorts 1-8 or ≥ 136 days for Cohort 9) that are missed or result in the conclusion of NE;
    - patient administered subsequent anti-cancer treatment prior to documented PD or death;
    - patient lost to follow-up;
    - patient withdrawal of consent for follow-up; or
    - patients alive and without PD at the time of analysis

Date of death will be considered an event for DOR and PFS only if death occurred in the absence of receiving subsequent anti-cancer therapy, and under one of the following scenarios:

- death occurs prior to PD and < 122 days for Cohorts 1-8 or < 136 days for Cohort 9 after the first dose of study treatment; or
- death occurs < 122 days for Cohorts 1-8 or < 136 days for Cohort 9 after the last evaluable disease assessment

11.6.6 Clinical Benefit Rate (CBR)

Clinical benefit rate (CBR) response will be categorized in accordance with RECIST v1.1. CBR is defined as the percent of patients documented to have a confirmed CR, PR, or SD.

Descriptive statistics (frequency and percentage) and 95% exact Clopper-Pearson CI for CBR rate will be presented for FAS and CAE.

11.6.7 Subgroup Analyses, including Prior Clinical Benefit (PCB) and No Prior Clinical Benefit (NPCB) Endpoints

Baseline characteristics to be evaluated in subgroup analyses include most recent tumor PD-L1 expression test result indicating high versus low expression and, for cohorts that have prior PD-(L)1 checkpoint inhibitor therapy experience (i.e. Cohorts 1 through 4, and Cohorts 7 through 9) outcome of prior treatment with checkpoint inhibitor therapy, specifically prior clinical benefit versus no prior clinical benefit, defined as:

- Prior clinical benefit (PCB): RECIST-defined partial or complete response or stable disease for at least 12 weeks (-2 week window permitted for radiograph scheduling) followed by radiographic progression of disease.
- No prior clinical benefit (NPCB): does not meet criteria for PCB and has radiographic progression of disease ≤ 12 weeks after initiation of treatment (+2 week window permitted for radiograph scheduling).
- Efficacy analyses will be presented descriptively per each subgroup listed above, for each cohort, as well as for all cohorts combined if deemed appropriate.

11.7 Safety Analyses

All safety summaries will be presented by cohort (including initial and contingent cohorts) and all cohorts combined. 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 subsequent anti-cancer therapy, whichever is earlier.

11.7.1 Extent of Study Drug Exposure and Exposure Variables

Study Treatment Duration

Study treatment duration (weeks) is defined as (the last dose date – the first dose date +1)/7. Weeks on treatment will be summarized separately for each study drug.

Days on Sitravatinib

Days on sitravatinib 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 Sitra Administration CRF page) – number of days with 0 mg dose + 1].

Cycles Started

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

Cumulative Dose Received

- 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 as a 240 mg intravenous infusion over 30 minutes every 2 weeks. An alternative dosing regimen of 480 mg intravenous infusion over 30 minutes every 4 weeks may be introduced during the study. 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 sitravatinib a patient receives during the study, that is, Sum of [(Stop date – Start date + 1) x Total Dose (mg per administration) x Dose Frequency] as recorded on the Sitravatinib Administration CRF forms. Dose modifications should be accounted for in the cumulative dose received calculations

- Cumalative dose received for pembrolizumab (mg) is defined as total amount of pembrolizumab a patient receives during the study as recorded on the Pembrolizumab Administration CRF forms. Pembrolizumab is planned to be administered as 200 mg intravenous infusion every 3 week.
- Cumulative dose received for enfortumab is defined as total amount of enfortumab a patient receives during the study as recorded on the Enfortumab Administration CRF forms. Enfortumab is planned to be administered as 1 mg/kg infusions on Days 1 and 8, every 3 weeks for combination regimine dose level "-1[2]" in Cohort 9. Enfortumab is planned to be administered as 1.25 mg/kg infusions on Days 1 and 8, every 3 weeks for combination regimine dose level "1" in Cohort 9.

Compliance

- Compliance is only applied to sitravatinib and is calculated as cumulative dose received (mg) / cumulative planned dose (mg) x 100, where the adjusted cumulative planned dose = (Planned dose in mg) * (study treatment duration in days - number of days on dose interruption due to AE - number of days on dose reduction due to AE) + ∑(planned reduced daily dose x number of days on dose reduction due to AE).

Dose Intensity

- Relative dose intensity for sitravatinib, nivolumab, pembrolizumab, enfortumab is defined as:
  - For sitravatinib: [cumulative dose received (mg) / cumulative planned dose (mg)] x 100, where cumulative planned dose is calculated as the starting daily dose multiplied by the study treatment duration in days, which does not take into account dose reduction or interruption.
  - For nivolumab: [cumulative nivolumab dose received (mg)] / [cumulative planned nivolumab dose (mg)] x 100, where cumulative planned dose is:

    $round\left(\frac{duration\ of\ nivolumab\ in\ weeks\ +2\ weeks}{2\ weeks}\right) \times 240\ mg$, for patients who received 240 mg as last dose

    $round\left(\frac{duration\ of\ nivolumab\ in\ weeks\ +4\ weeks}{2\ weeks}\right) \times 240\ mg$, for patients who received 480 mg as last dose

    Duration of nivolumab is last dose of nivolumab – first dose of nivolumab in weeks.
  - For pembrolizumab: [cumulative dose received (mg) / cumulative planned dose (mg)] x 100, where cumulative planned dose is calculated as

    $$round\left(\frac{duration\ of\ pembrolizumab\ in\ weeks + 3\ weeks}{3\ weeks}\right) \times 200\ mg$$

    Duration of nivolumab is last dose of nivolumab – first dose of nivolumab in weeks.
  - For enfortumab: [cumulative dose received (mg) / cumulative planned dose (mg)] x 100, where cumulative planned dose is calculated as:

    $$round\left(\frac{duration\ of\ enfortumab\ in\ weeks + 3\ weeks}{3\ weeks}\right) \times \min(starting\ dose \times baseline\ weight\ (kg)\ ,\ maximum\ dose) \times 2\ (Day\ 1\ and\ Day\ 8)$$

    Duration of enfortumab is last dose of enfortumab – first dose of enfortumab in weeks.

Descriptive statistics will be provided separately for each study drug, for the duration of exposure (weeks), the total number of cycles started, number of days on sitravatinib , 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 reason for dose reduction (only for sitravatinib), at least 1 dose interrupted and reasons for dose interruption will be presented separately for each study drug.

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

11.7.2 Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 21.0). 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 drug treatment. 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 or occur on Day 28 after the last dose should be followed until resolution or stabilization to a chronic condition, or administration of alternative cancer treatment, whichever is earlier.

Treatment-Emergent AEs (TEAEs)

Treatment emergent AEs (TEAEs) are AEs that begin after first dose of study treatment until 28 days after the last dose of study treatment and prior to the initiation of subsequent 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 SAEs ongoing or occur on Day 28 after the last dose should be followed until resolution or stabilization to a chronic condition, or administration of alternative cancer treatment, whichever is later. All AEs will be coded according to the MedDRA Version 21.0 dictionary by system organ class (SOC), preferred term (PT), and severity grade using NCI CTCAE Version 5.0 .

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.

All adverse event summary tables will be based on the safety population. An overall summary of TEAEs by cohort will be presented.

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 at the highest grade. The following summaries will be presented:

- Treatment-emergent adverse events
- Treatment-related treatment-emergent adverse events
- Treatment-emergent adverse events leading to all study drug discontinuation
- Treatment-emergent serious adverse events
- Treatment-emergent adverse events resulting in death
- Treatment-emergent adverse events with maximum CTCAE severity grade ≥ 3

All summaries will also be presented by:

- Sitravatinib-related treatment-emergent adverse events
- Nivolumab-related treatment-emergent adverse events
- Sitravatinib- or Nivolumab-related treatment-emergent adverse events
- Pembrolizumab-related treatment-emergent adverse events
- Enfortumab-related treatment-emergent adverse events

- Sitravatinib- or Pembrolizumab- or Enfortumab-related treatment-emergent adverse events

TEAEs will be presented by PT in descending order of frequency. In addition, TEAEs in the Safety population will be presented by grouped grade(Grade 1/2, Grade 3/4, Grade 5 and any) and PT in descending order of frequency.

Immune-related AEs will be summarized separately by SOC, PT, and cohort.

All AEs (including non-treatment-emergent events and serious events) recorded on the CRF will be listed using the all Enrolled Population. A listing of treatment-emergent adverse events leading to dose reduction, interruption or discontinuation of either study drug will be presented separately.

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 for TEAEs leading to death and SAEs:

- Treatment-related treatment-emergent adverse events
- Sitravatinib-related treatment-emergent adverse events
- Nivolumab-related treatment-emergent adverse events
- Sitravatinib- or Nivolumab-related treatment-emergent adverse events
- Pembrolizumab-related treatment-emergent adverse events
- Enfortumab-related treatment-emergent adverse events
- Sitravatinib- or Pembrolizumab- or Enfortumab-related treatment-emergent adverse events

A listing of patients with TEAEs that led to death will be presented. A listing of patients who experience an SAE will also be presented.

11.7.4 Laboratory Data

All laboratory data will be summarized in International System (SI) units, with certain parameters (creatinine, BUN, bilirubin, phosphate, and calcium) repeated using British imperial units commonly used in the US. 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.

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 by cohort and overall cohort combined 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), 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 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.
Clinical laboratory parameters to be collected routinely on-study are listed in Table 10 below.

Table 10 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	Direct bilirubin
	Indirect bilirubin
Coagulation	Lipase
International normalized ration (INR)	Amylase
Partial thromboplastin time (PTT)	Sodium
	Potassium
Urinalysis (dip stick)	Chloride
Blood	Bicarbonate [CO^2]
Protein	Blood urea nitrogen (BUN)
	Creatinine
Thyroid Function Test	Albumin
Thyroid stimulating hormone (TSH)	Total calcium
	Magnesium
	Uric acid
	Hemoglobin A1C (HgBA1c)

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.

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 cycle. 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, direct bilirubin, indirect bilirubin, lipase, amylase, creatinine, uric acid, BUN, albumin, sodium, potassium, chloride, magnesium, calcium and bicarbonate.

Descriptive statistics will be provided for each test result and for change from baseline by cycle. Multiple measurements taken during the visit for a patient will be represented by the most severe value as noted in Section 12.7.4.1. 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 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), 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 Thyroid stimulating hormone (TSH).

11.7.4.5 CTCAE Coding of Laboratory Data

Where laboratory values are categorized into NCI CTCAE Version 5.0 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, 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.

Vital signs and change from baseline will be summarized. All vital signs and change from baseline through the last Cycle will be summarized by cohort and all cohorts combined. 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.

Potentially clinically important vital sign results will be summarized separately. These criteria are defined as increases in blood pressure and weight changes:

- SBP (≥160 mmHg, ≥180 mmHg, ≥ 200 mmHg)
- DBP (≥100 mmHg, ≥120 mmHg)
- Weight increased ≥5% from baseline
- Weight decreased ≥10% from baseline

All vital signs will be listed.

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

11.7.6.1 Physical Examination

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.

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

11.7.6.2 Eye Exam (Cohort 9 only)

Patients with recent ocular complaints (within ≤ 3 months of screening) must have a complete eye examination at Screening Visit performed by a qualified ophthalmologist or optometrist, including but not limited to: uncorrected, corrected and best corrected visual acuity, slit lamp, tonometry examination, and dilated fundus examination. Prior ophthalmologic exam done within 3 months of screening is acceptable provided there are no new symptoms since that exam. End of Treatment Visit slit lamp examinations are required for all patients who experience corneal adverse events during the study and must be performed ≥ 28 days from last dose of enfortumab. Additional eye examinations are to be conducted as clinically indicated.

Eye exam data will be presented as Listings including values obtained on visual acuity tests within 3 months of screening, and End of Treatment Visit (as applicable), and any additional eye measurements (as needed), and corneal Adverse Events.

Eye exam Table will include patient id, baseline visual acuity values, change in visual actuiy value by test, and percent change of visual acuity test value till End of Treatment.
Another eye exam Table will include Number of Corneal Adverse Events (absolute and by percentage) by Cohort and for Total.

11.7.6.3 Electrocardiograms

Single and triplicate 12-Lead electrocardiogram (ECG) parameters will be collected. The following will be assessed: rhythm (sinus or other), heart rate (bpm), QRS, QT, RR, and the investigator interpretation. The QT interval corrected for heart rate by the Fridericia's formula (QTcF) will be manually calculated in the database.

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.

For each planned visit for which a triplicate ECG is obtained, the average the 3 values should be calculated for each parameter at each timepoint. The average values will be used for the ECG tables.

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 hours pre-dose.

In addition, listings and summaries will be generated for patients by Maximum ICH E14 Category with QTcF increased to value ≥480 and <500 msec, and value ≥500 msec, and patients with change from baseline QTcF increased by ≥30 to <60 msec, and by ≥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. A shift from baseline to worst CTCAE grade summary will also be presented.

A shift from baseline to worst CTCAE (v5.0) grade for QTcF values will also be presented.

QTcF will be graded per CTCAE v5.0. the grades are as follows:

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

Descriptive summaries for patients meeting the following ECG thresholds (based on the average of triplicate measurements at each time point), will also be provided:

- Absolute QTc ≤450 msec, >450 to ⩽480 msec, >480 to ≤500 msec, >500 msec
- Change from baseline QTc ≤30 msec, >30 to ≤60 msec, >60 msec
- PR >220 msec and change from baseline >25%
- QRS >110 msec and change from baseline >25%

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

11.7.6.4 Multigated Acquisition Scan or Echocardiogram

Echocardiogram (ECHO) or Multigated Acquisition Scan (MUGA) will be performed at screening, and thereafter at Cycle 3 Day 1, and as clinically indicated and also at the 7-Day post-treatment visit as in Schedule of Assessments Tables 1-3 of the protocol. Additional assessments of left ventricular ejection fraction (LVEF) may be performed as clinically indicated at the investigator's discretion if there are signs or symptoms of cardiotoxicity.

MUGA or ECHO parameters, including LVEF, will be summarized. Observed values and changes from baseline will be presented for each planned visit. Additionally, patients who have at least one on-treatment decrease in value will be summarized using the following four categories: 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%. More specifically, the summary table for LVEF (%) would reflect the following 4 categories with the number and percentage:

1. Decrease from Baseline of ≥10% and Absolute on-treatment Value ≥40%
2. Decrease from Baseline of ≥10% and Absolute on-treatment Value <40%
3. Decrease from Baseline of ≥20% and Absolute on-treatment Value ≥40%
4. Decrease from Baseline of ≥20% and Absolute on-treatment Value <40%

A separate listing of the MUGA or ECHO results will be presented.

11.7.6.5 Pregnancy Test

Pregnancy testing data will be listed for the Safety population.

11.7.6.6 Long Term Follow-up

Long term follow-up/survival data will be listed for the safety population. Additionally, all follow-up anti-cancer therapy will be listed.

11.7.6.7 Death Report

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

11.8 Other Endpoints

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

12.0 References

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Appendix 1 Glossary of Abbreviations

Glossary of Abbreviations:	
ADC	Antibody-Drug Conjugate
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Class
BOR	Best Overall Response
BUN	Blood Urea Nitrogen
C	Celsius
CBR	Clinical Benefit Rate
CI	Confidence Interval
CIT	Checkpoint Inhibitor Therapy
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
DLT	Dose-Limiting Toxicity
DR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EV	Enfortumab
FDA	Food and Drug Administration
INR	Internal Normalization Ratio
irAE	Immune-related Adverse Event
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NE	Not Evaluable
NPCB	No Prior clinical benefit

Glossary of Abbreviations:	
ORR	Objective Response Rate
OS	Overall Survival
PCB	Prior clinical benefit
PD	Progressive Disease
PD-1	Programmed Cell Death 1
PD-L1	Programmed Cell Death Ligand 1
PET	Positron Emission Tomography Scan
PFS	Progression-free Survival
PK	Pharmacokinetic
PPD	Predictive Probability Design
PR	Partial Response
PT	Preferred Term
PTT	Partial Thromboplastin Time
Q1	First Quartile
Q2W	Every 2 Weeks
Q3	Third Quartile
QD	Once Daily
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
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

Appendix 2 Dose De-Escalation Decision Table Using the mTPI Method

The table below will be used for decision making with regards to potential starting dose escalations in subsequent patients. The assessment is based on the number of patients with toxicity at a given dose regimen of sitravatinib in combination with pembrolizumab and enfortumab in the lead-in dose escalation evaluation (Cohort 9) as defined in **Error! Reference source not found.** and assumes a maximum toxicity level of no more than 30% at the tolerated dose. The letters in different colors are computed based on the decision rules under the mTPI-2 method (Guo-2017) and represent different dose-finding actions which include: E = Escalate to next higher dose; S = Stay at the current dose; D = De-escalate to the next lower dose; and U = The current dose in unacceptably toxic.

		Number of Patients Treated at Current Dose																													
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Number of Toxicities	0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
	1	D	D	D	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
	2		DU	D	D	D	D	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
	3			DU	DU	D	D	D	D	D	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
	4				DU	DU	DU	D	D	D	D	D	D	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E
	5					DU	DU	DU	DU	DU	D	D	D	D	D	D	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E
	6						DU	DU	DU	DU	DU	DU	D	D	D	D	D	D	D	S	S	S	S	S	S	E	E	E	E	E	E
	7							DU	DU	DU	DU	DU	DU	DU	D	D	D	D	D	D	D	D	S	S	S	S	S	S	E	E
	8								DU	DU	DU	DU	DU	DU	DU	DU	DU	D	D	D	D	D	D	D	D	S	S	S	S	S	S
	9									DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D	D	D	D	D	D	D	D	S	S	S
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E = Escalate to the next higher dose

S = Stay at the current dose

D = De-escalate to the next lower dose

U = The current dose is unacceptable toxic

MTD = 0.30

Sample size = 30

Epsilon1 (ε1) = 0.05

Epsilon1 (ε2) = 0.03

Appendix 3 Abbreviated Presentation of RECIST Version 1.1 Guidelines

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

Categorizing Lesions at Baseline

Measurable Lesions

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

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

Non-Measurable Disease

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

Normal Lesions

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

Tumor Assessments

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. All required scans must be done within the window of time specified in the Schedule of Assessments prior to treatment. If the baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

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

Target Lesions

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

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

Non-Target Lesions

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

Objective Response Status at Each Evaluation

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

Target Disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis < 10 mm). All target lesions must be assessed.
- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.
- Stable Disease (SD): Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.
- Progressive Disease (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy) with a minimum absolute increase of 5 mm.
- Indeterminate: Progression has not been documented, and
    - one or more target lesions have not been assessed,

- or assessment methods used were inconsistent with those used at baseline and impaired assessment,
- or one or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure),
- or one or more target lesions were excised or irradiated and have not reappeared or increased.

Non-Target Disease

- CR: Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be 'normal' in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.
- PD: Unequivocal progression of preexisting lesions. Generally, the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.
- Indeterminate: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

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

Lesion Changes That May Be Transient

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

Supplemental Investigations

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

Best Objective Response

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

Subjective Progression

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