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

NCT Number: NCT03606174

Document Date: 22 June 2020

CLINICAL RESEARCH PROTOCOL

DRUG(S):	Sitravatinib (MGCD516) Nivolumab (OPDIVO®) Pembrolizumab (KEYTRUDA®) Enfortumab vedotin-ejfv (PADCEV™)
STUDY NUMBER:	516-003
PROTOCOL TITLE:	A Phase 2 Study of Sitravatinib in Combination with PD-(L)1 Checkpoint Inhibitor Regimens in Patients with Advanced or Metastatic Urothelial Carcinoma
IND NUMBER:	138337
SPONSOR:	Mirati Therapeutics, Inc. 9393 Towne Centre Drive, Suite 200 San Diego, California, 92121, USA
ORIGINAL PROTOCOL DATE:	09 March 2018
VERSION NUMBER:	V4.0
VERSION DATE:	22 June 2020

DOCUMENT HISTORY

Document	Version Date	Summary of Changes
Original Protocol, Version 1.0	09 March 2018	NA
Amendment #1, Version 2.0	19 April 2018	• At the request of US Food and Drug Administration during IND review, the following changes were made. o Added limitations on continuation of study treatment in the event of RECIST-defined disease progression and the requirement for written informed consent to continue study treatment. o Specified that if one study treatment is interrupted or discontinued to manage adverse events, the other study treatment may continue in accordance with the protocol and OPDIVO Product Information. o Added details to sitravatinib dose modification to manage hematological and non-hematological adverse events, hypertension (added Table 9), decreased LVEF, and increase hepatic transaminases. o Added that if sitravatinib dosing is interrupted for ≥ 14 days, dose reduction should be considered. o Emphasized that OPDIVO Product Information must be consulted to ensure correct action is taken for nivolumab dose modification in the management of adverse events. • Removed absolute requirement for tumor tissue tests from Table 1, footnote #2. • Rearranged Section 5 subsections to address management of adverse events under one heading (Section 5.5) for clarity. • Addressed clerical errors and made minor clarifications.
Amendment #2, Version 3.0	13 September 2019	Study Design: • Added Appendix 8 – a contingent cohort study in patients previously treated with an antibody-drug conjugate, in response to emerging treatment options for the study population. • Updated the number of patients expected to participate in the study. Schedule of Assessments (Table 1 and Table 2): • Clarified visit windows for: o Day 1 of Cycles 2 and 3, and o ECHO or MUGA examinations. • Clarified that beyond treatment Cycle 3, Day 15 clinic visits (i.e., abbreviated physical examination and vital signs) are required only when the nivolumab Q2W dosing schedule is used.

Document	Version Date	Summary of Changes
		• Added flexibility in scheduling of tumor biopsies around C2D15. • Added requirement for a urinalysis to be performed prior to study-related biopsies of tumors involving the genitourinary tract. • Adjusted time of PK and ECG assessments in main study to later in the clinic day (from hour 4 to hour 7 after dosing) to improve PK parameter estimations and in response to US FDA request. Entry Criteria: • Inclusion criterion 4: updated to allow enrollment of patients having selected unresolved AEs of prior therapy including alopecia, and ≤ grade 2 dysgeusia or peripheral neuropathy. • Exclusion criteria o 4a: clarified that ≥ grade 3 immune-related AEs during prior treatment with CIT are of interest for enrollment exclusion, rather than all ≥ grade 3 related AEs. o 4b: aligned with product labeling by removal of hepatitis from the list of immune-related AEs. o 4c: deleted criterion excluding patients having prior Grade 1 immune-related AEs during CIT treatment. o 5c: clarified that medically-important autoimmune diseases are to be considered and added Sjögren's syndrome. o 17: added approximate 2-week washout window for prior systemic therapy. Study Treatment: • Corrected sitravatinib dispensing to every cycle beyond Cycle 12 rather than allowing dispensing every 2 cycles. • Added allowance for use of nivolumab regimen 480 mg administered every 4 weeks, per revised product labeling. • Updated guidance for sitravatinib management in the event of Grade 2 symptomatic toxicities early in treatment (Section 5.5.1.1). Study sites were informed of this change by Administrative Letter dated 15 May 2019. Clarified the reporting period for patient deaths to include at least 28 days after the last administration of study treatment, regardless of start of subsequent therapy.

Document	Version Date	Summary of Changes
		Appendix 2 Calculation of Glomerular Filtration Rate and Renal Impairment Scale: clarified use of individual patient BSA rather than standardized BSA in calculation of eGFR. Appendix 5 Contingent Cohort Study in Patients Previously Treated with Immunotherapies: clarified that eligible prior immunotherapies are not limited to those listed, in response to emerging treatment options for the study population. In addition, clarified several enrollment criteria in relation to the main protocol. Appendix 6 Contingent Cohort Study in CIT-Naïve Populations: clarified several enrollment criteria in relation to the main protocol. Appendix 7 Renal Impairment Evaluation: added evaluation of sitravatinib PK in patients having normal renal function to strengthen interpretation of PK observed in patients having mild or moderate renal impairment. Addressed clerical errors and made minor clarifications.
Amendment #3, Version 4.0	22 June 2020	Executive summary of main changes in Amendment #3: • Introduction of a new regimen of sitravatinib in combination with a PD-(L)1 checkpoint inhibitor (sitravatinib, pembrolizumab and enfortumab in Cohorts 9 and 10), in addition to the existing regimen (sitravatinib and nivolumab in Cohorts 1 through 8). Relevant background information has been updated throughout the protocol as a result. Information regarding a lead-in dose escalation evaluation with the new regimen is also provided. • Addition of sitravatinib malate capsule formulation. [Note that the free base capsule formulation will remain available for new patients in Cohorts 1 through 6, and for patients who start the study under a previous protocol version on the free base capsule formulation who will remain on free base capsule formulation for the duration of study treatment.] • Addition of starting dose and de-escalation schedule for sitravatinib malate capsule formulation daily dose as supported by the data from study 516-006. • Consolidation of all entry criteria in Section 4.1 and Section 4.2 for clarity (previously changes to entry criteria for contingent cohorts were mentioned in corresponding appendices). • Added status of all cohorts as of protocol version 4.0 for clarity. • Clarified temporary changes to specific protocol assessments and procedures that are allowable only during the COVID-19 pandemic. A detailed description of changes follows.

Document	Version Date	Summary of Changes
		Cover Page: • Updated Drugs to include drugs to be used as part of treatment regimen in Cohorts 9 and 10. • Updated Title to specify class of drug to be given in regimens with sitravatinib to reflect the new regimen to be used in Cohorts 9 and 10. Study Summary: • Added the rationale for using antibody-drug conjugates (ADCs) in combination with checkpoint inhibitors to treat cancer. • Added background information regarding pembrolizumab and enfortumab since they are components of the treatment regimen for Cohorts 9 and 10. • Updated the number in trial (with the increased sample size of Cohorts 7 and 8, and the proposed total enrollment in Cohorts 9 and 10) and added the status of contingent cohorts as of protocol version 4.0. • Primary objective updated to specify class of drug to be given in regimens with sitravatinib to be inclusive of the new regimen to be used in Cohorts 9 and 10. • Revised secondary objectives updated to "combination regimens" to be inclusive of the new regimen to be used in Cohorts 9 and 10. • Added secondary objectives for new Cohort 9 to identify the recommended phase 2 combinational doses (RP2Ds). • Added secondary endpoint of dose-limiting toxicities for new Cohort 9. • Study Design updated to reflect status of all cohorts as of protocol version 4.0, and added details regarding Cohorts 3-8 (that were previously only included in the appendices) and the new Cohorts 9 and 10 (sitravatinib in combination with pembrolizumab and enfortumab). • Study Schema was updated to include all 10 cohorts that are now included in the protocol. • Study Treatments was updated with the new sitravatinib, pembrolizumab and enfortumab regimen that is given every 3 weeks. Schedule of Assessments (Table 1): • Clarified that table applies to Cohorts 1 through 8 (sitravatinib and nivolumab). • Footnote #11: added disease evaluations for patients who discontinue study treatment due to reasons other

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		than objective disease progression at same frequency until progression, new cancer therapy or death. • Footnote #13: Added option to perform long-term follow-up by email in addition to telephone contact. • Footnote #14: Clarified timing of the End of Treatment Visit as within 7-14 days after decision to permanently discontinue study treatments. Schedule of PK, PD and ECG assessments (Table 2): • Clarified that table applies to Cohorts 1 through 8. • Footnote #1: Clarified PK collections in cases of sitravatinib dose interruptions. Schedule of Assessments (Table 3): • Added table for new Cohorts 9 and 10 (sitravatinib, pembrolizumab and enfortumab). Schedule of PK, PD and ECG assessments (Table 4): • Added table for new Cohorts 9 and 10. Section 1.1.3 Checkpoint Inhibitor Therapy in UC: • Added background pembrolizumab information. Section 1.1.4 Antibody-Drug Conjugates (ADCs): • Added definition of ADCs. Section 1.1.5 ADC Targeted Therapy in UC: • Added background ADCs information (emphasis on enfortumab) and provided rationale for the sitravatinib, pembrolizumab and enfortumab combination regimen. Section 1.2.2 Sitravatinib in Combination with a Checkpoint Inhibitor and an ADC: • Added preclinical and clinical data as background to support the rationale for the sitravatinib, pembrolizumab and enfortumab combination regimen. • Specified hypothesis that adding sitravatinib, may complement the therapies in mounting an anti-tumor immune response and further augment the antitumor efficacy observed with enfortumab and pembrolizumab combination. Section 1.3.1 Sitravatinib Drug Substance: • Added malate salt formulation of sitravatinib and clarified the initial formulation was “free base”. Sections 1.3.2 Nonclinical Data, 1.3.3 Sitravatinib Clinical Experience: • Added guidance, throughout, that the current IB should be referenced for current data. Section 1.3.3 Sitravatinib Clinical Experience:

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		• Added interim results from Study 516-006, a healthy volunteer study evaluating the bioavailability and PK of sitravatinib free base and sitravatinib malate capsule formulations. Section 1.3.3.2 Sitravatinib Clinical Safety: • Updated the results for relevant studies contributing to sitravatinib's clinical safety data (516-003, 516-001, and MRTX500) and the cumulative safety data based upon the current IB. Section 1.3.3.3 Sitravatinib Clinical Efficacy: • Added preliminary clinical activity results for relevant studies (516-003 and MRTX-500). Section 1.3.3.4 Sitravatinib Capsule Formulation Study: • Added interim results from Study 516-006, a healthy volunteer study evaluating the bioavailability and PK of sitravatinib free base and sitravatinib malate capsule formulations. Sections 1.4 Nivolumab, 1.5 Pembrolizumab and 1.6 Enfortumab: • Added pembrolizumab and enfortumab sections. • Added guidance, throughout protocol, that the current OPDIVO, KEYTRUDA and PADCEV USPIs should be referenced for current data. Sections 1.4.3 Nivolumab, 1.5.3 Pembrolizumab and 1.6.3 Enfortumab Clinical Data: • Updated OPDIVO information based on OPDIVO USPI dated June 2020. • Added KEYTRUDA information based on KEYTRUDA USPI dated April 2020. • Added PADVCEV information based on PADVCEV USPI dated December 2019. Section 1.7.1.2 Potential for Drug-Drug Interactions (DDIs) with Sitravatinib, Pembrolizumab and Enfortumab: • Added DDI information and a mitigation strategy for the dose escalation portion of new Cohort 9 where sitravatinib administered in combination pembrolizumab and enfortumab. Section 1.7.2.1 Potential for Increased Toxicity with the Combination of Sitravatinib and a PD-(L)1 Checkpoint Inhibitor: • Added relevant pembrolizumab information since it is part of the regimen in new Cohorts 9 and 10. Section 1.7.2.2 Potential for Increased Toxicity with the Combination of Sitravatinib, Pembrolizumab and Enfortumab: • Added information regarding the potential for commonly observed AEs of the agents included in the

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		regimen for Cohorts 9 and 10 to be observed with increased severity or frequency when administered as combination regimen and the well-precedented management of those AEs in patients receiving cancer therapy to support the addition of new Cohorts 9 and 10. Section 1.8 Study Rationale: • Added explanation that the newly enrolled patients in Cohorts 1-6 will continue to be treated with the free base formulation at a starting dose of 120 mg QD, while Cohorts 7-10 new patients will be treated at the equivalent starting dose of 100 mg QD with the malate capsule formulation. • Added rationale for combination regimen of sitravatinib, pembrolizumab and enfortumab in Cohorts 9 and 10, and strategy for a lead-in dose escalation evaluation followed by evaluation of clinical activity at the recommended dose. • Added rationale for the starting doses of sitravatinib, pembrolizumab and enfortumab to be studied in the lead-in dose escalation evaluation. Section 2.1.2 Secondary Objectives and 2.2.2 Secondary Endpoints • Added a secondary objective for new Cohort 9 to identify the RP2Ds with DLTs as its endpoint. Section 3 Study Design: • Updated to reflect status of all cohorts as of protocol version 4.0, and added details regarding Cohorts 3-8 (that were previously only included in the appendices) and the new Cohorts 9 and 10 (sitravatinib in combination with pembrolizumab and enfortumab). • Added explanation that the newly enrolled patients in Cohorts 1-6 will continue to be treated with the free base formulation at a starting dose of 120 mg QD, while Cohorts 7-10 new patients will be treated at the equivalent starting dose of 100 mg QD with the malate capsule formulation. Section 4.1 Inclusion Criteria: • Inclusion Criterion #2: Updated with the cohort-specific requirements, Cohorts 1 through 10. • Inclusion Criterion #3: Updated with the cohort-specific requirements, Cohorts 1 through 9. • Inclusion Criterion #4: Updated with the cohort-specific modification for preexisting sensory or motor neuropathy, and resolution of toxicities from prior therapy, Cohorts 9 and 10.

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		• Inclusion Criterion #6: Updated with the cohort-specific modification to allow ECOG 2, Cohort 10. • Inclusion Criterion #7: Updated with the cohort-specific modifications and requirements, Cohorts 9 and 10. Section 4.2 Exclusion Criteria: • Exclusion Criterion #3: Updated with the Cohort-specific requirements, Cohorts 1, 2, 5 and 6. • Exclusion Criterion #22-#26: Added as cohort-specific exclusionary criteria to ensure safety for patients enrolling in Cohorts 9-10 due to the unique safety profile of enfortumab. Section 5.1.1 Formulation, Packaging and Storage • Added information regarding the sitravatinib malate capsule product. • Added explanation that the newly enrolled patients in Cohorts 1-6 will continue to be treated with the free base formulation at a starting dose of 120 mg QD, while Cohorts 7-10 new patients will be treated at the equivalent starting dose of 100 mg QD with the malate capsule formulation. • Clarified patients on study treatment with the free base capsule formulation at the time the malate capsule formulation is introduced will remain on the free base capsule formulation until treatment discontinuation. Section 5.1.2 Preparation, Dispensing, Administration and Accountability: • Added explanation that the newly enrolled patients in Cohorts 1-6 will continue to be treated with the free base formulation at a starting dose of 120 mg QD, while Cohorts 7-10 new patients will be treated at the equivalent starting dose of 100 mg QD with the malate capsule formulation. • Added starting dose of malate capsule formulation for Cohort 9 as 35 mg QD. • Added clarification that there is an ongoing food-effect study that may eliminate the fasting requirement for taking sitravatinib and that any change in the fasting requirement will be communicated in an Administrative Letter. Section 5.1.3 Sitravatinib Dose Modification or Discontinuation: • Removed outdated information regarding starting dose of 120 mg QD for the free base formulation. • Deleted requirement for Investigator to contact the Sponsor to reduce a patient's dose below 60 mg once daily due to sitravatinib-related AEs.

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		• Clarified that continuous treatment with dose reductions is preferred over repeated dose interruptions. • Added starting dose for malate capsule formulation. Table 5 Sitravatinib Sequential Dose Reductions for Individual Patients on Free Base Capsule Formulation: • Added formulation to title name for clarity to differentiate from the malate capsule formulation. • Added 40 mg once daily as a dose level. Table 6 Sitravatinib Sequential Dose Reductions for Individual Patients on Malate Capsule Formulation: • Added table due to new formulation that will be used for patients enrolling into Cohorts 7-10. Section 5.2 Nivolumab Study Drug: • Added guidance, throughout protocol, that the current OPDIVO USPI should be referenced for current data. Section 5.2.1 Formulation and Packaging: • Removed details regarding nivolumab formulation and packaging and stated that current OPDIVO USPI should be referenced for description of formulation and packaging. Section 5.2.2 Preparation and Dispensing: • Removed instructions for preparing nivolumab and when to dispense nivolumab and stated that current OPDIVO USPI should be referenced for how to prepare and dispense nivolumab. Section 5.2.3 Administration: • Clarified the window of +/- 5 minutes around infusion time of nivolumab. • Removed instructions for administering nivolumab and stated that current OPDIVO USPI should be referenced for how to administer nivolumab. Section 5.3 Pembrolizumab Study Drug: • Added as part of combination regimen to be used in new Cohorts 9 and 10. • Clarified that pembrolizumab will be obtained from commercial sources. • Advised that the current KEYTRUDA USPI should be referenced for formulation, packaging, preparation, dispensing, administration and dose modifications. Section 5.4 Enfortumab Study Drug: • Added as part of combination regimen to be used in new Cohorts 9 and 10.

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		• Clarified that enfortumab will be obtained from commercial sources. • Advised that the current PADCEV USPI should be referenced for formulation, packaging, preparation, dispensing, administration and dose modifications. Table 7 Enfortumab Sequential Dose Reductions for Individual Patients: • Added table due to new combination regimen to be used in new Cohorts 9 and 10. Section 5.5.1.1 General Management of Non-Hematological Toxicities: • Added reference to Table 6 for patients requiring a dose reduction who are receiving the sitravatinib malate capsule formulation. Table 8 Sitravatinib Dose Modifications – Non-Hematological Drug-Related Toxicities: • Footnote #2: Added reference to USPIs for KEYTRUDA and PADCEV. Section 5.5.1.3.3 Diarrhea: • Due to different checkpoint inhibitor (pembrolizumab) to be used in Cohorts 9 and 10, added clarification that diarrhea should be evaluated to determine whether it may be immune-mediated colitis due to nivolumab or pembrolizumab, related to sitravatinib, or due to another cause. Sections 5.5.3 Pembrolizumab and 5.5.4 Pembrolizumab Adverse Event Management Guidelines: • Added sections since these agents are included in the regimen for new Cohorts 9 and 10. Section 5.5.5 Management of Immune-Related Adverse Events: • Updated with the sitravatinib, pembrolizumab and enfortumab combination regimen. • Added references to the KEYTRUDA USPI and the PADCEV USPI throughout the section. Section 5.5.6 Management of Hy's Law Cases: • Expanded the list of other causes that should be excluded when evaluating liver function tests that meet Hy's Law criterion. • Clarified actions to take with all on-study checkpoint inhibitor combination regimens due to new regimen (sitravatinib, pembrolizumab and enfortumab) added in Cohorts 9 and 10. • Clarified that Hy's Law cases need to be reported as SAEs.

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		Section 5.6 Medication Error: • Updated with the sitravatinib, pembrolizumab and enfortumab combination regimen. Section 5.7.1 Concomitant Medication(s): • Gastric Acid Medications with Sitravatinib: Revised to clarify that treatment with antacids and/or H2 antagonist are permitted and to provide guidance with regards to timing of antacid and/or H2 antagonist administration in relation to sitravatinib dosing. • Medications with QTc Prolonging Activity: Added cautionary advice that medications with conditional risk of Torsades de Pointes should be used with caution during sitravatinib treatment. • Clarified that P-gp and BCRP transporters and CYP3A4 substrates should be used with caution during treatment with sitravatinib in alignment with Appendix 3. • Added that use of P-gp inhibitors/inducers and strong CYP3A4 inhibitors are prohibited during treatment with enfortumab in alignment with Appendix 10. • Added reference to Cohort 9 restrictions for transfusions and growth factors. Section 5.7.2 Concomitant Medication(s) Restrictions in Cycle 1 of Lead-In Dose Escalation Evaluation (Cohort 9) for Patients Undergoing a DLT Assessment: • Added for new Cohort 9 to ensure accurate assessment of safety and DLTs of the combination regimen. Section 5.7.4 Other Anticancer or Experimental Therapy: • Added language indicating that certain ongoing hormonal therapies taken to prevent recurrence of a malignancy not under study may be permitted after discussion with and agreement of Sponsor. Section 6.4 Long-Term Follow-up and End of Study Assessment: • Added option to contact patients by email for the long-term follow-up. Section 7.1 Efficacy: • Added possibility of future central radiological review for patients enrolled into Cohorts 7-10 and requested that sites ensure copies of scans are retained. An Administrative Letter or protocol amendment will be issued if a central radiological review is implemented. Section 7.2.3 Eye Examination (Only for Cohorts 9 and 10): • Added to further assess potential risks associated with enfortumab treatment. Table 11 Laboratory Safety Parameters:

Document	Version Date	Summary of Changes
		• Added glucose test for Cohorts 9 and 10 only, as it is a requirement to determine if the dose of enfortumab may be given at each scheduled administration. Section 8.2.1 Laboratory Abnormalities: • Clarified actions to take with all on-study checkpoint inhibitor combination regimens due to new regimen (sitravatinib, pembrolizumab and enfortumab) added in Cohorts 9 and 10. Section 9.1 Hypothesis and Sample Size: • Added summary of the study design, hypothesis and statistical considerations by cohort, for Cohorts 1 through 10 (previously only mentioned in appendices). Section 9.3.1 Full Analysis Population: • Changed name of modified intent-to-treat (mITT) population to a full analysis population (FAP) and defined FAP, as it is a more accurate nomenclature. • Clarified decisions that will be based on the FAP. Section 9.3.2 Clinical Activity Evaluable Population: • Clarified that the clinical activity evaluable population will be summarized based upon the Predictive Probability Design for Cohorts 1 through 6, and based upon the Simon 2-stage optimal design for Cohorts 9 (dose expansion portion) and 10. Section 9.3.7 DLT Evaluable Population: • Added for new Cohort 9 to be used to make dose escalation decisions during the lead-in dose escalation evaluation. Section 9.4.2 Clinical Benefit Rate: • Revised definition of clinical benefit rate to align with RECIST 1.1. guidance on Stable Disease. Section 9.4.6 Subgroup Analyses: • Added clarification as to which cohorts would be included in the subgroup analysis of the outcome of prior treatment with checkpoint inhibitor therapy. Section 10.5 Confidentiality: • Revised based upon updated protocol template. Section 16 References: • Updated accordingly based on changes throughout the protocol. Appendix 3 Medications or Substances to Be Avoided or Used with Caution During Treatment with Sitravatinib: • Addition of a more complete list of examples of drugs that have a known or conditional risk of Torsades de Pointes.

Document	Version Date	Summary of Changes
		• Removed information regarding sensitive substrates and substrates with narrow therapeutic index for CYP2B6, CYP2C8, and CYP2D6 based on further evaluation of sitravatinib's potential to inhibit these enzymes. Appendix 5 Contingent Study Cohorts in Patients Previously Receiving Treatment with Selected Immunotherapies: • Removed details that had been moved to the applicable sections of the main protocol to reduce redundancy. Appendix 6 Contingent Study Cohorts in Checkpoint Inhibitor Therapy Naïve Populations: • Removed details that had been moved to the applicable sections of the main protocol to reduce redundancy. Appendix 7 Evaluation of the Pharmacokinetics of Sitravatinib in Patients with Renal Impairment: • Clarified that the specified PK evaluation will only include patients who were treated with the sitravatinib and nivolumab combination regimen (Cohorts 1 through 8). Appendix 8 Contingent Study Cohorts in Patients Previously Receiving Treatment with an Antibody-Drug Conjugate: • Removed details that had been moved to the applicable sections of the main protocol to reduce redundancy. • Changed the study design from Predictive Probability Designs to confidence interval method, revised the hypothesis and sample size, and included an interim futility analysis. Clarified that the maximum sample size of each cohort increased to 55 evaluable patients. Appendix 9 Contingent Study Cohorts Evaluating Sitravatinib Combination with a Checkpoint Inhibitor and an Antibody-Drug Conjugate: • Added to describe Cohorts 9 and 10 in detail. Appendix 10 Examples of Prohibited P-GP Inhibitors and Strong CYP3A4 Inhibitors During Treatment with Enfortumab: • Added to help prevent prohibited medications from being taken while patients in Cohorts 9 and 10 are treated with enfortumab. Appendix 11 Dose De-Escalation Decision Table Using the mTPI Method: • Added to guide decision making with regards to dose escalations in subsequent patients during the lead-in dose escalation portion of Cohort 9. Appendix 12 COVID-19 Pandemic Changes to Study Conduct: • Added appendix allowing temporary changes to specific protocol assessments and procedures that are allowable only during the COVID-19 pandemic.

Document	Version Date	Summary of Changes
		Addressed clerical errors and made minor clarifications throughout the protocol.

STUDY SUMMARY

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

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

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

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

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

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

Sitravatinib is an orally-available, potent small molecule inhibitor of a closely related spectrum of RTKs including MET, Axl, MERTK, VEGFR family, PDGFR family, KIT, FLT3, Trk family, RET, DDR2, and selected Eph family members. The TKI profile of sitravatinib suggests the potential for synergistic anti-tumor effect when administered in combination with a checkpoint inhibitor.

Until recently, there were no established treatment options for patients with platinum-refractory urothelial carcinoma. Indeed, second-line chemotherapy was associated with modest efficacy, and survival times of approximately 7 months underscored the need for alternate treatment approaches. Since 2016, treatment options for platinum-refractory or platinum-ineligible advanced urothelial carcinoma have been expanded to include agents targeting programmed death protein-1 and its ligand, and there are now 5 FDA-approved immunotherapies in this setting. While overall survival benefits of immunotherapy have been demonstrated in a large-scale randomized controlled trial, response rates are relatively low and not all patients benefit from

therapy. Consequently, there is a need for new treatment options in the post-platinum and post-immunotherapy settings.

Nivolumab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and selectively blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. Nivolumab has been approved for the treatment of patients with advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy.

Combining an immunotherapeutic PD-(L)1 checkpoint inhibitor with an agent that has both immune modulatory and antitumor properties could augment the antitumor efficacy observed with either agent alone. This study will evaluate the clinical activity of nivolumab in combination with sitravatinib in patients with advanced or metastatic urothelial carcinoma.

The antitumor activity of antibody drug conjugates (ADCs) that are linked to the microtubule-inhibitor monomethyl auristatin E (MMAE) has been extensively studied and characterized as resulting primarily from the intracellular payload release, leading to mitotic arrest and apoptotic cell death. Emerging data indicates a potential immune modulatory activity with these ADCs by inducing immunogenic cell death (ICD) that enhances innate and adaptive antitumor immunity in vitro and in vivo, in addition to other Fc-mediated effector mechanisms including antibody-dependent cellular phagocytosis and cytotoxicity involvement. In vivo administration of these ADCs leads to proinflammatory immune responses directed against the tumor and this activity is further potentiated by PD-1 checkpoint inhibitor therapy as demonstrated by accelerated tumor regressions and greater antitumor activity than either agent alone, demonstrating complementary modes of action for these agents and providing a rationale for exploring therapeutic strategies that combine ADCs with other immune stimulatory regimens. Multiple clinical trials are ongoing to evaluate the efficacy of similar combinations.

Pembrolizumab is a humanized IgG4 monoclonal antibody that binds to the PD-1 receptor and selectively blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. Pembrolizumab has been approved for the treatment of patients with advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-based chemotherapy.

Enfortumab vedotin (enfortumab) is an investigational ADC that is comprised of a fully human anti-Nectin-4 IgG1 monoclonal antibody conjugated to MMAE via a protease-cleavable linker. Nectin-4, also known as poliovirus receptor-related protein 4 (PVRL4), is an adhesion protein located on the surface of cells, with weak to moderate expression in normal skin. Copy number gain of the *PVRL4* gene is a frequent event in carcinogenesis and promotes epithelial-to-mesenchymal transition, invasion and metastasis, resulting in high expression of Nectin-4 in several solid tumors, particularly urothelial carcinomas. Enfortumab binds to cells that express Nectin-4 with high affinity, triggering the internalization and release of MMAE in target cells, inducing cell cycle arrest and apoptotic cell death. Enfortumab has been approved under accelerated approval based on tumor response rate for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a PD-(L)1 checkpoint inhibitor, and a platinum-based chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting.

Early efficacy results from enfortumab in combination with pembrolizumab in frontline cisplatin-ineligible urothelial carcinoma in the ongoing EV-103 study have demonstrated encouraging activity with a safety profile that appears manageable and tolerable. Addition of sitravatinib to this combination might further augment clinical activity by selectively inhibiting key molecular and cellular pathways strongly implicated in checkpoint inhibitor resistance. This study may evaluate the safety of sitravatinib administered in combination with pembrolizumab and enfortumab starting with a lead-in dose finding evaluation in patients with locally advanced or metastatic urothelial carcinoma who have previously received a PD(L1)-1 inhibitor and a platinum-based chemotherapy. If a tolerable dose is identified for sitravatinib in combination with pembrolizumab and enfortumab the clinical activity of this combination may be further explored in patients with metastatic urothelial carcinoma.

Target Population: Patients eligible for this study will have advanced or metastatic urothelial carcinoma. Initial cohorts will enroll patients with documented disease progression on or after checkpoint inhibitor therapy. In the event results in the initial cohorts are of high interest for efficacy, patients naïve to checkpoint inhibitor therapy may be enrolled in additional study cohorts described in the protocol.

Number in Trial: Initial patient cohorts (Cohorts 1 and 2): as many as 80 patients.

Patient cohorts to be implemented in the event of high interest for efficacy:

- Contingent cohorts implemented and active as of this protocol version 4.0 (Cohorts 3 through 9): as many as 345 patients.
- Contingent cohort not yet implemented as of this protocol version 4.0 (Cohort 10): as many as 49 patients.

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.

Secondary Objectives:

- To evaluate the safety and tolerability of the combination regimens in the selected population.
- To evaluate secondary efficacy endpoints of the combination regimens in the selected population.
- To evaluate the pharmacokinetics (PK) of 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.

Exploratory Objectives:

- To assess the effect of the combination regimens on circulating PD-L1, immune cell populations and cytokines.
- To assess the effect of the combination regimens 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.

Primary Endpoints: Objective Response Rate (ORR) as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1).

Secondary Endpoints:

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

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.

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. Initially, the study will include patients who experienced progression of disease on or after treatment with a checkpoint inhibitor as the most recent treatment. In the event that results in the initial cohorts are of high interest for efficacy,

contingency plans are described in the protocol to add new cohorts to include patients who previously received treatment with selected systemic therapies or who are treatment-naïve. Details, including the composition of the combination regimens (either sitravatinib in combination with nivolumab, or sitravatinib in combination with pembrolizumab and enfortumab), are provided in Section 3 of the protocol and associated appendices.

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, and PK of sitravatinib. The Schedule of Assessments to be performed in the study is presented in Table 1 and Table 3. The schedule for collection of PK and pharmacodynamic samples and ECG assessment time points are presented in Table 2 and Table 4.

The initial study population will include patients with documented disease progression on or after 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. As of this protocol version 4.0, enrollment into Cohort 1 is complete.

- 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.

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. 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 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.

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 to add one or more study cohorts.

Appendix 5 describes addition of Cohort 3 and Cohort 4 (cohorts which allow other prior selected immunotherapy in addition to anti-PD-(L)1, including but not limited to 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 and still enrolling, 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 describes addition of Cohort 5 and Cohort 6 [anti-PD-(L)1 naïve cohorts]. The statistical design for these cohorts is described in the appendix. 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 describes addition of Cohort 7 and Cohort 8 [post-ADC (antibody-drug conjugate) cohorts]. The statistical design for these new cohorts is described in the appendix. These contingent cohorts described below were implemented by Administrative Letter and still enrolling, as depicted in Figure 1.

- 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.

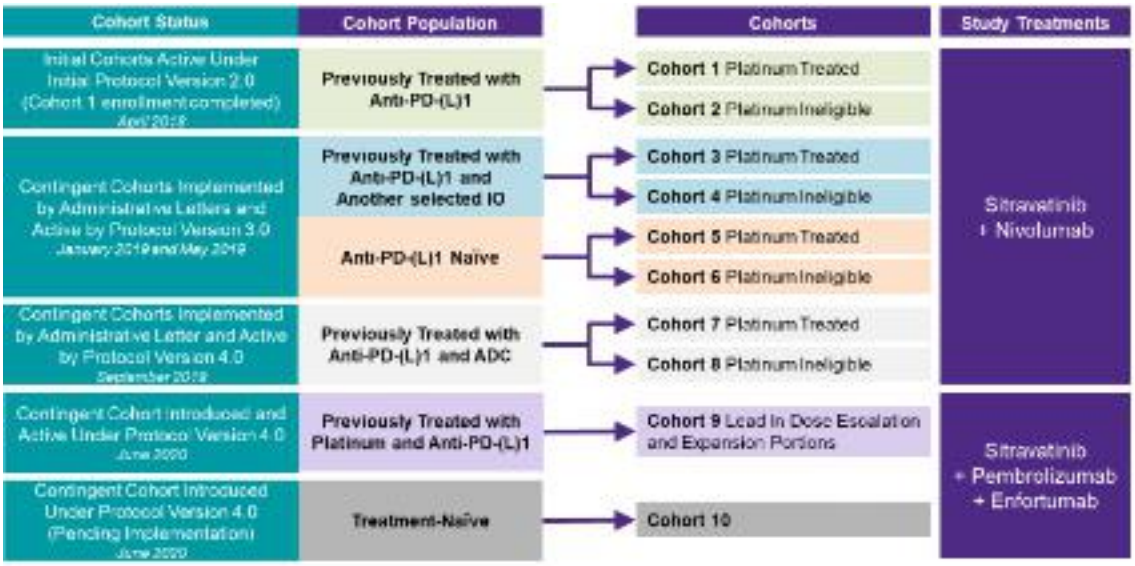
- Cohort 8: Patients with documented disease progression on or after a previous anti-PD-(L)1 and ADC (in combination or separately, and in any order), and considered ineligible for platinum-based chemotherapy.

Appendix 9 describes addition of Cohort 9 and Cohort 10 to evaluate sitravatinib in combination with pembrolizumab and enfortumab. The appendix 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, whereas Cohort 10 is introduced in this protocol Version 4.0 and may be implemented by Administrative Letter, as described below and depicted in Figure 1.

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

- Cohort 10: Patients with previously untreated unresectable, locally advanced or metastatic urothelial cancer.

Figure 1: Study Schema



The evaluation of the pharmacokinetics (PK) of sitravatinib in patients with renal impairment was implemented by an Administrative Letter dated December 2018 and applies to Cohorts 1 through 8. This evaluation is active and ongoing.

	Disease response and progression as documented by the Investigator in the Case Report Form (CRF) will be the basis for patient management and study expansion decision making. Unconfirmed objective responses recorded in the CRF may be used as the initial basis for expansion of study enrollment; however, follow-up evaluations on patients with unconfirmed responses must continue to support the decision to continue to the full number of patients to be included in the next stage.
Study Treatments:	Throughout the study, treatment will be delivered in 21-day or 28-day cycles based on study cohort. Nivolumab will be administered by intravenous infusion, 240 mg every 2 weeks (Q2W) or 480 mg every 4 weeks (Q4W), in accordance with approved labeling. Pembrolizumab will be administered by intravenous infusion, 200 mg Q3W, in accordance with approved labeling. Enfortumab will 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 evaluated if necessary). Sitravatinib capsules will be administered orally, once daily (QD), continuously. Guidelines for study drug formulation, administration and dose reduction in the event of toxicity are provided in Sections 5.1.2 and 5.1.3. Patients will continue to receive study treatment at the discretion of the Investigator until disease progression, unacceptable adverse events, patient refusal or death. Patients experiencing clinical benefit in the judgment of the Investigator may continue study treatment beyond disease progression as defined by RECIST 1.1. Patients discontinuing treatment will be followed for receipt of subsequent anti-cancer therapies and survival.
Statistical Considerations:	This Phase 2 study will use Predictive Probability Designs (Lee-2008) for initial cohorts. In creating the statistical designs, the Type 1 error (α) is constrained to <0.05 and Power ($1-\beta$) is constrained to $\geq$0.90. Statistical designs of the contingent cohorts are provided in Section 9 of the protocol and associated appendices. The ORR using nivolumab in the population of patients with advanced/metastatic urothelial carcinoma who experienced disease progression on or after treatment with a checkpoint inhibitor is assumed to be 5% (p_0); thus, this rate is considered uninteresting. The target ORR using sitravatinib in combination with nivolumab in this study population is 30% (p_1). 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 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% Confidence Interval (CI) around the ORR point estimate and to further characterize the durability of disease control.

Table 1: Schedule of Assessments: Cohorts 1 through 8

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 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					

Table 1: Schedule of Assessments: Cohorts 1 through 8 (Continued)

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
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					
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 (see Table 11) 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, 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: Cohorts 9 and 10

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	

Table 3: Schedule of Assessments: Cohorts 9 and 10 (Continued)

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			

Table 3: Schedule of Assessments: Cohorts 9 and 10 (Continued)

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) 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.

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. 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: Cohorts 9 through 11

	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 as defined in Appendix 2, 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).

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LIST OF ABBREVIATIONS

ADC	Antibody-Drug Conjugate
AE	Adverse Event
ALT	Alanine Aminotransferase
APC	Antigen Presenting Cells
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BCRP	Breast Cancer Resistance Protein
$C_{ave,ss}$	Average Steady State Plasma Drug Concentration During Multiple-Dose Administration
CBR	Clinical Benefit Rate
CFR	Code of Federal Regulations
CI	Confidence Interval
CIT	Checkpoint Inhibitor Therapy
C_{max}	Maximum Plasma Concentration
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography Scan
CTA	Clinical Trial Application
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumor Deoxyribonucleic Acid
DDI	Drug-Drug Interaction
DLT	Dose-Limiting Toxicity
DOR	Duration of Response
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EIU	Exposure In-Utero
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HDPE	High-Density Polyethylene
hERG	human Ether-a-go-go Related Gene
HGF	Hepatocyte Growth Factor

LIST OF ABBREVIATIONS (CONTINUED)

hr	Hour
IC_{50}	Half Maximal Inhibitory Concentration
ICD	Immunogenic Cell Death
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IFN-γ	Interferon Gamma
IgG4	Immunoglobulin G4
IND	Investigational New Drug
INR	International Normalized Ration
irAE	Immune-related Adverse Event
IRB	Institutional Review Board
IUD	Intrauterine Device
kg	Kilogram
MAb	Monoclonal Antibody
MDSC	Myeloid-Derived Suppressor Cell
MDSCs	Myeloid-Derived Suppressor Cells
MedDRA	Medical Dictionary for Regulatory Activities
MET	Mesenchymal-Epithelial Transition
mg	Milligram
mITT	Modified Intent-to-Treat
mL	Milliliter
MMAE	Microtubule-inhibitor Monomethyl Auristatin E
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MSCs	Mesenchymal Stem Cells
MTD	Maximum Tolerated Dose
MUGA	Multigated Acquisition Scan
NCI	National Cancer Institute
NE	Not Evaluable
NK	Natural Killer
NPCB	No Prior Clinical Benefit
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate

LIST OF ABBREVIATIONS (CONTINUED)

OS	Overall Survival
PCB	Prior Clinical Benefit
PD	Objective Progression of Disease
PD-1	Programmed Cell Death 1
PD-L1	Programmed Cell Death Ligand 1
PFS	Progression-Free Survival
P-gp	P-glycoprotein
PK	Pharmacokinetics
PKAP	Pharmacokinetic Analysis Plan
PPE	Palmar-plantar Erythrodysesthesia
PR	Partial Response
PTT	Partial Thromboplastin Time
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
Q4W	Every 4 Weeks
QD	Once Daily
QTc	Corrected QT Interval
RP2D	Recommended Phase 2 Combinatorial Dose
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
RTKs	Receptor Tyrosine Kinases
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
TAM	Tyro3, Axl and MERTK
TCR	T-Cell Receptor
TKIs	Tyrosine Kinase Inhibitors
TME	Tumor Microenvironment
Tregs	T Regulatory Cells
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization

LIST OF ABBREVIATIONS (CONTINUED)

WOCBP	Women of Childbearing Potential
µg	Microgram
µM	Micromolar

1 INTRODUCTION AND RATIONALE

1.1 Disease and Therapeutic Strategy

1.1.1 Urothelial Carcinoma

Urothelial carcinoma comprises approximately 90% of bladder cancer cases, which are a major cause of morbidity and mortality, resulting in an estimated 165,000 deaths annually worldwide (Miyazaki-2017; Antoni-2017). Approximately 25% of patients are diagnosed with locally advanced or metastatic urothelial carcinoma, and while platinum-based chemotherapy is the cornerstone of first-line therapy, most patients experience treatment resistance or intolerance (Bambury-2013; Burger-2013; von der Maase-2005). In addition, due to renal impairment, about 25-50% of patients with metastatic urothelial carcinoma are not able to receive platinum-based chemotherapy (Dash-2006).

Until recently, there were no established treatment options for patients with platinum-refractory urothelial carcinoma (Bellmunt-2009; Choueiri-2012; Vaughn-2002). Indeed, second-line chemotherapy was associated with modest efficacy and, survival times of approximately 7 months underscored the need for alternate treatment approaches. Since 2016, treatment options for platinum-refractory or platinum-ineligible advanced urothelial carcinoma have been expanded to include agents targeting programmed death protein-1 (PD-1) and its ligand (PD-L1), and there are now 5 FDA-approved immunotherapies in this setting (Rosenberg-2016; Sharma-2016; Massard-2016; Bellmunt-2017a; Apolo-2017; Balar-2017a; Balar-2017b). While overall survival benefits of immunotherapy have been demonstrated in a large-scale randomized controlled trial (Bellmunt-2017a), response rates are relatively low.

1.1.2 Checkpoint Pathway

The PD-1 receptor along with the ligands PD-L1 and PD-L2 constitutes an immune checkpoint pathway that inhibits T-cell activation when engaged (Mellman-2011; Topalian-2015). PD-1 is expressed on T-cells whereas PD-L1 and PD-L2 are expressed on some cancer cells and immune cell types. PD-L1 is the predominant ligand expressed in solid tumors and is upregulated by IFNγ. PD-L1 functions to limit collateral damage in normal tissues where an immune response has been triggered. Upregulation of PD-1 ligands is utilized by tumors to help evade detection and elimination by the host immune system tumor response.

1.1.3 Checkpoint Inhibitor Therapy in Urothelial Carcinoma

Checkpoint inhibitors studied in patients with urothelial carcinoma include nivolumab, atezolizumab, avelumab, durvalumab, and pembrolizumab (Sharma-2016; Sharma-2017; Rosenberg-2016; Patel-2018; Massard-2016; Bellmunt-2017a; Apolo-2017; Balar-2017a; Balar-2017b). Objective Response Rates for single agent checkpoint inhibitors hover around 20% (Bellmunt-2017b; Aggen-2017; Davarpanah-2017). The effect of tumor

PD-L1 expression on clinical response in urothelial carcinoma has been variable and depended on the assay and the checkpoint inhibitor.

Nivolumab, a fully human IgG4, PD-1 receptor antagonist, binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the anti-tumor immune response. It has been approved by the FDA for the treatment of patients with advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy.

Pembrolizumab, a fully humanized IgG4, PD-1 receptor antagonist, binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the anti-tumor immune response. Pembrolizumab has been approved by the FDA for the treatment of patients with advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-based chemotherapy, and of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score ≥10] as determined by an FDA-approved test, or in patients who are not eligible for any platinum-based chemotherapy regardless of PD-L1 status.

Combining an immunotherapeutic PD-(L)1 checkpoint inhibitor with an agent that has both immune modulatory and antitumor properties and targets the molecular and cellular mechanisms of resistance to checkpoint inhibitor therapy could enhance the antitumor efficacy observed with either agent alone.

1.1.4 Antibody-Drug Conjugates (ADCs)

Antibody-drug conjugates (ADCs), comprising of a highly specific monoclonal antibody (mAb) for a tumor antigen (Ag) and a highly active cytotoxic agent connected via a linker molecule, are designed as a targeted therapy by selective delivery of cytotoxic drugs to cancer cells while sparing healthy cells resulting in a broad therapeutic window (Khongorzul-2020; Vlachostergios-2018). Upon antibody-antigen binding on the surface of cancer cells, the conjugate is internalized by endocytosis and its cytotoxic payload is released after lysosomal degradation.

1.1.5 ADC Targeted Therapy in Urothelial Carcinoma

ADCs studied in patients with advanced urothelial carcinoma include enfortumab and sacituzumab govitecan. Objective Response Rates for single agent ADCs in platinum-based chemotherapy and/or checkpoint inhibitor therapy pretreated vary between 29 to 44% (Rosenberg-2019; Tagawa-2019). Based on evidence of tolerable toxicity and clinical activity, ADCs are being explored in the frontline metastatic setting in combination regimens with checkpoint inhibitor therapy and/or platinum-based chemotherapy.

Enfortumab is an investigational ADC that is comprised of a fully human anti-Nectin-4 IgG1 kappa mAb conjugated to the microtubule-inhibitor monomethyl auristatin E (MMAE) via a protease-cleavable linker. Nectin-4, also known as poliovirus receptor-related protein 4 (PVRL4), is an adhesion protein located on the surface of cells, with weak to moderate expression in normal skin. Copy number gain of the *PVRL4* gene is a frequent event in carcinogenesis and promotes epithelial-to-mesenchymal transition, invasion and metastasis, resulting in high expression of Nectin-4 in several solid tumors, particularly urothelial carcinomas. Enfortumab binds to cells that express Nectin-4 with high affinity, triggering the internalization and release of MMAE in target cells. MMAE disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic cell death (Rosenberg-2019; Vlachostergios-2018). It has been approved under accelerated approval by the FDA based on tumor response rate for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a PD-(L)1 checkpoint inhibitor, and a platinum-based chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Preclinical studies show that ADCs linked to MMAE induce immunogenic cell death and may enhance anti-tumor activity such that the combination of enfortumab and an immunotherapeutic PD-(L)1 checkpoint inhibitor may have greater anti-tumor activity than either agent alone (Rosenberg-2020). Based on initial results from the EV-103 trial, enfortumab in combination with pembrolizumab has been granted Breakthrough Therapy designation for the treatment of patients with unresectable locally-advanced or metastatic urothelial cancer who are unable to receive cisplatin-based chemotherapy in the first-line setting, and is being explored in treatment-naïve, platinum-eligible patients in a Phase 3 study (EV-302 trial).

With its distinct immune modulatory mechanism of action which primarily targets the molecular and cellular mechanisms of resistance to checkpoint inhibitor therapy in key immune suppressive cell types, sitravatinib in combination with enfortumab and pembrolizumab could further augment the antitumor efficacy observed with enfortumab and pembrolizumab combination regimen.

1.2 Overall Rationale for the Proposed Combination Regimens

1.2.1 Sitravatinib in Combination with a Checkpoint Inhibitor

Mechanisms of resistance to checkpoint inhibitor therapy have been described based on fundamental knowledge of the immune system as well as emerging clinical data. Expression of PD-L1 in immune and / or tumor cells appears to correlate with response in some but not all urothelial carcinoma clinical studies (Rosenberg-2016; Bellmunt-2017a; Sharma-2017; Apolo-2017; Patel-2018; Massard-2016; Hahn-2017). In the tumor microenvironment, PD-L1 can be upregulated in tumor cells via oncogenic signaling or in response to immune stimulatory factors such as interferon gamma (IFN-γ). Therefore,

the absence of PD-L1 expression may reflect a tumor cell population and microenvironment with a suppressed immune response.

Several immune cell types normally function to suppress immune responses, are often found in abundance in cancer, and may underlie resistance mechanisms to checkpoint blockade (Vanneman-2012). T Regulatory cells (Tregs), Myeloid-Derived Suppressor Cells (MDSCs) and M2-polarized macrophages, in particular, are immunosuppressive in nature as they counteract pro-inflammatory immune responses and lead to tolerance. Inhibition of the accumulation and/or function of these cell types therefore represents a rational combination strategy to reprogram the immunosuppressive tumor microenvironment and increase the effectiveness of PD-(L)1 therapy. As described in further detail below, sitravatinib selectively inhibits key molecular and cellular pathways strongly implicated in checkpoint inhibitor resistance and therefore represents a rational strategy to augment or restore anti-tumor immunity when combined with nivolumab, a checkpoint inhibitor therapy.

1.2.2 Sitravatinib in Combination with a Checkpoint Inhibitor and an Antibody-Drug Conjugate (ADC)

The antitumor activity of ADCs that, similar to enfortumab, are linked to MMAE such as brentuximab vedotin, ladiratuzumab vedotin and tisotumab vedotin resulting primarily from the intracellular payload release, leading to mitotic arrest and apoptotic cell death, has been extensively studied. Emerging data indicates a potential immune modulatory activity with these ADCs by inducing immunogenic cell death (ICD) that enhances innate and adaptive antitumor immunity in vitro and in vivo (Cao-2016; Cao-2017; Cao-2018; Alley-2019). Preclinical studies reveal induction of key hallmarks of ICD including activation of ER stress response pathways, ATP secretion, and release of HMGB1, which are important for immune cell activation and recruitment into the tumor microenvironment. Other Fc-mediated effector mechanisms like antibody-dependent cellular phagocytosis and cytotoxicity are also involved. Addition of ADC-killed tumor-like cells to autologous PBMCs results in the expansion of cytotoxic T-cells. In vivo administration of these ADCs leads to directed proinflammatory immune responses against the tumor and this activity is further potentiated by PD-1 checkpoint inhibitor therapy as demonstrated by accelerated tumor regressions and greater antitumor activity than either agent alone, demonstrating complementary modes of action for these agents and providing a rationale for exploring therapeutic strategies that combine ADCs with other immune stimulatory regimens. Multiple clinical trials are ongoing to evaluate the efficacy of similar combinations. In particular, early efficacy results from enfortumab in combination with the PD-1 checkpoint inhibitor pembrolizumab in frontline cisplatin-ineligible urothelial carcinoma in the ongoing EV-103 study has shown encouraging activity with a safety profile that appears manageable and tolerable. Sitravatinib targets the molecular and cellular mechanisms of resistance to checkpoint inhibitor therapy that are primarily operative in innate and adaptive immune cell types and is distinct from the mechanism of action of the tumor cell-targeting enfortumab and checkpoint inhibitor therapy. Therefore, sitravatinib in combination with enfortumab and pembrolizumab is

hypothesized to complement these therapies in mounting a productive anti-tumor immune response and could further augment the antitumor efficacy observed with enfortumab and pembrolizumab combination regimen (refer to Section 1.2.1).

1.3 Sitravatinib

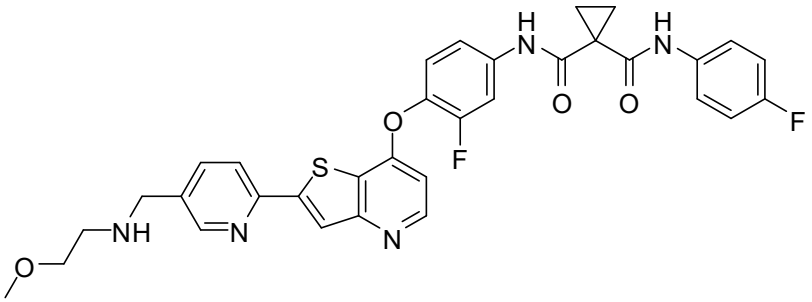
Sitravatinib (MGCD516) is an orally available, potent small molecule inhibitor of a closely related spectrum of receptor tyrosine kinases (RTKs) including MET, Axl, MERTK, VEGFR family, PDGFR family, KIT, FLT3, Trk family, RET, DDR2, and selected Eph family members. Receptor tyrosine kinases (RTKs) are key regulators of signaling pathways leading to cell growth, survival, and migration (Blume-Jensen-2001). These kinases are dysregulated in many cancers through overexpression, genetic alteration or co-expression with high affinity ligands (Blume-Jensen-2001). Multiple sitravatinib RTK targets are genetically altered in a variety of cancers and act as oncogenic drivers, promoting cancer development and progression. In addition to the immunostimulatory effects of Axl and MET inhibition, sitravatinib may further condition the TME in favor of antitumor activity by its immunomodulatory effects mediated through VEGFR and KIT inhibition. Preclinical data with sitravatinib indicate that it can increase expression of PD-L1 on tumor cells in vitro and in vivo. Pilot studies in syngeneic mouse tumor models also suggest that sitravatinib increases the proliferation and fraction of systemic/spleen CD4+ and CD8+ T lymphocytes and reduces the number of systemic MDSCs. Additional studies to investigate the effects of sitravatinib in the tumor microenvironment are ongoing or planned.

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

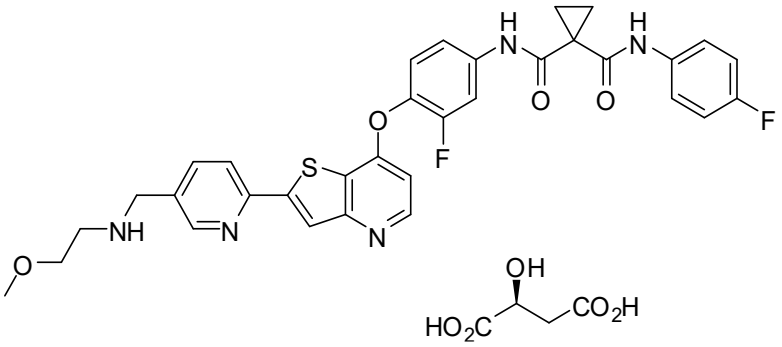
1.3.1 Sitravatinib Drug Substance

The chemical structure, formula, and molecular weight of sitravatinib (MGCD516) free base and malate salt are as follows:

Sitravatinib (MGCD516) Free Base



Sitravatinib (MGCD516) Malate



Chemical Formula: MGCD516 Free Base: $C_{33}H_{29}F_2N_5O_4S$
MGCD516 Malate: $C_{37}H_{35}F_2N_5O_9S$

Molecular Weight: MGCD516 Free Base: 629.68
MGCD516 Malate: 763.76

1.3.2 Nonclinical Data

Complete information concerning sitravatinib nonclinical data is available in the Investigator's Brochure.

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

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

In a bidirectional permeability study with Caco-2 cell lines, sitravatinib is classified as a highly permeable compound, and not a substrate of P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP). A P-gp and BCRP inhibition study using Caco-2 cells suggested that MGCD516 is a significant inhibitor of P-gp and BCRP with IC_{50} value of 0.838 and 1.51 μM, respectively, these values are much higher than the systemic steady state exposure levels observed clinically.

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

Sitravatinib (MGCD516) was evaluated for cytochrome P-450-mediated metabolism using human liver microsomes and recombinant human enzymes. Results suggest that multiple enzymes, including CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1, and 3A4 are involved in the metabolism of sitravatinib.

The effect of treating primary cultures of cryopreserved human hepatocytes with MGCD516 on the expression of cytochrome P450 (CYP) enzymes was investigated. Overall, treatment of cultured human hepatocytes with up to 30 μM MGCD516 caused little or no increase (< 2.0-fold change or < 20% of the positive control) in CYP1A2 activity, CYP1A2 mRNA levels, or CYP3A4 activity. However, MGCD516 (up to 3 and 10 μM) caused concentration dependent increases (>2-fold change and > 20% of the positive control) in CYP2B6 activity, CYP2B6 mRNA levels, and CYP3A4 mRNA levels in one or more human hepatocyte cultures.

There was little or no evidence of direct inhibition of CYP1A2, CYP2A6 or CYP2E1 by MGCD516 or time- or metabolism-dependent inhibition of any of the CYP enzymes evaluated. Under the experimental conditions examined, MGCD516 demonstrated direct inhibition of CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 (as measured by testosterone 6β-hydoxylation and midazolam 1′-hydroxylation) with IC_{50} values of 2.9 μM, 11 μM, 10 μM, 1.9 μM, 11 μM and 0.81 μM, respectively. In addition, approximate 50% direct inhibition was observed for CYP2B6 at the highest concentration of MGCD516 evaluated (20 μM); thus, the IC_{50} value was reported as greater than 20 μM.

Because the potency for MGCD516 against its intended clinical targets is generally less than 0.1 μM, it may be unlikely that concentrations required for robust direct systemic inhibition/induction of the tested CYPs will be achieved at projected clinical dose and exposure levels.

1.3.3 Sitravatinib Clinical Experience

1.3.3.1 Sitravatinib Pharmacokinetics

Complete information concerning sitravatinib pharmacokinetics is available in the Investigator's Brochure.

After single dose administration of sitravatinib free base capsules, sitravatinib reaches peak concentration in a median time of 3 to 8 hours. Exposure parameters (maximum concentration [C_{max}] and area under the curve [AUC]) are dose proportional with doses up to 200 mg. Mean elimination half-life varies between 42 and 58 hours after oral administration.

Study 516-006 evaluated the relative bioavailability and PK of sitravatinib in plasma following single doses of sitravatinib free base and sitravatinib malate capsule formulations in healthy subjects in a 2-part, open-label, crossover study (Section 1.3.3.4).

In Part 1, the same single dose of 80 mg sitravatinib was compared as free base and malate capsule formulations. Geometric mean C_{max}, $AUC_{0-\infty}$ and AUC_{0-168} was 1.27-, 1.24- and 1.24-fold higher following malate capsules administration compared to free base capsules administration. From Part 1, it was determined that the malate capsule formulation was statistically significantly more bioavailable than the free base formulation, and that a free base to malate ratio of approximately 1.25 would give similar PK exposure.

In Part 2, malate capsule formulation dose was adjusted and the geometric mean C_{max} was comparable (55.1 and 56.4 ng/mL, respectively) following single dose administration of 120 mg sitravatinib free base formulation and a lower 100 mg sitravatinib dose of sitravatinib malate capsule formulation. The geometric mean AUC_{0-168} was 2962 and 2943 ng*h/mL for 120 mg sitravatinib free base and 100 mg sitravatinib malate capsule formulations, respectively. The geometric mean $t_{1/2}$ was similar following malate capsule formulation administration compared to free base capsule formulation administration, with estimates being 35.0 and 34.3 hours, respectively, and individual $t_{1/2}$ values ranging from 25.4 to 52.0 hours and from 23.2 to 55.4 hours, respectively. Inferential statistical analysis showed that the ratio and 90% confidence interval of the geometric least squares (LS) means of $AUC_{0-\infty}$, AUC_{0-t} and C_{max} were 98.9 [91.8, 106.6], 98.8 [91.6, 106.5] and 102.4% [92.9, 112.7], respectively. Study 516-006 demonstrated bioequivalence between the 120 mg sitravatinib free base and 100 mg sitravatinib malate capsule formulations (Section 1.3.3.4).

1.3.3.2 Sitravatinib Clinical Safety

Sitravatinib monotherapy and sitravatinib in combination with PD-(L)1 checkpoint inhibitors are being evaluated as part of the clinical development program. During the course of the study, the Investigator's Brochure (IB) should be referenced for current data.

Sitravatinib has been administered to cancer patients in multiple clinical studies, including monotherapy studies (516-001 and BGB-900-104), combination studies with the PD-1 checkpoint inhibitor nivolumab (MRTX-500, 516-002, 516-003 and 516-005), and combination studies with the PD-1 checkpoint inhibitor tislelizumab (BGB-900-103 and BGB-900-104). Sitravatinib has also been administered as single agent in healthy subject

studies (516-006 and 516-007). Details regarding the clinical studies most relevant for this study, 516-003, 516-001 and MRTX-500, are provided below.

Study 516-001 is a multi-center Phase 1/1b clinical trial of sitravatinib as monotherapy in patients with advanced solid tumor diseases. The Phase 1 dose-escalation study evaluated dose levels between 10 mg and 200 mg administered QD. The maximum tolerated dose was 150 mg QD. Based on long-term tolerability, the recommended Phase 2 dose is 120 mg QD. The Phase 1b segment is ongoing, evaluating the clinical activity of sitravatinib in patients having tumors with selected histological diagnoses and/or tumor gene alterations targeted by sitravatinib.

Study MRTX-500 is an open-label, parallel Phase 2 evaluation of nivolumab in combination with 3 investigational agents, glesatinib, sitravatinib or mocetinostat, in patients with locally advanced, unresectable or metastatic non-squamous NSCLC. Only the sitravatinib plus nivolumab treatment arm will be discussed in this protocol. Patients who have experienced disease progression either on or after prior treatment with a checkpoint inhibitor therapy (CIT-experienced) as well as those who have experienced disease progression after treatment with platinum-based doublet chemotherapy (CIT-naïve) are enrolled. The primary objective is to evaluate the clinical activity the combination study treatments using ORR in accordance with RECIST 1.1. Secondary objectives include evaluation of safety, secondary efficacy endpoints, and PK for the investigational agents. The study began with a lead-in evaluation of sitravatinib in combination with nivolumab administered by intravenous infusion, 240 mg Q2W. Sitravatinib is administered orally, once daily in cycles of 28 days. The starting dose for sitravatinib was 120 mg QD administered orally, in 28-day cycles. No protocol defined DLTs were reported in the first 6 evaluable patients treated at the sitravatinib starting dose of 120mg QD in combination with nivolumab administered by intravenous infusion, 240 mg Q2W. Based on the experience of patients enrolled into Studies 516-001 and MRTX-500, 120 mg QD was selected as the recommended Phase 2 dose of sitravatinib in combination with nivolumab.

As of 26 June 2019, safety data are available for a total of 422 patients treated with sitravatinib, either as a single agent (n = 189), in combination with the PD-1 inhibitor nivolumab (n = 184), or in combination with the PD-1 inhibitor tislelizumab (n = 49). In addition, safety data are available for 16 healthy male subjects administered single agent sitravatinib.

DLTs with single-agent administration of sitravatinib in Study 516-001 included Grade 3 PPE at 80 mg, and intolerable Grade 2 neuropathy, intolerable Grade 2 fatigue, and intolerable Grade 2 mucositis at 200 mg. In Study MRTX-500, there were no DLTs observed during the lead-in evaluation of the combination of nivolumab (240 mg IV Q2W) and sitravatinib (120 mg QD).

Sitravatinib-related adverse events (AEs) reported in ≥ 20% of 186 patients in sitravatinib monotherapy studies were diarrhea (50%), fatigue (42%), hypertension (39%), nausea

(29%), decreased appetite (27%), vomiting (24%), and palmar-plantar erythrodysesthesia (20%). Treatment-related Grade 3+ AEs reported in ≥5% of patients were hypertension (19%), diarrhea (10%), fatigue (7%), lipase increased (5%), and PPE (5%). Treatment-related Grade 4 AEs were reported in 3 patients and included lipase increased in 2 patients (1%) and febrile neutropenia in 1 patient (1%). A treatment-related Grade 5 AE of cardiac arrest was reported in 1 patient (1%).

Treatment-related AEs reported in ≥20% of 184 patients treated with sitravatinib in combination with nivolumab were diarrhea (50%), fatigue (46%), nausea (34%), decreased appetite (33%), hypertension (27%) weight decreased (26%), dysphonia (24%), vomiting (23%), and hypothyroidism (20%). Treatment-related Grade 3 AEs reported in ≥5% of patients were hypertension (19%), diarrhea (10%), fatigue (7%), and lipase increased (5%). Treatment-related Grade 4 AEs were reported in 4 patients (2%) overall, and included gastric ulcer perforation, hypertensive crisis, lipase increased, and lymphocyte count decreased in 1 patient each (1%). Treatment-related Grade 5 AEs of cardiac arrest were reported in 2 patients (1%).

In particular, treatment-related AEs reported in ≥20% of 40 patients treated with sitravatinib in combination with nivolumab in Study 516-003 as of 26 June 2019 (enrolled mostly in Cohorts 1 through 4) were fatigue (58%), diarrhea (55%), decreased appetite (38%), dysphonia (38%), nausea (30%), lipase increased (28%), alanine aminotransferase increased (25%), PPE (25%), hypertension (20%), dysgeusia (20%), vomiting (20%), and proteinuria (20%). Treatment-related Grade 3 AEs reported in ≥5% of patients were hypertension (20%), diarrhea (10%), fatigue (10%), lipase increased (10%), and PPE (5%). No treatment-related Grade 4 or Grade 5 AEs were reported.

Based on review of the AEs reported with sitravatinib in context of the mechanism of action, nonclinical data, frequency, and Investigator assessment of causality, the following AEs have been assessed as expected serious adverse drug reactions (SARs) for sitravatinib, or serious adverse events (SAEs) with at least a reasonable possibility of a causal relationship to sitravatinib administered as monotherapy or in combination with other agents: deep vein thrombosis/embolism/pulmonary embolism, diarrhea, ejection fraction decreased, fatigue, hypertension, nausea, PPE, and vomiting. Refer to the current IB for updated information during the course of the study.

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

Based on reported clinical experience with sitravatinib and similar agents, and nonclinical data with sitravatinib, guidance to the Investigator is provided for selected adverse events in Section 5.5.1.

1.3.3.3 Sitravatinib Clinical Efficacy

As of protocol Version 4.0, early clinical activity with the combination of sitravatinib and nivolumab in Study 516-003 is promising with multiple cohorts (Cohorts 1, 2, 3 and 5) having met the efficacy criteria per the PPD design to advance to Stage 2, and Cohort 1 having further advanced to the Expansion stage. Other cohorts are pending such decisions as enrollment progresses. As of 26 July 2019, updated data from an interim analysis of clinical activity from Cohort 1 at the time of expansion from Stage 2 to the Expansion stage of the PPD design, showed a preliminary objective response rate (ORR) of 27% among 22 clinical activity evaluable patients (Msaouel-2019). Cohort 1 has since completed enrollment and final efficacy updates including secondary efficacy endpoints are awaited. Similarly, early efficacy updates are awaited for the remaining active cohorts of Study 516-003.

Final efficacy results are awaited from both the Phase 1b segment of Study 516-001, and Study MRTX-500.

Study MRTX-500 uses a Predictive Probability Design (Lee-2008) for each treatment arm and stratum. For patients who are CIT-experienced, enrollment is stratified by prior outcome of treatment with a checkpoint inhibitor: those with prior clinical benefit (PCB) or no prior clinical benefit (NPCB) to prior CIT. Patients who are CIT-naïve are stratified according to their PD-L1 status: no/low PD-L1 expression or high PD-L1 expression. There was no limit to the number of prior therapies.

Preliminary results from patients enrolled into the prior clinical benefit (PCB) stratum of MRTX-500 were updated as of 04 September 2019, and included 79 patients enrolled into the PCB stratum of MRTX-500. Patients in the PCB stratum have experienced clinical benefit (confirmed CR or PR or stable disease for at least 12 weeks) on their prior CIT. The preliminary median overall survival for this stratum was 15.6 months. Fifty-four patients were evaluable for response; 8 patients had a confirmed response (2 CR, 6 PR). The median duration of response (DOR) was 170 days (range: 64, NA).

1.3.3.4 Sitravatinib Capsule Formulation Study

Investigation of alternative formulations is for the purpose of optimizing product characteristics and manufacturing efficiency.

Study 516-006 (interim report) was a Phase 1, 2-part, open-label, single-dose, crossover study designed to evaluate the relative bioavailability of sitravatinib free base and sitravatinib malate capsule formulations in healthy subjects. In each part, subjects were randomized into 2 treatment sequences (either test then reference or reference then test formulations) and participated in two 7-day treatment periods separated by a washout period. Part 1 assessed the relative bioavailability and PK of a single oral dose of 80 mg sitravatinib administered as free base capsule formulation (reference product) and malate capsule formulation (test product). From Part 1, it was determined that the malate capsule formulation is statistically significantly more bioavailable than the free base

capsule formulation, and that a free base to malate ratio of approximately 1.25 would give similar PK exposure. Subsequently, Part 2 assessed the relative bioavailability and PK of a single oral dose of 120 mg sitravatinib free base capsule formulation (reference product) and 100 mg sitravatinib malate capsule formulation (test product). The administration of 100 mg malate capsule formulation compared to 120 mg free base capsule formulation were similar based on descriptive statistics; for 100 mg malate capsule formulation vs. 120 mg free base capsule formulation, the geometric mean $AUC_{0-\infty}$, AUC_{0-t} and C_{max} was 3074 vs. 3089 ng*h/mL, 2943 vs. 2962 ng*h/mL and 56.4 vs. 55.1 ng/mL, respectively. The inferential statistical analysis showed that the ratio and 90% confidence interval of the geometric least squares means of $AUC_{0-\infty}$, AUC_{0-t} and C_{max} were within the regulatory acceptance range of 80-125%, demonstrating that the 120 mg sitravatinib free base and 100 mg malate capsule formulations are bioequivalent (FDA-2014).

An evaluation of sitravatinib PK using different formulations of capsules is also being conducted as a sub-study within Study MRTX-500 and is ongoing. The sub-study will use the sitravatinib free base capsule formulation as the reference product to evaluate the PK of other formulations of the malate capsule product. The sub-study will include dedicated patient cohorts for each formulation and dose level evaluated. Patients eligible for this sub-study will have locally advanced, unresectable or metastatic non-squamous NSCLC. After a lead-in evaluation, sitravatinib will be administered in combination with nivolumab.

1.4 Nivolumab

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

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

Background information in addition to that presented below is available in the current OPDIVO US Prescribing Information.

1.4.1 Nivolumab Drug Substance

Generic Name: Nivolumab

Other Name: OPDIVO®

Molecular Weight: 146 kDa

1.4.2 Nivolumab Nonclinical Data

The nonclinical experience is described in the OPDIVO US Prescribing Information.

1.4.3 Nivolumab Clinical Data

The following reports information included in the OPDIVO US Prescribing Information dated June 2020. Refer to the current Prescribing Information for updates during the conduct of this clinical trial.

1.4.3.1 Nivolumab Pharmacokinetics

The PK of single-agent nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of OPDIVO Q2W or Q3W as a 60-minute infusion. The predicted exposure of nivolumab after a 30-minute infusion is comparable to that observed with a 60-minute infusion. The geometric mean (% coefficient of variation [CV%]) clearance (CL) is 8.2 mL/h (53.9%), geometric mean volume of distribution at steady state (V_{ss}) is 6.8 L (27.3%), and geometric mean elimination half-life ($t_{1/2}$) is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was approximately 3.7-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered Q2W.

The following factors had no clinically important effect on the clearance of nivolumab: age (29 to 87 years), weight (35 to 160 kg), sex, race, baseline LDH, PD-L1 expression, solid tumor type, tumor size, renal impairment (eGFR ≥15 mL/min/1.73 m^2), and mild (total bilirubin [TB] less than or equal to the ULN and AST greater than ULN or TB >1 to 1.5 times ULN and any AST) or moderate hepatic impairment (TB >1.5 to 3 times ULN and any AST). Nivolumab has not been studied in patients with severe hepatic impairment (TB >3 times ULN and any AST).

1.4.3.2 Nivolumab Anti-Drug Antibodies

Of 2085 patients who were treated with OPDIVO as a single agent at a dose of 3 mg/kg Q2W and evaluable for the presence of anti-nivolumab antibodies, 11% tested positive for treatment-emergent anti-nivolumab antibodies by an electrochemiluminescent (ECL) assay and 0.7% had neutralizing antibodies against nivolumab. There was no evidence of altered pharmacokinetic profile or increased incidence of infusion reactions with anti-nivolumab antibody development.

1.4.3.3 Nivolumab Adverse Reactions Common in Clinical Trials

Refer to the current OPDIVO US Prescribing Information for information concerning adverse reactions occurring in clinical trials.

As of June 2020, the most common adverse reactions (≥20%) in patients administered OPDIVO as a single agent were fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia, headache, abdominal pain, and vomiting.

1.4.3.4 Nivolumab Immune-Mediated Adverse Events

Refer to the current OPDIVO US Prescribing Information for information concerning immune-mediated adverse events occurring during treatment with nivolumab.

As of June 2020, the OPDIVO US Prescribing Information includes warnings and precautions for a range of immune-mediated adverse events documented in patients across cancer indications, including, pneumonitis, colitis, hepatitis, endocrinopathies (such as adrenal insufficiency, hypophysitis, hypothyroidism and hyperthyroidism, Type 1 diabetes mellitus), nephritis and renal dysfunction, skin adverse reactions, encephalitis, other rarer immune-mediated adverse events, and infusion reactions.

1.4.3.5 Nivolumab Safety Reported in Urothelial Carcinoma Clinical Trials

Refer to the current OPDIVO US Prescribing Information for safety information concerning OPDIVO in clinical trials enrolling patients with urothelial carcinoma.

In both studies reported below, patients received 3 mg/kg of nivolumab administered intravenously over 60 minutes Q2W until unacceptable toxicity or either radiographic or clinical progression.

The CheckMate 032 study (Sharma-2016) was a Phase 1/2 trial that included 78 patients with advanced or metastatic urothelial carcinoma who experienced progression during or following one prior platinum-based chemotherapy regimen. Grade 3 or 4 treatment-related AEs occurred in 22% of the patients and included elevated lipase (5%), elevated amylase (4%), fatigue, maculopapular rash, dyspnea, decreased lymphocyte count, and decreased neutrophil count (3% each). Treatment-related AEs of special interest potentially associated with the use of nivolumab were skin (42%), gastrointestinal (10%), renal (9%), hepatic (5%), and pulmonary adverse events (3%). Forty-six percent of the patients experienced SAEs considered related to nivolumab treatment, including colitis, diarrhea, mouth ulceration, nausea, oral pain, thrombocytopenia, fatigue, hyponatremia, acute kidney injury, and pneumonitis. Two patients discontinued treatment due to treatment-related AEs of pneumonitis and thrombocytopenia, both grade 4 events.

The CheckMate 275 study (Sharma-2017) was a single-arm Phase 2 trial in 270 patients with metastatic or surgically unresectable locally advanced disease who had experienced disease progression during or following platinum-containing chemotherapy or had disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum containing chemotherapy. Grade 3 or 4 AEs occurred in 18% of patients including fatigue and diarrhea (2% each). Treatment-related AEs of special interest (potentially immunomediated) were skin (17%) and endocrine (14%). SAEs occurred in 54% of

patients, including at least 2% of patients experiencing urinary tract infection, sepsis, diarrhea, small intestine obstruction, and general physical health deterioration. Nivolumab was discontinued for AEs in 5% of patients. Of the 14 deaths not related to disease progression, three were attributed to treatment, including pneumonitis, acute respiratory failure, and cardiovascular failure (1 each).

1.4.3.6 Nivolumab Efficacy Reported in Urothelial Carcinoma Clinical Trials

Refer to the current OPDIVO US Prescribing Information for efficacy information concerning OPDIVO in clinical trials enrolling patients with urothelial carcinoma.

In the CheckMate 032 study (Sharma-2016), the median duration of therapy for the 78 treated patients was 17 weeks (range 1-46 weeks) and the minimum follow-up was 9 months (median 15.2 months). The ORR as confirmed by the Investigator was 24.4%.

In the CheckMate 275 study (Sharma-2017), the median duration of therapy for the 270 treated patients was 3.3 months (range: 0 to 13.4+ months) and the minimum follow-up was 6 months (median 7 months). The overall ORR as confirmed by central review was 19.6%. Response to nivolumab appears to be independent of tumor cell PD-L1 expression as objective response rates of 28.4%, 23.8% and 16.1% were reported for tumor cell PD-L1 expression of >5%, ≥ 1%, or <1%, respectively. Median overall survival was 8·74 months. Median overall survival for patients with PD-L1 expression ≥ 1% was 11.30 months compared to 5.95 months for patients with <1%. Despite these promising results, not all patients benefit from the treatment and patients will eventually exhibit disease progression.

1.5 Pembrolizumab

Pembrolizumab (KEYTRUDA®) is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin.

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

Background information in addition to that presented below is available in the KEYTRUDA US Prescribing Information.

1.5.1 Pembrolizumab Drug Substance

- Generic Name: Pembrolizumab
- Other Name: KEYTRUDA®
- Molecular Weight: 149 kDa

1.5.2 Pembrolizumab Nonclinical Data

The nonclinical experience is described in the KEYTRUDA US Prescribing Information.

1.5.3 Pembrolizumab Clinical Data

The following reports information included in the KEYTRUDA US Prescribing Information dated April 2020. Refer to the current Prescribing Information for updates during the conduct of this clinical trial.

1.5.3.1 Pembrolizumab Pharmacokinetics

The PK of pembrolizumab was characterized using a population PK analysis with concentration data collected from 2993 patients with various cancers who received pembrolizumab doses of 1 to 10 mg/kg Q2W, 2 to 10 mg/kg Q3W, or 200 mg Q3W. The geometric mean (% coefficient of variation [CV%]) clearance (CL) is 195 mL/d (40%), geometric mean volume of distribution at steady state (V_{ss}) is 6.0 L (20%), and geometric mean terminal elimination half-life ($t_{1/2}$) is 22 days (32%). Steady-state concentrations of pembrolizumab were reached by 16 weeks of repeated dosing with a Q3W regimen, and systemic accumulation was approximately 2.1-fold. The steady-state exposure to pembrolizumab increased dose proportionally over the dose range of 2 to 10 mg/kg administered Q3W.

The population PK analysis suggested that the following factors had no clinically important effect on the clearance of pembrolizumab: age (15 to 94 years), sex, race (89% White), renal impairment (eGFR ≥15 mL/min/1.73 m^2), mild hepatic impairment (total bilirubin [TB] less than or equal to the upper limit of normal [ULN] and AST greater than ULN or TB <1 to 1.5 times ULN or AST>ULN), or tumor burden. The impact of moderate or severe hepatic impairment on the PK of pembrolizumab is unknown.

1.5.3.2 Pembrolizumab Anti-Drug Antibodies

Of 1289 patients who were treated with KEYTRUDA as a single agent, at a dose of 2 mg/kg Q3W, 200 mg Q3W, or 10 mg/kg Q2W or Q3W and evaluable for the presence of anti-pembrolizumab antibodies, 2% tested positive for treatment-emergent anti-pembrolizumab antibodies by an electrochemiluminescent (ECL) assay of whom 0.5% had neutralizing antibodies against pembrolizumab. There was no evidence of an altered

pharmacokinetic profile or increased incidence of infusion reactions with anti-pembrolizumab binding antibody development.

1.5.3.3 Pembrolizumab Adverse Reactions Common in Clinical Trials

Refer to the current KEYTRUDA US Prescribing Information for information concerning adverse reactions occurring in clinical trials.

As of April 2020, the most common adverse reactions (≥20%) in patients administered KEYTRUDA as a single agent were fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain.

As of April 2020, the most common adverse reactions (≥20%) in patients administered KEYTRUDA in combination with chemotherapy were fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, pyrexia, alopecia, peripheral neuropathy, mucosal inflammation, and stomatitis.

As of April 2020, the most common adverse reactions (≥20%) in patients administered KEYTRUDA in combination with lenvatinib were fatigue, hypertension, musculoskeletal pain, diarrhea, decreased appetite, hypothyroidism, nausea, stomatitis, vomiting, decreased weight, abdominal pain, headache, constipation, urinary tract infection, dysphonia, hemorrhagic events, hypomagnesemia, PPE, dyspnea, cough, and rash.

1.5.3.4 Pembrolizumab Immune-Mediated Adverse Events

Refer to the current KEYTRUDA US Prescribing Information, for information concerning immune-mediated adverse events occurring during treatment with nivolumab.

As of April 2020, the KEYTRUDA US Prescribing Information includes warnings and precautions for a range of immune-mediated adverse events documented in patients across cancer indications, including, pneumonitis, colitis, hepatitis, endocrinopathies (such as adrenal insufficiency, hypophysitis, hypothyroidism and hyperthyroidism, Type 1 diabetes mellitus), nephritis and renal dysfunction, skin adverse reactions (including Stevens Johnson syndrome [SJS] and toxic epidermal necrolysis [TEN]), other rarer immune-mediated adverse events, and infusion reactions.

1.5.3.5 Pembrolizumab Safety Reported in Urothelial Carcinoma Clinical Trials

Refer to the current KEYTRUDA US Prescribing Information for safety information concerning KEYTRUDA in clinical trials enrolling patients with urothelial carcinoma.

In both studies reported below, patients received 200 mg of pembrolizumab administered intravenously over 30 minutes Q3W until unacceptable toxicity or progressive disease, or up to 24 months of therapy without disease progression.

The KEYNOTE-045 study (Bellmunt-2017; Fradet-2019) was a randomized Phase 3 trial of pembrolizumab (n=270) versus Investigator's choice of chemotherapy with paclitaxel (n=84), docetaxel (n=84) or vinflunine (n=87) in patients with advanced or metastatic urothelial carcinoma that experienced progression during or following one prior platinum-based chemotherapy regimen. The most common AEs (reported in ≥20% of patients) were fatigue (38%), musculoskeletal pain (32%), pruritus (23%), decreased appetite, and nausea (21% each), and rash (20%). AEs of Grade 3, 4 or 5 severity that were observed in two or more patients who were treated with pembrolizumab were pneumonitis (2%), and colitis, diarrhea, fatigue, anemia and nephritis (1% each); there was only one Grade 5 event (<1%), which was pneumonitis. Treatment-related AEs of special interest potentially associated with the use of pembrolizumab were hypothyroidism (6%), hyperthyroidism, and pneumonitis (4% each), colitis (2%), infusion reaction, nephritis, severe skin reaction, and thyroiditis (1% each), and adrenal insufficiency (<1%). Twelve percent of the patients experienced SAEs considered related to pembrolizumab. None of the treatment-related SAEs in the pembrolizumab arm occurred with a frequency of >2%; the most frequently occurring (in >1% of patients) were colitis, and pneumonitis (2% each), and interstitial lung disease (1%). Pembrolizumab was discontinued due to AEs in 8% of patients. The most common AE resulting in permanent discontinuation of pembrolizumab was pneumonitis (2%).

The KEYNOTE-052 study (Balar-2017; O'Donnell-2017; O'Donnell-2019) was a single-arm Phase 2 trial in 374 cisplatin-ineligible patients with advanced urothelial cancer who had not been previously treated with systemic chemotherapy. The most common AEs (reported in ≥20% of patients) were fatigue (38%), musculoskeletal pain (24%), decreased appetite (22%), constipation, and rash (21% each), and diarrhea (20%). The most common Grade 3 or 4 treatment-related adverse events were alkaline phosphatase increase, fatigue, and colitis (2% each), and hepatitis, and muscle weakness (1% each). There was only one Grade 5 event (<1%), which was myositis. Other immune-mediated adverse occurring in ≥2 or more patients were hypothyroidism (11%), pneumonitis (5%), colitis, hyperthyroidism, and severe skin reaction (3%), hepatitis, and adrenal insufficiency (2% each), thyroiditis, type 1 diabetes mellitus (1% each), hypophysitis, myocarditis, nephritis, and pancreatitis (<1% each). Serious adverse reactions occurred in 42% of patients. The most frequent serious adverse reactions (≥2%) were urinary tract infection, hematuria, acute kidney injury, pneumonia, and urosepsis. Pembrolizumab was discontinued due to adverse reactions in 11% of patients.

1.5.3.6 Pembrolizumab Efficacy Reported in Urothelial Carcinoma Clinical Trials

Refer to the current KEYTRUDA US Prescribing Information for efficacy information concerning KEYTRUDA in clinical trials enrolling patients with urothelial carcinoma.

In the KEYNOTE-045 study (Bellmunt-2017; Fradet-2019), the median duration of therapy in the pembrolizumab group was 3.5 months (range, <0.1 to 20.0) and the median follow-up was 27.7 months. The overall ORR as confirmed by central review in the

pembrolizumab group was 21% (20% for patients with CPS ≥10). The median DOR was not reached (range, 1.6+ to 30.0+ months). Median overall survival was 10.1 months. Pembrolizumab continued to demonstrate an OS benefit over chemotherapy in all subgroups examined, including those with visceral disease and liver metastases, and across the different levels of PD-L1 expression and risk groups.

In the KEYNOTE-052 study (Balar-2017; O'Donnell-2017; O'Donnell-2019), the overall ORR as confirmed by central review was 29%, compared to 47% for patients with CPS ≥10. With a median follow-up of 15.3 months, the median DOR was 30.1 months (range, 18.8 months to not reached) in the overall population; and was not reached for patients with CPS ≥10. Median overall survival was 11.3 months (range, 9.7 to 13.1 months), compared to 18.5 months (range, 12.2 to 28.5 months) for patients with CPS ≥10.

1.6 Enfortumab

Enfortumab vedotin-ejfv (enfortumab, PADCEV™) is a Nectin-4 directed antibody-drug conjugate (ADC) comprised of a fully human anti-Nectin-4 IgG1 kappa monoclonal antibody (AGS-22C3) conjugated to the small molecule microtubule disrupting agent, monomethyl auristatin E (MMAE) via a protease-cleavable maleimidocaproyl valine-citrulline linker (SGD-1006).

Enfortumab vedotin-ejfv is an ADC. The antibody is a human IgG1 directed against Nectin-4, an adhesion protein located on the surface of cells. The small molecule, MMAE, is a microtubule-disrupting agent, attached to the antibody via a protease-cleavable linker. Nonclinical data suggest that the anticancer activity of enfortumab vedotin-ejfv is due to the binding of the ADC to Nectin-4-expressing cells, followed by internalization of the ADC-Nectin-4 complex, and the release of MMAE via proteolytic cleavage. Release of MMAE disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic cell death.

Background information in addition to that presented below is available in the PADCEV US Prescribing Information.

1.6.1 Enfortumab Drug Substance

- Generic Name: Enfortumab Vedotin-ejfv
- Other Name: PADCEV™
- Molecular Weight: 152 kDa

1.6.2 Enfortumab Nonclinical Data

The nonclinical experience is described in the PADCEV US Prescribing Information.

1.6.3 Enfortumab Clinical Data

The following reports information included in the PADCEV US Prescribing Information dated December 2019. Refer to the current Prescribing Information for updates during the conduct of this clinical trial.

1.6.3.1 Enfortumab Pharmacokinetics

Population pharmacokinetic analysis included data from 369 patients based on three Phase 1 studies and one Phase 2 study. Enfortumab pharmacokinetics were characterized after single and multiple doses in patients with locally advanced or metastatic urothelial carcinoma (UC) and other solid tumors. Enfortumab exhibited linear dose-proportional PK at doses ranging from 0.5 to 1.25 mg/kg when administered as an intravenous infusion over ~30 minutes on days 1, 8, and 15 of a 28-day cycle in patients with locally advanced or metastatic UC. Peak enfortumab concentrations were attained at the end of infusion. In contrast, plasma concentrations of free MMAE increased until ~2 days after enfortumab dosing. The mean clearance (CL) of enfortumab and free MMAE in patients was 0.10 L/h and 2.7 L/h, respectively, in patients. Elimination of MMAE appeared to be limited by its rate of release from enfortumab. The estimated mean volume of distribution of ADC at steady state (V_{ss}) was 11 liters following administration of enfortumab. ADC and MMAE exhibited multi-exponential declines with an elimination half-life of 3.4 days and 2.4 days, respectively. Steady-state concentrations of ADC and MMAE were reached after 1 treatment cycle with a 1.25 mg/kg Q3W regimen, and minimal accumulation of the ADC and MMAE was observed following repeat administration of enfortumab in patients.

Based on population pharmacokinetic analysis, no clinically significant differences in the pharmacokinetics of enfortumab were observed based on age (24 to 87 years), sex, or race/ethnicity (Caucasian, Asian, Black, or others).

Based on population pharmacokinetics analysis, there was a 48% AUC increase in unconjugated MMAE exposure observed in patients with mild hepatic impairment (bilirubin of 1 to 1.5 the upper limit of normal [ULN] and AST less than ULN, or bilirubin less than or equal to ULN and AST greater than ULN, n=31) compared to normal hepatic function. The effect of moderate or severe hepatic impairment (AST or ALT greater than 2.5 times ULN or total bilirubin greater than 1.5 times ULN) or liver transplantation on the pharmacokinetics of ADC or unconjugated MMAE is unknown.

The pharmacokinetics of enfortumab and MMAE were evaluated after the administration of 1.25 mg/kg of enfortumab to patients with mild (creatinine clearance; CrCL greater than 60 to 90 mL/min; n=135), moderate (CrCL 30 to 60 mL/min; n=147) and severe (CrCL less than 30 mL/min; n=8) renal impairment. No significant differences in exposure (AUC) of ADC and MMAE were observed in patients with mild, moderate or severe renal impairment compared to patients with normal renal function. The effect of

end stage renal disease with or without dialysis on the pharmacokinetics of ADC or unconjugated MMAE is unknown.

1.6.3.2 Enfortumab Anti-Drug Antibodies

Of 365 patients who were treated with PADCEV as a single agent Q3W (1.0 and 1.25 mg/kg Q3W) and evaluable for the presence of for immunogenicity to PADCEV, 1% were confirmed to be transiently positive for anti-therapeutic antibody (ATA), and 0.3% were confirmed to be persistently positive for ATA at any post-baseline time point. No impact of ATA on efficacy, safety and pharmacokinetics was observed.

1.6.3.3 Enfortumab Adverse Reactions Common in Clinical Trials

Refer to the current PADCEV US Prescribing Information for information concerning adverse reactions occurring in clinical trials.

As of December 2019, the most common AEs (≥20%) in patients administered PADCEV as a single agent included fatigue, peripheral neuropathy, decreased appetite, rash, alopecia, nausea, dysgeusia, diarrhea, dry eye, pruritus and dry skin. Hyperglycemia occurred in patients treated with PADCEV, including death, and diabetic ketoacidosis (DKA) in those with and without pre-existing diabetes mellitus. The incidence of Grade 3-4 hyperglycemia increased consistently in patients with higher body mass index and in patients with higher baseline A1C. In EV-201, 8% of patients developed Grade 3-4 hyperglycemia.

The most common treatment-related AEs (≥20%) from initial safety updates in Study EV-103 (Rosenberg-2020) in patients administered PADCEV in combination with pembrolizumab were rash, fatigue, alopecia, peripheral sensory neuropathy, diarrhea, decreased appetite, dysgeusia, nausea, pruritus, anemia, and weight decreased. Additional AEs of clinical interest included immune-mediated AEs requiring systemic steroids (29%; including 18% ≥Grade 3) and hyperglycemia (11%; including 7% ≥Grade 3).

1.6.3.4 Enfortumab Safety Reported in Urothelial Carcinoma Clinical Trials

Refer to the current PADCEV US Prescribing Information for safety information concerning PADCEV in clinical trials enrolling patients with urothelial carcinoma.

In the enfortumab monotherapy study below, patients received 1.25 mg/kg (up to a maximum dose of 125 mg) of enfortumab given as an intravenous infusion over 30 minutes on Days 1, 8 and 15 of a 28-day cycle until disease progression or unacceptable toxicity. In the combination study below of enfortumab with pembrolizumab, patients received 1.25 mg/kg of enfortumab given as an intravenous infusion over 30 minutes on Days 1 and 8 of a 21-day cycle and 200 mg of pembrolizumab administered intravenously over 30 minutes on Day 1 of Q3W until disease progression or unacceptable toxicity.

The EV-201 study (Petrylak-2019; Rosenberg-2019) was a single-arm Phase 2 trial of enfortumab monotherapy in 125 patients with locally advanced or metastatic urothelial carcinoma who were previously treated with platinum chemotherapy and a PD-(L)1 checkpoint inhibitor. The most common AEs (reported in ≥20% of patients) were fatigue and peripheral neuropathy (56%), decreased appetite and rash (52% each), alopecia (50%), nausea (45%), dysgeusia and diarrhea (42% each), dry eye (40%), and dry skin and pruritus (26% each). The most common Grade 3, 4, or 5 AEs (reported in ≥5% of patients) were rash (13%), and fatigue and diarrhea (6% each). Grade 5 AEs occurred in 3% of patients, including acute respiratory failure, aspiration pneumonia, cardiac disorder, and sepsis (each 1%). An AE of clinical interest was treatment-related hyperglycemia which occurred in 11% of patients, of which 8% were Grade 3 or 4. SAEs occurred in 46% of patients. The most frequent SAEs (≥3%) were urinary tract infection (6%), cellulitis (5%), febrile neutropenia and diarrhea (4%), and sepsis, acute kidney injury, dyspnea and rash (3% each). Enfortumab was discontinued due to AEs in 16% of patients. The most common AE resulting in permanent discontinuation of enfortumab was peripheral neuropathy (6%).

The EV-103 study (Rosenberg-2020, Hoimes-2019) was a single-arm Phase 1/2 trial of enfortumab combination therapies including enfortumab plus pembrolizumab in 45 cisplatin-ineligible, treatment-naïve patients with locally-advanced or metastatic urothelial carcinoma. The study initiated with a 5-patient dose escalation that led into an additional 40-patient expansion. The dose escalation confirmed the combination regimen doses consisting of pembrolizumab at 200 mg Q3W and enfortumab at 1.25 mg/kg on days 1 and 8 of 3-week cycles. It is worth noting that the pembrolizumab dose and frequency in the combination matches single agent pembrolizumab dosing, whereas the enfortumab dosing was similar but the frequency was matched to a 3-week cycle (from the usual 4-week cycle with single agent use). The most common treatment-related AEs (reported in ≥20% of patients) were rash (62%), alopecia, fatigue and peripheral neuropathy (49% each), diarrhea (44%), decreased appetite (38%), dysgeusia (33%), nausea and pruritus (29% each), and anemia and weight decreased (20% each). The most common Grade 3, 4, or 5 treatment-related AEs (reported in ≥5% of patients) were fatigue and rash maculo-papular (9% each), and anemia and diarrhea (7% each). There was only one treatment-related Grade 5 AE (2%), which was multiple organ dysfunction syndrome. Additional AEs of clinical interest included immune-mediated AEs requiring systemic steroids (29%; including 18% ≥Grade 3) and hyperglycemia (11%; including 7% ≥Grade 3). Treatment-related SAEs occurred in 16% of patients. The only treatment-related SAE occurring in ≥1 patient was colitis (4%). Enfortumab and pembrolizumab were discontinued due to treatment-related AEs in 13% of patients. The most common AE resulting in permanent discontinuation of enfortumab and pembrolizumab was peripheral neuropathy (7%).

1.6.3.5 Enfortumab Efficacy Reported in Urothelial Carcinoma Clinical Trials

Refer to the current PADCEV US Prescribing Information for safety information concerning PADCEV in clinical trials enrolling patients with urothelial carcinoma.

In the EV-201 study (Petrylak-2019; Rosenberg-2019), the median duration of therapy was 4.6 months (maximum duration of 15.6 months) and the median follow-up was 10.2 months. The overall ORR as confirmed by central review was 44% (including a 12% complete response rate). The median DOR was 7.6 months (range, 0.95 to 11.30+ months). Median overall survival was 11.7 months.

In the EV-103 study (Rosenberg-2020; Hoimes-2019), the median follow-up was 10.4 months. The overall ORR as confirmed by central review was 73% (including a 16% complete response rate) with activity regardless of PD-L1 expression level. With a median follow-up was 10.4 months, the median DOR was not reached (range, 1.2 to 12.9+ months). Median overall survival was also not reached, with a 12-month overall survival rate of 82%.

1.7 Expectations for Safety of Sitravatinib Combination Regimens

1.7.1 Potential for Drug-Drug Interactions with Sitravatinib Combination Regimens

1.7.1.1 Potential for Drug-Drug Interactions with the Combination of Sitravatinib and Nivolumab

Sitravatinib administered in combination with nivolumab is unlikely to result in clinically relevant drug-drug interactions (DDI) based on absorption, metabolism, elimination or protein binding. Nivolumab is a mAb and is intravenously administered, whereas sitravatinib is a small molecule therapeutic administered orally; no absorption interactions are expected.

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

1.7.1.2 Potential for Drug-Drug Interactions with the Combination of Sitravatinib, Pembrolizumab and Enfortumab

Sitravatinib administered in combination pembrolizumab and enfortumab is unlikely to result in drug-drug interactions (DDI) based on absorption, metabolism, elimination or protein binding. Both pembrolizumab and enfortumab are mAbs and are intravenously administered, whereas sitravatinib is a small molecule therapeutic administered orally; no absorption interactions are expected. The only potential for DDI stems from MMAE

being an in vitro substrate of both CYP3A4 and P glycoprotein (P-gp) (see below), and sitravatinib being an in vitro inhibitor of both CYP3A4 and P-gp. To mitigate the potential for increased MMAE exposure with the combination of sitravatinib, pembrolizumab and enfortumab and any subsequent clinical impact, the lead-in dose escalation evaluation (Cohort 9) of the combination will initiate with a sitravatinib starting dose representing three dose levels (~65%) below the dose administered as a single-agent and in combination with nivolumab in Phase 2 and Phase 3 trials. In addition, a dose de-escalation step for enfortumab may be undertaken as appropriate. Refer to Appendix 9 for study design details of cohorts investigating the combination of sitravatinib, pembrolizumab and enfortumab.

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

On the other hand, whereas no clinical studies evaluating the drug-drug interaction potential of enfortumab have been conducted, in vitro studies indicate that MMAE is a substrate of CYP3A4. Concomitant use with a strong CYP3A4 inhibitor may increase free MMAE exposure, which may increase the incidence or severity of enfortumab toxicities (PADCEV US Prescribing Information). Since in vitro studies suggest sitravatinib could be an inhibitor of CYP3A4, there is the potential that co-administration with sitravatinib could result in increased MMAE exposure.

Finally, no clinical studies evaluating the drug-drug interaction potential of enfortumab have been conducted, in vitro studies indicate that MMAE is a substrate of P-gp, but not an inhibitor of P-gp (PADCEV US Prescribing Information). Since in vitro studies suggest sitravatinib could be an inhibitor of P-gp, there is the potential that co-administration with sitravatinib could result in increased MMAE exposure.

1.7.2 Potential for Increased Toxicity with Sitravatinib Combination Regimens

1.7.2.1 Potential for Increased Toxicity with Combination of Sitravatinib and a PD-(L)1 Checkpoint Inhibitor

Frequent AEs, such as fatigue, musculoskeletal pain, decreased appetite, cough, and constipation, which are non-specific and typical of cancer treatment regimens have been observed with PD-1 checkpoint inhibitors (including nivolumab and pembrolizumab) and sitravatinib monotherapy. Potential exists for these AEs to be observed with increased severity or frequency during use of the combined agents. Management of these effects in patients receiving cancer therapy is well precedented.

Importantly, immune-related AEs (irAEs) using PD-1 checkpoint inhibitors monotherapy include pneumonitis, colitis, hepatitis, endocrinopathies (such as adrenal insufficiency,

hypophysitis, hypothyroidism and hyperthyroidism, Type 1 diabetes mellitus), nephritis/renal dysfunction, skin adverse reactions, and encephalitis. While sitravatinib may have immunostimulatory effects, autoimmune adverse effects have not been reported in clinical trials of this investigational study agent, including to date in combination with nivolumab, nor are they recognized as class effects for this agent. However, the potential for sitravatinib to exacerbate or promote these adverse events when administered in combination with nivolumab should be borne in mind. AE incidence data presented below are as reported in the OPDIVO US Prescribing Information dated June 2020, the KEYTRUDA US Prescribing Information dated April 2020 and the Sitravatinib Investigator's Brochure dated November 2019. Updates to these data during the conduct of this clinical trial will be found in the current OPDIVO US Prescribing Information, the current KEYTRUDA US Prescribing Information and current Sitravatinib Investigator's Brochure.

A clinically relevant overlap in toxicity may arise between the immune-mediated colitis attributed to PD-1 checkpoint inhibitors (such as nivolumab and pembrolizumab) and the non-specific, most often mild to moderate diarrhea observed with sitravatinib. Immune-mediated colitis has been reported in 2.9% (58/1994) and 1.7% (48/2799) of patients treated with nivolumab and pembrolizumab, respectively; with respective median times to onset of 5.3 months (range: 2 days to 20.9 months) and 3.5 months (range: 10 days to 16.2 months). Diarrhea has been reported in approximately 50% of patients treated with sitravatinib monotherapy, most often beginning within the first month of the start of treatment. Diarrhea (any grade) is less common with nivolumab and pembrolizumab, occurring in approximately 17% and 18-20%, respectively, of urothelial carcinoma patients treated with nivolumab at 3 mg/kg Q2W in the CheckMate 275 clinical trial (Sharma-2017) and pembrolizumab at 200 mg Q3W in both the KEYNOTE-045 (Bellmunt-2017) and KEYNOTE-052 (Balar-2017) clinical trials. The time to onset may be helpful in distinguishing diarrhea that may be attributed to autoimmune effects versus non-specific toxicity.

Tyrosine kinase inhibitors in general, and MET inhibitors in particular, have been associated with non-specific, most often mild to moderate elevation in AST and ALT. Mild to moderate elevations in liver transaminases have also been observed in 18% of patient treated with sitravatinib monotherapy. The elevations observed with sitravatinib generally occur within the first cycle of treatment and resolve with interruption of treatment. In patients receiving nivolumab or pembrolizumab as a single agent, immune-mediated hepatitis occurred in 1.8% (35/1994) and 0.7% (19/2799) of patients, respectively; with respective median times to onset of 3.3 months (range: 6 days to 9 months) and 1.3 months (range: 8 days to 21.4 months).

Hypothyroidism, including thyroiditis, was reported in 15% and 9%, respectively, of urothelial carcinoma patients treated with nivolumab and pembrolizumab monotherapy. Hypothyroidism has been reported in approximately 17% of patients treated with sitravatinib.

A clinically relevant overlap in toxicity may arise between the immune-related rash attributed to PD-1 checkpoint inhibitors (such as nivolumab and pembrolizumab) and the non-specific, most often mild (Grade 1) rash observed with sitravatinib. Rash, described as dermatitis, dermatitis acneiform, dermatitis bullous, generalized, macular, maculopapular or pruritic, has been reported in 16% and 20-21%, respectively, of urothelial carcinoma patients treated with nivolumab and pembrolizumab monotherapy. Rash has been reported in 11% of patients treated with sitravatinib.

1.7.2.2 Potential for Increased Toxicity with the Combination of Sitravatinib, Pembrolizumab and Enfortumab

Frequent AEs, such as fatigue, weight decreased, musculoskeletal pain, decreased appetite, cough, nausea, and constipation, which are non-specific and typical of cancer treatment regimens have been observed with sitravatinib monotherapy, and with the combination of pembrolizumab and enfortumab. Potential exists for these AEs to be observed with increased severity or frequency with the combination of sitravatinib, pembrolizumab and enfortumab. Management of these effects in patients receiving cancer therapy is well precedented.

Importantly, immune-related AEs (irAEs) using PD-1 checkpoint inhibitors monotherapy include pneumonitis, colitis, hepatitis, endocrinopathies (such as adrenal insufficiency, hypophysitis, hypothyroidism and hyperthyroidism, Type 1 diabetes mellitus), nephritis/renal dysfunction, skin adverse reactions, and encephalitis. Immune-mediated AEs requiring systemic steroids occurred in 29% (13/45) of urothelial carcinoma patients receiving the combination of pembrolizumab and enfortumab in Study EV-103 (Rosenberg-2020; Hoimes-2019). While sitravatinib may have immunostimulatory effects, autoimmune adverse effects have not been reported in sitravatinib monotherapy studies, nor are they recognized as class effects for this agent. And whereas the incidence of irAEs in combination with checkpoint inhibitors has not been fully characterized, early safety reviews do not indicate a significant increase in the incidence of irAEs with the combination compared to checkpoint inhibitor monotherapy. However, the potential for sitravatinib to exacerbate or promote these adverse events when administered in combination with pembrolizumab and enfortumab should be borne in mind. AE incidence data presented below are as reported in the KEYTRUDA US Prescribing Information dated April 2020, the PADCEV US Prescribing Information dated December 2019 and the Sitravatinib Investigator's Brochure dated November 2019. Updates to these data during the conduct of this clinical trial will be found in the current KEYTRUDA US Prescribing Information, the current PADCEV US Prescribing Information and current Sitravatinib Investigator's Brochure.

A clinically relevant overlap in toxicity may arise between the immune-mediated colitis attributed to PD-1 checkpoint inhibitors (such as pembrolizumab) and the non-specific, most often mild to moderate diarrhea observed with sitravatinib. Immune-mediated colitis has been reported in 1.7% (48/2799) of patients treated with pembrolizumab, with a median time to onset of 3.5 months (range: 10 days to 16.2 months). Diarrhea has been

reported in approximately 50% of patients treated with sitravatinib monotherapy, most often beginning within the first month of the start of treatment. Diarrhea (any grade) is less common with pembrolizumab, occurring in approximately 18-20% of urothelial carcinoma patients treated with pembrolizumab (Bellmunt-2017; Balar-2017). However, diarrhea is common with the combination of pembrolizumab and enfortumab occurring in 44% (20/45) of urothelial carcinoma patients receiving the combination of pembrolizumab and enfortumab in Study EV-103 (Rosenberg-2020). The time to onset may be helpful in distinguishing diarrhea that may be attributed to autoimmune effects versus non-specific toxicity.

Tyrosine kinase inhibitors in general, and MET inhibitors in particular, have been associated with non-specific, most often mild to moderate elevation in AST and ALT. Mild to moderate elevations in liver transaminases have also been observed in 18% of patient treated with sitravatinib monotherapy. The elevations observed with sitravatinib generally occur within the first cycle of treatment and resolve with interruption of treatment. In patients receiving pembrolizumab as a single agent, immune-mediated hepatitis occurred in 0.7% (19/2799) of patients, with a median time to onset of 1.3 months (range: 8 days to 21.4 months). Enfortumab monotherapy is not associated with increases in AST or ALT. Increases in transaminases will be closely monitored.

Hypothyroidism, including thyroiditis, was reported in 7% of urothelial carcinoma patients treated with pembrolizumab monotherapy. Hypothyroidism has been reported in approximately 17% of patients treated with sitravatinib. Enfortumab monotherapy is not associated with thyroid dysfunction. Thyroid dysfunctions will be closely monitored.

A clinically relevant overlap in toxicity may arise between the immune-related rash attributed to PD-1 checkpoint inhibitors (such as nivolumab and pembrolizumab) and the non-specific, most often mild (Grade 1) rash observed with sitravatinib. Rash, described as dermatitis, dermatitis acneiform, dermatitis bullous, generalized, macular, maculopapular or pruritic, has been reported in 20-21% and 31%, respectively, of urothelial carcinoma patients treated with pembrolizumab monotherapy and combination of pembrolizumab and enfortumab. Rash has been reported in 11% of patients treated with sitravatinib.

Increased lipase has been observed in patients treated with sitravatinib and other inhibitors of the VEGF pathway. Although the mechanism has not been fully elucidated, inhibition of VEGF may lead to acinar cell apoptosis resulting in the release of autodigestive enzymes (Sevin-2012). Most sitravatinib treatment-emergent events of increased amylase and lipase were asymptomatic while some were associated with signs and/or symptoms of pancreatitis. Treatment-related increased lipase has been observed in 10% of patients treated with sitravatinib monotherapy. Increased lipase is rare with pembrolizumab monotherapy, however it occurs in 18% (8/45) of urothelial carcinoma patients receiving the combination of pembrolizumab and enfortumab in Study EV-103 (Rosenberg-2020).

Finally, whereas sitravatinib administered in combination pembrolizumab and enfortumab is unlikely to result in drug-drug interactions (DDI), the only potential for DDIs stems from MMAE being an in vitro substrate of both CYP3A4 and P-glycoprotein (P-gp) (see below), and sitravatinib being an in vitro inhibitor of both CYP3A4 and P-gp (see Section 1.7.1.2). To mitigate the potential for increased MMAE exposure with the combination of sitravatinib, pembrolizumab and enfortumab and any subsequent clinical impact, the lead-in dose escalation evaluation (Cohort 9) of the combination will initiate with a sitravatinib starting dose representing three dose levels (~65%) below the dose administered as a single-agent and in combination with nivolumab in Phase 2 and Phase 3 trials. In addition, a dose de-escalation step for enfortumab may be undertaken as appropriate. Refer to Appendix 9 for study design details of cohorts investigating the combination of sitravatinib, pembrolizumab and enfortumab.

1.8 Study Rationale

Immune checkpoint inhibitors targeting the PD-(L)1 pathway have demonstrated clinical activity in patients with urothelial carcinoma. While checkpoint inhibitor therapy leads to durable clinical responses in a subset of patients, strategies to improve its clinical efficacy and overcome innate or acquired resistance to checkpoint inhibitor monotherapy are needed. Combination therapy with agents that target the molecular and cellular mechanisms of resistance to checkpoint inhibitor therapy is a rational approach to improving outcomes in patients.

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

may complement PD-(L)1 checkpoint inhibition to unleash the host anti-cancer immune response.

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

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

Sitravatinib is an orally-available, potent small molecule inhibitor of a closely related spectrum of receptor tyrosine kinases (RTKs) including MET, Axl, MERTK, VEGFR family, PDGFR family, KIT, FLT3, Trk family, RET, DDR2, and selected Eph family members.

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

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

This study will evaluate the clinical activity of nivolumab in combination with sitravatinib. Nivolumab will be administered in accordance with approved labeling, by intravenous infusion, 240 mg every 2 weeks (Q2W) or 480 mg every 4 weeks (Q4W). Under previous versions of this protocol, sitravatinib was administered in accordance with findings of the prior nivolumab combination study (MRTX-500), orally, with the starting dose of 120 mg once daily (QD) of the free base capsule formulation (in 28-day cycles). Nonclinical studies indicate that sitravatinib administered to patients at 120 mg QD should achieve the plasma exposure required for inhibition of VEGF and TAM receptors, necessary to achieve antitumor efficacy in the combination setting. 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 1.3.3.4. Patients who began treatment with the free base capsule formulation will remain on the free base capsule formulation throughout the duration of the study.

Pembrolizumab is a humanized IgG4 monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. Enfortumab is a Nectin-4 directed antibody-drug conjugate (ADC) comprised of a fully human anti-Nectin-4 IgG1 kappa monoclonal antibody (AGS-22C3) conjugated to the small molecule microtubule disrupting agent, monomethyl auristatin E (MMAE). Binding of the ADC to Nectin-4-expressing cells such as urothelial carcinoma cells, leads to internalization of the ADC-Nectin-4 complex and intratumoral release of MMAE disrupting the microtubule network within the cell, and subsequently inducing cell cycle arrest and apoptotic cell death. Emerging preclinical data indicates a potential immune modulatory activity with ADCs that are linked to MMAE by inducing immunogenic cell death, antibody-dependent cellular phagocytosis and cytotoxicity (Cao-2016; Cao-2017; Cao-2018; Alley-2019). In vivo administration of these ADCs leads to directed proinflammatory immune responses against the tumor and this activity is further potentiated by PD-1 checkpoint inhibitor therapy as demonstrated by accelerated tumor regressions and greater antitumor activity than either agent alone, demonstrating complementary modes of action for these agents and providing a rationale for exploring therapeutic strategies that combine ADCs with other immune stimulatory regimens. Early efficacy results from enfortumab in combination with pembrolizumab in frontline cisplatin-ineligible urothelial carcinoma in the ongoing EV-103 Phase 2 trial has shown encouraging activity with a safety profile that appears manageable and tolerable.

Addition of sitravatinib to this combination might further augment clinical activity by selectively inhibiting key molecular and cellular pathways strongly implicated in checkpoint inhibitor resistance.

This study may evaluate the safety of sitravatinib administered in combination with pembrolizumab and enfortumab starting with a lead-in dose escalation evaluation of up to three dose levels of sitravatinib in combination with up to two dose levels of pembrolizumab and enfortumab combination regimen. The starting dose for sitravatinib using the malate formulation will represent three dose levels below the dose administered as a single agent and in combination (with nivolumab) Phase 2 and Phase 3 trials. The starting doses for pembrolizumab and enfortumab will represent the recommended doses from the EV-103 Phase 2 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, dose de-escalation step for enfortumab may be undertaken as appropriate. If a tolerable dose is identified for sitravatinib in combination with pembrolizumab and enfortumab, the clinical activity of this combination may be evaluated in 2 populations of patients with urothelial carcinoma.

2 STUDY OBJECTIVES

2.1 Objectives

2.1.1 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.

2.1.2 Secondary Objectives

- To evaluate the safety and tolerability of the combination regimens in the selected population.
- To evaluate secondary efficacy endpoints of the combination regimens in the selected population.
- To evaluate the pharmacokinetics (PK) of 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.

2.1.3 Exploratory Objectives

- To assess the effect of the combination regimens on circulating PD-L1, immune cell populations and cytokines.
- To assess the effect of the combination regimens 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 tumor gene alterations in circulation and in tumor tissue with treatment outcome.

2.2 Endpoints

2.2.1 Primary Endpoints

ORR as defined by RECIST 1.1.

2.2.2 Secondary Endpoints

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

2.2.3 Exploratory Endpoints

- Circulating PD-L1 concentration.
- Circulating immune cell populations.

- Circulating cytokine concentrations.
- ctDNA.
- T-Cell Receptor Sequencing.
- Tumor PD-L1 expression.
- Immune cell populations in the tumor.
- Gene expression signatures in the tumor.
- Tumor gene alterations.

3 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 the combination of sitravatinib in combination with the PD-1 checkpoint inhibitor nivolumab, and may subsequently evaluate 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) DLTs. The Schedule of Assessments to be performed in the study are presented in Table 1 and Table 3. The schedule for collection of pharmacokinetic and pharmacodynamic samples and ECG assessment time points are presented in Table 2 and Table 4.

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, stratified into 2 cohorts based on whether patients were previously treated with or were ineligible for a platinum-based chemotherapy, as depicted in Figure 1.

- Cohort 1: Patients who were previously treated with a platinum-based chemotherapy.

- Cohort 2: Patients ineligible for platinum-based chemotherapy.

Enrollment will occur in 3 stages. Stage 1 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 will 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 ORR and secondary efficacy endpoints, enrollment may be expanded to as many as 40 patients 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.

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 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 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 and still enrolling, 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 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 appendix. 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 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 appendix. These contingent cohorts described below were implemented by Administrative Letter and still enrolling, as depicted in Figure 1.

- 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 describes addition of Cohort 9 and Cohort 10 to evaluate sitravatinib in combination with pembrolizumab and enfortumab. The appendix 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 protocol Version 4.0, whereas Cohort 10 is introduced in protocol Version 4.0 and may be implemented by Administrative Letter, as described below and depicted in Figure 1.

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

- Cohort 10: Patients with previously untreated unresectable, locally advanced or metastatic urothelial cancer.

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 Appendix 9). 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 and 10) should be administered after sitravatinib (and specifically after the 30 minute PK sampling on applicable study visits), whereas enfortumab (for Cohort 9 and 10) 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 1.3.3.4. 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 Cohorts 9 and 10. Guidelines for sitravatinib administration and dose reduction in the event of toxicity are provided in Section 5.1.

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 describes the plan for this assessment.

Correlative Endpoints

Investigation of correlative endpoints will involve collection of blood and tumor tissue samples as indicated in Table 1 and Table 2, Table 3, and Table 4. Further detail on sample collection and analyses are presented in Section 7.3 and the Study Laboratory Manual. Protocol guidance of special interest is listed below.

- Freshly biopsied tumor tissue collections at pre-treatment and on-treatment timepoints are highly desirable however, tumor biopsies having significant risk should not be performed and tumor lesions evaluated on-treatment as measurable lesions per RECIST 1.1 should not be disturbed for study biopsies. Archival samples may be submitted as pre-treatment samples if more recent tumor specimens or fresh biopsies cannot be obtained. An on-treatment tumor biopsy as close to Cycle 2 Day 15 as possible is desirable for all treated patients and is not

dependent on the type of pre-treatment tumor tissue submitted (i.e., archival or freshly collected biopsy).

- Tumor PD-L1 expression in freshly biopsied tumor tissue will be determined by the PD-L1 (28-8) companion diagnostics assay completed through the central laboratory. If tumor tissue from a patient has previously undergone PD-L1 testing, results to be collected in the Case Report Form (CRF) include the type of assay employed and percent tumor and/or immune cell staining.

- Tumor gene expression in freshly biopsied tumor samples will be determined using next generation sequencing performed by a central laboratory. For patients in whom tumor tissue has previously been tested using next generation sequencing, presence of specific tumor gene mutations and estimation of total mutation burden will be collected in the CRF.

Disease response and progression as documented by the Investigator in the CRF will be the basis for patient management and study expansion decision-making. Unconfirmed objective responses recorded in the CRF may be used as the initial basis for expansion of study enrollment; however, follow-up evaluations on patients with unconfirmed responses must continue to support the decision to continue to the full number of patients to be included in the next stage.

Patients will continue to receive study treatment at the discretion of the Investigator until disease progression, unacceptable adverse events, patient refusal or death. Patients experiencing clinical benefit in the judgment of the Investigator may continue study treatment beyond disease progression as defined by RECIST 1.1, if the progression is not rapid, symptomatic, or requiring urgent medical intervention. Patients considering continuation of study treatment beyond RECIST-defined disease progression must be provided with and sign an informed consent form notifying the patient that they have other treatment options available and any potential clinical benefit that the patient may be foregoing by continuing study treatment.

Patients discontinuing treatment will be followed for receipt of subsequent anti-cancer therapies and survival.

4 SUBJECT SELECTION AND ENROLLMENT

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

4.1 Inclusion Criteria

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

1. Histologically confirmed urothelial (transitional cell) carcinoma with metastatic disease or with unresectable, locally advanced disease.

2. Most recent treatment must have included a PD-(L)1 checkpoint inhibitor (e.g., nivolumab, pembrolizumab, durvalumab, atezolizumab or avelumab) with radiographic progression of disease on or after treatment. ***Note: This criterion only applies to Cohorts 1 and 2 and is to be substituted with criteria below for other cohorts:***

    a. ***Cohorts 3 and 4 (Appendix 5):*** Most recent treatment must have included a PD-(L)1 checkpoint inhibitor (e.g., nivolumab, pembrolizumab, durvalumab, atezolizumab or avelumab) with radiographic progression of disease on or after treatment. Patients must have previously received treatment with selected immunotherapies, including but not limited to anti-CTLA-4, anti-OX40 or anti-CD137 therapy.

    b. ***Cohorts 5 and 6 (Appendix 6):*** Patients must not have received prior therapy with a PD-(L)1 checkpoint inhibitor (CIT-naïve).

    c. ***Cohorts 7 and 8 (Appendix 8):*** Patients must have experienced radiographic progression of disease on or after treatment with a PD-(L)1 checkpoint inhibitor (CIT; e.g., nivolumab, pembrolizumab, durvalumab, atezolizumab or avelumab) and an antibody-drug conjugate (ADC; e.g. enfortumab vedotin, sacituzumab govitecan), in any order or in combination together. Patients who discontinued CIT or ADC treatment due to toxicity are eligible provided that the patients have evidence of disease progression following discontinuation. The CIT or ADC treatment need not be the most recent therapy. Patients for whom the most recent therapy has been a non-CIT or ADC-based regimen are eligible if the patients have radiographic progression of disease on or after the most recent therapy.

    d. ***Cohort 9 (Appendix 9):*** Patients must have experienced radiographic progression of disease on or after treatment with a PD-(L)1 checkpoint inhibitor (CIT; e.g., nivolumab, pembrolizumab, durvalumab, atezolizumab or avelumab). Patients who discontinued CIT due to toxicity are eligible provided that the patients have evidence of disease progression following discontinuation. The CIT need not be the most recent therapy. Patients for whom the most recent therapy has been a non-CIT-based regimen are eligible if the patients have radiographic progression of disease on or after the most recent therapy.

e. ***Cohort 10 (Appendix 9):*** Patients must not have received prior systemic therapy for locally-advanced or metastatic urothelial carcinoma. Peri-operative chemotherapy with progression or relapse > 1 year from the last date of treatment is permitted.

3. Prior treatment with a platinum-based chemotherapy regimen:

   a. ***Cohort 1, Cohort 3 (Appendix 5), Cohort 5 (Appendix 6), and Cohort 7 (Appendix 8), and Cohort 9 (Appendix 9):*** Patients must have received prior chemotherapy which included a platinum agent. Therapy may have been administered in the peri-operative or metastatic setting. In the case of peri-operative treatment, disease progression or relapse must have occurred within 1 year of the last date of treatment.

   b. ***Cohort 2, Cohort 4 (Appendix 5), Cohort 6 (Appendix 6), and Cohort 8 (Appendix 8):*** Patients must have been ineligible for platinum-based chemotherapy.

4. Resolution of toxicities from prior therapy to baseline or Grade 1 (excluding any grade alopecia and ≤ Grade 2 dysgeusia or peripheral neuropathy). ***Note: This criterion is modified for Cohorts 9 and 10 (Appendix 9) as follows:*** Absence of preexisting ≥ Grade 2 sensory or motor neuropathy, and resolution of toxicities from prior therapy to baseline or Grade 1 (excluding any grade alopecia and ≤ Grade 2 dysgeusia).

5. Measurable disease as per RECIST version 1.1.

6. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.***Note: This criterion is modified for Cohort 10 (Appendix 9) as follows:*** ECOG performance status 0, 1 or 2.

7. Adequate bone marrow and organ function demonstrated by:

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

   b. Hemoglobin ≥ 9.0 g/dL. ***Note for the lead-in dose escalation portion of Cohort 9 (Appendix 9):*** no RBC transfusions are allowed within 14 days of the first dose of enfortumab.

   c. Platelet count ≥ 50 × 10^9/L (≥ 50,000 per mm^3). ***Note: This criterion is modified for Cohorts 9 and 10 (Appendix 9) as follows:*** Platelet count ≥ 100 × 10^9/L (≥ 100,000 per mm^3). For the lead-in dose escalation portion of Cohort 9, no platelet transfusions are allowed within 14 days of the first dose of enfortumab.

d. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × Upper Limit of Normal (ULN), or ≤ 5.0 × ULN for patients with documented liver metastases. ***Note: This criterion is modified for Cohorts 9 and 10 (Appendix 9) as follows:*** ALT and AST ≤ 2.5 × ULN, or ≤ 3.0 × ULN for patients with documented liver metastases.

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

f. Serum creatinine:

i. patient weight > 55 kgs (~120 lbs), ≤ 3.0 × ULN or calculated* Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI, Levey-2009) glomerular filtration rate (GFR) ≥ 30 mL/min.

ii. patient weight ≤ 55 kgs (~120 lbs), ≤ 3.0 × ULN and calculated* CKD-EPI glomerular filtration rate ≥ 30 mL/min.

Link to CKD-EPI calculator and information for use provided in Appendix 2.

g. ***Cohorts 9 and 10 (Appendix 9):*** Serum albumin ≥ 2.5 g/dL.

h. ***Cohorts 9 and 10 (Appendix 9):*** INR < 1.3 or ≤ institutional ULN (or ≤ 3.0 if on therapeutic anticoagulation).

8. ≥ 18 years of age.

9. Women of childbearing potential (WOCBP) or men whose partner is a WOCBP agrees to use contraception while participating in this study, and for a period of 6 months following termination of study treatment.

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

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

4.2 Exclusion Criteria

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

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

2. Patients with carcinomatous meningitis.

3. Prior therapies:

   a. ***Cohorts 1 and 2, and Cohorts 5 and 6 (Appendix 6):*** Immunotherapies not previously specified, including anti-CTLA-4, anti-OX40 and anti–CD137.

   b. Combination therapy with a PD-(L)1 checkpoint inhibitor and cancer therapy having the same mechanism of action as sitravatinib (e.g., tyrosine kinase with similar target profile).

4. Unacceptable toxicity on prior PD-(L)1 checkpoint inhibitor treatment:

   a. ≥ Grade 3 immune-related AE with a PD-(L)1 checkpoint inhibitor.

   b. Grade 2 immune-related AE associated with a PD-(L)1 checkpoint inhibitor unless the AE resolved or was well controlled by withholding the checkpoint inhibitor and/or treatment with steroids, with the exception of prior colitis, encephalitis, myocarditis, uveitis and pneumonitis, which are exclusionary.

   c. Criterion deleted in Version 3.0 of protocol: Grade 1 immune-related AE associated with a PD-(L)1 checkpoint inhibitor unless the AE resolved or could be well controlled.

   d. CNS or ocular AE of any grade related to a PD-(L)1 checkpoint inhibitor.

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

5. Active or prior documented autoimmune disease:

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

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

   c. Active or prior documented and medically-important autoimmune disease within the past 2 years. ***Note:*** Patients with Type I diabetes, vitiligo, Graves' disease, residual hypothyroidism due to an autoimmune condition only requiring hormone replacement, or psoriasis or Sjögren's syndrome not requiring systemic treatment (within the past 2 years) are not excluded.

6. Active or prior immunocompromising conditions:

   a. Current or prior use of immunosuppressive medication within 28 days before the first dose of study treatment, with the exceptions of intranasal and inhaled

corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.

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

c. History of primary immunodeficiency.

d. History of allogeneic transplant.

7. History of severe hypersensitivity reaction to any monoclonal antibody

8. Use of live vaccines against infectious disease (e.g. varicella) within 28 days of initiation of study therapy; killed vaccinations (e.g. influenza) are allowed at any appropriate time before and during the study.

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

10. History of hypersensitivity to study treatment excipient.

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

12. Any of the following cardiac abnormalities:

    a. Unstable angina pectoris.

    b. Congestive heart failure ≥ NYHA Class 3.

    c. QTc >480 milliseconds.

    d. LVEF < 40%

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

14. Uncontrolled arterial hypertension (> 150 mm Hg systolic or > 100 mm Hg diastolic) on multiple observations despite standard of care treatment

15. Undergone major surgery within 4 weeks of first dose date.

16. History of significant hemorrhage within 4 weeks of first dose date.

17. Undergone radiation or systemic therapy within approximately 2 weeks of first dose date.

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

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

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

21. Any serious illness, uncontrolled inter-current illness, psychiatric illness, active or uncontrolled infection, or other medical history, including laboratory results, which, in the Investigator's opinion, would be likely to interfere with the patient's participation in the study, or with the interpretation of the results.

22. ***Cohorts 9 and 10 (Appendix 9):*** Any P-gp inducers/inhibitors or strong CYP3A4 inhibitors (see Appendix 10 for examples) within 2 weeks of first dose date of enfortumab.

23. ***Cohorts 9 and 10 (Appendix 9):*** Thromboembolic events and/or bleeding disorders ≤ 14 days (e.g., DVT or PE) prior to the first dose of study drug.

24. ***Cohorts 9 and 10 (Appendix 9):*** Decompensated liver disease as evidenced by clinically significant ascites refractory to diuretic therapy, hepatic encephalopathy, or coagulopathy.

25. ***Cohorts 9 and 10 (Appendix 9):*** History of uncontrolled diabetes mellitus or diabetic neuropathy within 3 months of the first dose of study drug. Uncontrolled diabetes is defined as hemoglobin A1C (HbA1c) ≥ 8% or HbA1c > 7 to < 8% with associated diabetes symptoms (polyuria or polydipsia) that are not otherwise explained.

26. ***Cohorts 9 and 10 (Appendix 9):*** Has ocular conditions such as:

    a. Active infection or corneal ulcer (e.g., keratitis).

    b. Monocularity.

    c. History of corneal transplantation.

    d. Contact lens dependent (if using contact lens, must be able to switch to glasses during the entire study duration).

    e. Uncontrolled glaucoma (topical medications allowed).

    f. Uncontrolled or evolving retinopathy, wet macular degeneration, uveitis, papilledema, or optic disc disorder.

4.3 Life Style Guidelines

Patients who are biologically capable of having children and sexually active must agree to use an acceptable method of contraception for the duration of the treatment period and for at least 6 months after the last dose of study treatment. The Investigator will counsel the patient on selection of contraception method and instruct the patient in its consistent and correct use. Examples of acceptable forms of contraception include:

1. Oral, inserted, injected or implanted hormonal methods of contraception, provided it has been used for an adequate period of time to ensure effectiveness.

2. Correctly placed copper containing intrauterine device (IUD).

3. Male condom or female condom used WITH a spermicide.

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

5. Bilateral tubal ligation or bilateral salpingectomy.

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

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

4.4 Enrollment into Study

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

5 STUDY TREATMENTS

5.1 Sitravatinib

5.1.1 Formulation, Packaging and Storage

This study began patient treatment with the sitravatinib free base capsule formulation used in previous clinical trials. Cohorts 1 through 6 will continue to receive the free base formulation. For Cohorts 7 through 10, transition to use of an alternative formulation, sitravatinib malate capsule formulation, is being implemented with protocol Version 4.0. Newly enrolled patients in Cohorts 7 through 10 will receive the malate capsule formulation. Patients on study treatment with the free base capsule formulation at the time the malate capsule formulation is introduced will remain on the free base capsule formulation until treatment discontinuation. The formulations are described below.

- The composition of the drug product used in previous clinical trials consists of a blend of sitravatinib (MGCD516) free base drug substance, microcrystalline cellulose, polysorbate 80, and colloidal silicon dioxide. The blend is filled into hard gelatin capsules. To help differentiate between the products, the free base formulation will be labeled with the drug product code “MGCD516”.

- The sitravatinib malate capsule product consists of a blend of sitravatinib malate drug substance, microcrystalline cellulose, mannitol, croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate; the blend is filled into hard gelatin capsules. To help differentiate between the products, the malate formulation will be labeled with the drug product name “Sitravatinib”.

The strengths of all sitravatinib capsule formulations are expressed based on sitravatinib free base weight. Dose strengths of sitravatinib and additional packaging differences between formulations will be provided in the Pharmacy Study Manual.

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

Sitravatinib medication labels comply with the legal requirements of the United States.

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

Refer to the Pharmacy Study Manual for details.

5.1.2 Preparation, Dispensing, Administration and Accountability

Only qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents.

Study site personnel will dispense bottles containing sitravatinib capsules on Day 1 of each treatment cycle. Sufficient supply will be provided for each cycle and extra capsules may be provided to cover additional days in case of delayed clinic visits or lost capsules. Study capsules will be dispensed in HDPE bottles provided by the Sponsor.

Sitravatinib capsules will be administered orally, once daily (QD), in a continuous regimen expressed in 28-day cycles for the sitravatinib and nivolumab combination cohorts and in 21-day cycles for the sitravatinib, pembrolizumab and enfortumab combination cohorts.

- For all patients in Cohorts 1 through 6, the starting dose using the free base formulation is 120 mg QD.
- For newly enrolled patients in Cohorts 7 and 8, the starting dose using the malate capsule formulation is 100 mg QD. The starting dose using the free base capsule formulation (for patients who began treatment on free base capsule formulation at the time the malate capsule formulation is introduced) is 120 mg QD.
- For the sitravatinib, pembrolizumab and enfortumab combination cohorts, the sitravatinib starting dose for the lead-in dose escalation portion of Cohort 9 using the malate capsule formulation will be 35 mg QD which represents three dose levels below the dose administered as a single agent and in combination (with nivolumab) Phase 2 and Phase 3 trials. If a dose is identified for sitravatinib in combination with pembrolizumab and enfortumab, this recommended starting dose will be used for subsequent contingent sitravatinib, pembrolizumab and enfortumab combination cohorts (dose expansion portion of Cohort 9 and Cohort 10).

Depending on safety observations, the sitravatinib dose during treatment may be reduced in accordance with Table 5 for patients administered the free base capsule formulation and in accordance with Table 6 for patients administered the malate capsule formulation.

The following guidelines should be followed for sitravatinib administration:

- Dosing in the morning is preferred.
- Capsules should be taken on an empty stomach (at least 2-hour fast before each dose and no food for a minimum of 1 hour after each dose). The fasting requirement may be eliminated based on the outcome of an ongoing food-effect study under a separate study protocol. Any change in fasting will be implemented

by Administrative Letter to Investigators and reiterated in the next protocol amendment required within the study.

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

On days when nivolumab, pembrolizumab or enfortumab are administered, the daily dose of sitravatinib should precede the nivolumab, pembrolizumab or enfortumab infusion for logistical reasons. This order of dosing is of particular interest on days when blood sampling is scheduled for sitravatinib PK.

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

Patients will be asked to record their daily dosing on Sponsor provided diary cards and report any missed doses or lost doses at the next clinic visit. On the back of each Sponsor provided diary card, written dosing instructions for sitravatinib capsules are provided (e.g., fasting instructions, take with water, etc.). Patients should be told to bring study treatment bottle(s) (empty or not) and completed dosing diaries with them to the clinic visit for a compliance check and capsule count. Study site personnel will retain the bottle(s) until a monitor has completed reconciliation and retain dosing diaries with site study files.

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

5.1.3 Sitravatinib Dose Modification and Discontinuation

This protocol provides guidance for dose modification of sitravatinib (i.e., interruption, dose reduction or discontinuation) for AEs attributed to sitravatinib. For adverse events attributed to nivolumab, pembrolizumab or enfortumab see the current OPDIVO US Prescribing Information, KEYTRUDA US Prescribing Information and PADCEV US Prescribing Information, Section 5.2.4 for dose nivolumab modifications, Section 5.3.4 for dose for pembrolizumab modifications, and Section 5.4.4 for dose for enfortumab modifications.

Available dose levels for each of the sitravatinib formulations are outlined in Table 5 and Table 6. Dose modifications guidelines for the malate capsule formulation (Table 6)

follow comparable dose reduction proportions used for the free base capsule formulation. Guidelines for sitravatinib dose modifications to be implemented to manage adverse events are described in Section 5.3.1 and 5.3.3. Once the dose has been reduced, re-escalation is generally not recommended but may be considered on a case-by-case basis with approval from the Medical Monitor. If the administration of sitravatinib is interrupted for reasons other than toxicity, then treatment with the study drug may be resumed at the same dose.

The starting dose for sitravatinib using the free base capsule formulation is 120 mg QD.

Table 5: Sitravatinib Sequential Dose Reductions for Individual Patients on Free Base Capsule Formulation

120 mg once daily
80 mg once daily
60 mg once daily
40 mg once daily

The starting dose for sitravatinib using the malate capsule formulation is 100 mg QD.

Table 6: Sitravatinib Sequential Dose Reductions for Individual Patients on Malate Capsule Formulation

100 mg once daily
70 mg once daily
50 mg once daily
35 mg once daily
20 mg once daily*

* This dose level is only available for Cohorts 9 and 10.

In the event of sitravatinib-related AE, dose reduction with continuous treatment is preferred over repeated dose interruption. If treatment with sitravatinib is delayed for ≥ 14 days, then resumption at a reduced dose should be considered. If treatment with sitravatinib is withheld for ≥ 28 consecutive days, then permanent discontinuation of sitravatinib should be considered. If one study drug is interrupted or discontinued, administration of the other study drug may continue at the discretion of the Investigator.

5.2 Nivolumab Study Drug

Nivolumab will be obtained from commercial sources and managed in accordance with the OPDIVO US Prescribing Information. The following reports information and guidance included in the OPDIVO US Prescribing Information dated June 2020. Refer the current OPDIVO US Prescribing Information provided by the manufacturer for updates during the conduct of this clinical trial.

5.2.1 Formulation and Packaging

Refer to the current OPDIVO US Prescribing Information.

5.2.2 Preparation and Dispensing

Refer to the current OPDIVO US Prescribing Information.

5.2.3 Administration

Nivolumab (OPDIVO) will be administered in this study as an intravenous infusion over approximately 30 minutes (+/- 5 minutes) at 240 mg every 2 weeks (Q2W) or 480 mg every 4 weeks (Q4W), at the discretion of the Investigator and in accordance with the current OPDIVO US Prescribing Information. Note: nivolumab should be administered after sitravatinib (and specifically after the 30 minute PK sampling on applicable study visits).

5.2.4 Nivolumab Dose Modification

Required dose modifications (i.e., interruption or discontinuation) for nivolumab should be performed per the current OPDIVO US Prescribing Information, in addition to potential dose modifications for sitravatinib in accordance to Section 5.1.3.

If one agent is interrupted or discontinued, administration of the other agent may continue at the discretion of the Investigator.

Change from OPDIVO US Prescribing Information for This Study

One change from the Prescribing Information will be implemented in this study. This protocol allows enrollment of patients having a limited degree of renal impairment. For this reason, the guidance for management of patients who experience nephritis and renal dysfunction that is not thought to be immune-mediated will be adjusted. The Prescribing Information indicates that dosing should be withheld in the event of serum creatinine more than 1.5 and up to 6 times the upper limit of normal and discontinued permanently if more than 6 times the upper limit of normal.

In this study, the baseline (screening) value will substitute for the upper limit of normal. Nivolumab dosing should be withheld if the serum creatinine increases to more than 1.5 and up to 6 times the baseline (screening) value and discontinued permanently if more than 6 times the baseline (screening) value.

5.3 Pembrolizumab Study Drug

Pembrolizumab will be obtained from commercial sources and managed in accordance with the KEYTRUDA US Prescribing Information. The following reports information and guidance included in the KEYTRUDA US Prescribing Information dated April 2020.

Refer to the current KEYTRUDA US Prescribing Information provided by the manufacturer for updates during the conduct of this clinical trial.

5.3.1 Formulation and Packaging

Refer to the current KEYTRUDA US Prescribing Information.

5.3.2 Preparation and Dispensing

Refer to the current KEYTRUDA US Prescribing Information.

5.3.3 Administration

Pembrolizumab (KEYTRUDA) will be administered in this study as an intravenous infusion over approximately 30 minutes (+/- 5 minutes) at 200 mg every 3 weeks (Q3W), in accordance with the current KEYTRUDA US Prescribing Information. Note: pembrolizumab should be administered after sitravatinib (and specifically after the 30 minute PK sampling on applicable study visits), and at least 30 minutes before enfortumab.

5.3.4 Pembrolizumab Dose Modification

Required dose modifications (i.e., interruption or discontinuation) for pembrolizumab should be performed per the current KEYTRUDA US Prescribing Information, in addition to potential dose modifications for sitravatinib in accordance to Section 5.1.3 and dose modifications for enfortumab per the current PADCEV US Prescribing Information in Section 5.4.4.

If one agent is interrupted or discontinued, administration of the other agent may continue at the discretion of the Investigator.

5.4 Enfortumab Study Drug

Enfortumab will be obtained from commercial sources and managed in accordance with the PADCEV US Prescribing Information. The following reports information and guidance included in the PADCEV US Prescribing Information dated December 2019. Refer the current PADCEV US Prescribing Information provided by the manufacturer for updates during the conduct of this clinical trial.

5.4.1 Formulation and Packaging

Refer to the current PADCEV US Prescribing Information.

5.4.2 Preparation and Dispensing

Refer the current PADCEV US Prescribing Information.

5.4.3 Administration

Dosing is based on patient weight. Enfortumab will be administered at mg/kg doses based on the patient's actual body weight at Cycle 1 Day 1. For on-study dosing, the dose must be adjusted if the patient's weight changes by ≥ 10% from their Cycle 1 Day 1 weight, or if enfortumab dose modification criteria (see Section 5.4.4) are met. Other dose adjustments for changes in body weight <10% are permitted per institutional standard. For patients who weigh > 100 kg, the dose will be calculated based on 100 kg weight. Institutional dose rounding rules may be applied to this protocol, but otherwise, doses of the investigational product will be rounded to the nearest milligram.

Enfortumab (PADCEV) will be administered in this study as an intravenous infusion over approximately 30 minutes (+/- 5 minutes) at the selected dose level (see Appendix 9) on Days 1, and 8 of a 21-day cycle, at the discretion of the Investigator and in accordance with the current PADCEV US Prescribing Information. Note: enfortumab should be administered at least 30 minutes after pembrolizumab.

Patients will receive enfortumab administration only if their laboratory results of blood drawn within 24 hours prior to dosing meets the following study drug administration laboratory criteria:

- Blood glucose ≤ 250 mg/dL.

5.4.4 Enfortumab Dose Modification

Required dose modifications (i.e., interruption, dose reduction or discontinuation) for enfortumab should be performed per the current PADCEV US Prescribing Information, in addition to potential dose modifications for sitravatinib in accordance to Section 5.1.3 and dose modifications for pembrolizumab per the current KEYTRUDA US Prescribing Information in Section 5.3.4. Available dose levels for enfortumab are outlined in Table 7.

Table 7: Enfortumab Sequential Dose Reductions for Individual Patients

1.25 mg/kg up to 125 mg
1.0 mg/kg up to 100 mg
0.75 mg/kg up to 75 mg
0.5 mg/kg up to 50 mg

If one agent is interrupted or discontinued, administration of the other agent may continue at the discretion of the Investigator.

5.5 Management of Adverse Events

5.5.1 Sitravatinib-Related Adverse Events

5.5.1.1 General Management of Non-Hematological Toxicities

In the event of symptomatic sitravatinib-related AEs, dose reduction to a level that can be administered continuously is preferred over continuing dosing until interruption becomes necessary. Symptomatic Grade 2 sitravatinib-related non-hematological AEs occurring any time on study, particularly early in treatment (e.g., Cycle 1 Day 15 or Cycle 2 Day 1), are recommended to be managed using dose reduction to the next lower dose level, per the reduction schedule outlined in Table 5 (free base capsule formulation) and Table 6 (malate capsule formulation), rather than treatment interruption.

Non-hematological toxicities ≥ Grade 3 and considered to be related to sitravatinib treatment should be managed with sitravatinib interruption, with or without dose reduction, until resolution of toxicity to ≤ Grade 1 or to baseline value. If the toxicity is adequately managed by routine supportive care (such as electrolyte supplementation), or is a Grade 3 amylase or lipase elevation, treatment may be resumed at the same dose; if not, treatment may be resumed at a reduced dose as outlined in Table 8. Recurrence of the toxicity may be managed similarly. If sitravatinib is interrupted for ≥ 28 days, permanent discontinuation of sitravatinib should be considered.

Table 8: Sitravatinib Dose Modifications – Non-Hematological Drug-Related Toxicities[1]

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

1 Management of adverse events of interest for sitravatinib are presented in Section 5.5.1.3.
2 The current OPDIVO US Prescribing Information, KEYTRUDA US Prescribing Information and PADCEV US Prescribing Information must be consulted to determine appropriate dose modifications for nivolumab, pembrolizumab and enfortumab.
3 Patients may resume at the same dose in the following cases:
   a. Grade 3 or 4 electrolyte abnormality that is not clinically complicated and resolves spontaneously or with conventional medical treatment within 72 hours;
   b. Grade 3 or 4 amylase or lipase elevation that is not associated with symptoms or clinical manifestations of pancreatitis.

5.5.1.2 General Management of Hematological Toxicities

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

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

5.5.1.3 Management of Selected Adverse Event

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

5.5.1.3.1 Hypertension

Hypertension, including Grade 3 events, has been reported with sitravatinib. Dihydropyridine calcium channel blockers such as nifedipine, amlodipine, and nicardipine may be considered if anti-hypertensive therapy is required and should be considered for patients with Grade 3 hypertension without clinically significant increases in blood pressure (BP) (Table 9). On the other hand, in cases of Grade 3 hypertension with clinically significant increases in blood pressure (Table 9), temporary suspension of sitravatinib dosing is recommended until blood pressure is controlled. Treatment with sitravatinib may resume at the same or a lower dose at the discretion of the Investigator. If significant hypertension recurs, options include change in medical management of the patient, reduction of sitravatinib dose, or discontinuation of study treatment, at the discretion of the Investigator. In the event of Grade 4 hypertension, sitravatinib should be permanently discontinued (Table 9).

Table 9: Sitravatinib Dose Modification for Increased Blood Pressure

Toxicity	Interruption	Reduction
Grade 1 or 2 hypertension	Investigator discretion, as per Table 8.	
Grade 3 hypertension without clinically significant increases in BP as defined below	Investigator discretion. Consider anti-hypertensives per Section 5.5.1.3.1.	
Grade 3 hypertension with clinically significant increases in BP *defined as* either an increase of ≥ 30 mmHg in systolic BP to ≥ 180 mmHg *or* increase of ≥ 20 mmHg in diastolic BP to ≥ 110 mmHg, confirmed with repeated testing after at least 5 minutes	Hold until ≤ Grade 2 or return to baseline	Investigator discretion
Grade 4 hypertension	Discontinue sitravatinib	Discontinue sitravatinib

5.5.1.3.2 Palmar-Plantar Erythrodysesthesia

Palmar plantar erythrodysesthesia (PPE) has been reported as a dose-limiting toxicity in the Phase 1 study of sitravatinib. Measures that can be taken to manage PPE include avoidance of exposure of hands and feet to hot water when washing dishes or bathing, or to other sources of heat, avoidance of activities that cause unnecessary force or friction (rubbing) on the hands or feet, avoiding contact with harsh chemicals such as cleaning products, use of tools or household items that result in pressure on the hands, such as garden tools, knives, and screwdrivers, and wearing of loose fitting, well-ventilated shoes and clothes. Treatment may include use of topical moisturizing agents, topical anesthetics, or topical anti-inflammatory medications such as corticosteroid creams. In more severe cases, dose interruption and reduction may be warranted.

5.5.1.3.3 Diarrhea

Diarrhea should be evaluated to determine whether it may be immune-mediated colitis due to nivolumab or pembrolizumab (Section 5.5.5.1.1), related to sitravatinib, or due to another cause. Diarrhea has been reported with sitravatinib treatment, though the mechanism remains unclear, as with other small molecule RTK inhibitors. Patients should be counseled that diarrhea is a possible side effect and advised to take loperamide or a similar medication as needed if diarrhea develops. Any patients developing dehydration or clinically significant electrolyte abnormalities should interrupt treatment, but treatment may be restarted once diarrhea is controlled.

5.5.1.3.4 Hemorrhagic Events

The risk of hemorrhagic events with sitravatinib is unknown; however, such events have been reported with inhibitors of VEGFR. Patients with active hemoptysis or gastrointestinal bleeding should not take sitravatinib, and suspension of treatment is recommended for patients developing clinically significant bleeding.

5.5.1.3.5 Thrombotic Events

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

5.5.1.3.6 Thyroid Dysfunction Other than Immune-Mediated

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

5.5.1.3.7 Decreased Left Ventricular Ejection Fraction

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

5.5.1.3.8 Proteinuria

Although the risk with sitravatinib is unknown, proteinuria has been described with other inhibitors of the VEGFR pathway. Patients who develop ≥2+ proteinuria should undergo 24-hour urine collection for assessment of urine protein; treatment with sitravatinib should be discontinued in the presence of ≥2 grams of proteinuria/24 hours and may restart when protein levels decrease to less than 2 grams/24 hours. Patients who develop nephrotic syndrome should be withdrawn from treatment with sitravatinib.

5.5.2 Nivolumab Adverse Event Management Guidelines

Refer to the OPDIVO US Prescribing Information for guidance concerning management of adverse events, including immune-mediated adverse events, during treatment with nivolumab.

5.5.3 Pembrolizumab Adverse Event Management Guidelines

Refer to the KEYTRUDA US Prescribing Information for guidance concerning management of adverse events, including immune-mediated adverse events, during treatment with nivolumab.

5.5.4 Enfortumab Adverse Event Management Guidelines

Refer to the PADCEV US Prescribing Information for guidance concerning management of adverse events, including immune-mediated adverse events, during treatment with nivolumab.

5.5.5 Management of Immune-Related Adverse Events

Sitravatinib has not been associated with immune-mediated AEs. However, the potential exists for one or more of the treatments to contribute to immune-mediated AEs associated with nivolumab or pembrolizumab treatment. In the event of a Grade 2 immune-related AE during study treatment, administration of study treatments (sitravatinib and nivolumab, or sitravatinib, pembrolizumab and enfortumab) should be interrupted until the event stabilizes to Grade ≤1 (consistent with guidance provided in the OPDIVO US Prescribing Information and KEYTRUDA US Prescribing Information). At the time of resumption of sitravatinib dosing, a dose reduction may be implemented at the discretion of the Investigator.

Management of Grade 3 and 4 immune-mediated adverse events should be performed in accordance with the OPDIVO US Prescribing Information and KEYTRUDA US Prescribing Information. However, recurrent Grade 3, or any Grade 4, immune-mediated adverse events should generally be managed with permanent discontinuation of nivolumab or pembrolizumab. Administration of sitravatinib should be interrupted and may be resumed at the same or lower dose at the discretion of the Investigator after the event stabilizes to Grade ≤ 1.

5.5.5.1.1 Diarrhea/Colitis

The management of diarrhea should be guided by clinical judgment and an assessment of the most likely causative etiology, with special consideration given to the potential for immune-mediated colitis. The presence of abdominal pain, mucus or blood in the stool or peritoneal signs should raise the index of suspicion for immune-mediated colitis, as these features are generally not observed with sitravatinib treatment-associated diarrhea. The diarrhea observed with sitravatinib generally improves within several days of interrupting study medication, with close observation may help establish the most likely causality. However, if any features of the clinical presentation, including timing of presentation, failure to improve with dose interruption, laboratory or radiologic tests suggests the presence of immune-mediated colitis, all study medications should be withheld and treatment with immuno-suppressive therapy initiated as detailed in the OPDIVO US Prescribing Information and KEYTRUDA US Prescribing Information.

5.5.5.1.2 Increased Transaminases

The management of increases in AST and ALT should be guided by the clinical judgment of the Investigator, including an assessment of the most likely causative etiology, with special consideration given to the potential for immune-mediated hepatitis. Increased

transaminases should be evaluated to determine whether confounding factors exist, such as viral infection, metastatic lesions or biliary obstruction.

For cases where transaminase increases are not likely to be immune-mediated, treatment management decisions should be made using Investigator discretion in consideration of clinical factors. Recommended treatment modifications for sitravatinib are provided in Table 10. However, if any features of the clinical presentation, including timing of presentation, failure to improve with dose interruption, laboratory or radiologic tests suggests the presence of immune-mediated hepatitis, all study medications should be withheld and treatment with immuno-suppressive therapy initiated as detailed in the OPDIVO US Prescribing Information and KEYTRUDA US Prescribing Information.

Table 10: Sitravatinib Dose Modification for Increased Hepatic Transaminases

Toxicity	Treatment Delay	Dose Modification
Grade 1 (>ULN to 3.0 × ULN)	May be implemented based on Investigator and patient discretion	
Grade 2 (>3.0 to 5.0 × ULN)	Not required[1]	Decrease by 1 dose level[1]
Grade 3/4 (>5.0 × ULN)	Hold until ≤ Grade 1 or return to baseline[1]	If resolution occurs within 29 days, decrease by 1 dose level[1] If no resolution within 29 days, discontinue sitravatinib[1]

1 The current OPDIVO US Prescribing Information and KEYTRUDA US Prescribing Information (and Section 5.5.5, in case the event is deemed to be an immune-mediated adverse event) must be consulted to determine appropriate dose modifications for nivolumab or pembrolizumab.

5.5.6 Management of Hy's Law Cases

In the event a patient develops concurrent increase in AST and/or ALT ≥ 3 × ULN, bilirubin ≥ 2 × ULN but without concurrent increases in alkaline phosphatase (i.e., alkaline phosphatase < 2 × ULN), that is not attributable to other causes (e.g., liver metastases, biliary obstruction, viral hepatitis, concomitant medication, etc.), study treatments (sitravatinib and nivolumab, *or* sitravatinib, pembrolizumab and enfortumab) should be permanently discontinued and steroids administered. Hy's Law cases should be reported as SAEs (Section 8.4).

5.6 Medication Error

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

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

5.7 Concomitant Therapies

5.7.1 Concomitant Medication(s)

Concomitant medications must be locally approved and used at doses and regimens that are considered standard-of-care for the treated indication. Treatment for co-morbidities, disease signs and symptoms and treatment emergent adverse events should be provided as necessary in the judgment of the Investigator. Patients may continue to use any ongoing medications not prohibited by the inclusion/exclusion criteria or treatment plan. Medications to be used with caution or avoided are listed for sitravatinib in Appendix 3. In addition, see Section 5.7.3 for restrictions on concomitant use of other anticancer or experimental therapy. Prohibited medications are listed for enfortumab in Appendix 10. Finally, additional restrictions for patients in Cycle 1 who are undergoing a DLT assessment in Cohort 9 are covered in Section 5.7.2.

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

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

Gastric Acid Medications with Sitravatinib: Proton pump inhibitors (PPIs) should be avoided during on-study treatment with sitravatinib. Switching from PPIs to H2 antagonists (H_2A) or antacids is preferred. Use of H_2A/antacids should be avoided at least 6 hours before and 1 hour after administration of sitravatinib. Ideally, sitravatinib and the H_2A/antacid should be taken at different times of the day, such as in the following examples:

- If the H_2A/antacid is taken once daily in the morning: take sitravatinib in the morning, after overnight fasting, and take the H_2A/antacid at least 1 hour later;
- If the H_2A/antacid is taken once daily in the evening: take the H_2A/antacid at least 6 hours prior to the next morning dose of sitravatinib;
- If the H_2A/antacid is taken twice daily, and sitravatinib is administered in the morning: take sitravatinib in the morning, after overnight fasting, and take the H_2A/antacid at least 1 hour later then, take the evening dose of the H_2A/antacid at least 6 hours prior to the next morning dose of sitravatinib;

- If the H_2A/antacid is taken twice daily, and sitravatinib is administered in the evening: take the H2 antagonist or antacid in the morning, wait at least 6 hours (and fast for at least 2 hours) before taking sitravatinib, then take the evening dose of H_2A/antacid at least 1 hour after sitravatinib.

Medications with QTc Prolonging Activity: The risk of QTc prolongation in patients receiving sitravatinib has not been characterized. Use of medications known to prolong QTc and pose risk of Torsades de Pointes (examples listed in Appendix 3) is to be avoided. Use of medications with conditional risk of Torsades de Pointes should be used with caution during sitravatinib treatment (examples listed in Appendix 3).

P-gp and BCRP transporters with Sitravatinib: Sitravatinib is a strong inhibitor of P-gp and BCRP transporters (Section 1.3.2). Concomitant medications that are sensitive substrates or substrates with narrow therapeutic index for these transporters (examples listed in Appendix 3) should be used with caution during sitravatinib treatment.

Strong P-gp Inhibitors with Enfortumab: Concomitant use of enfortumab and medications that are strong inducers/inhibitors of P-gp may affect exposure to MMAE and are prohibited (examples listed in Appendix 10). Whereas no clinical studies evaluating the drug-drug interaction potential of enfortumab have been conducted, in vitro studies indicate that monomethyl auristatin E (MMAE), the payload component of enfortumab, is a substrate of P-gp (PADCEV US Prescribing Information).

CYP3A4 Substrates with Sitravatinib: In vitro data imply that sitravatinib is a strong direct inhibitor of CYP3A4 (Section 1.3.2). Concomitant medications that are sensitive substrates or substrates with narrow therapeutic index for CYP3A4 (examples listed in Appendix 3) should be used with caution during sitravatinib treatment.

Strong CYP3A4 Inhibitors with Enfortumab: Concomitant use of enfortumab with a strong CYP3A4 inhibitor may increase free MMAE exposure, which may increase the incidence or severity of enfortumab toxicities (PADCEV US Prescribing Information). and are prohibited (examples listed in Appendix 10). Whereas no clinical studies evaluating the drug-drug interaction potential of enfortumab have been conducted, in vitro studies indicate that MMAE is a substrate of CYP3A4 (PADCEV US Prescribing Information).

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

Transfusions: Patients may receive transfusions as necessary. See Section 5.7.2 for Cohort 9 restrictions.

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

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

Growth Factors: Therapeutic colony-stimulating factors should be used in accordance with ASCO guidelines. See Section 5.7.2 for Cohort 9 restrictions.

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

Vaccines: Live attenuated vaccines within 28 days of nivolumab dosing are to be avoided. Inactivated vaccines, such as the injectable influenza vaccine, are permitted.

5.7.2 Concomitant Medication(s) Restrictions in Cycle 1 of Lead-In Dose Escalation Evaluation (Cohort 9) for Patients Undergoing a DLT Assessment

Treatment with the following concomitant supportive therapies are prohibited for patients in Cycle 1 who are undergoing a DLT assessment:

- Prophylactic use of colony-stimulating factors including G-CSF, PEGylated G-CSF or GM-CSF.
- Thrombopoietin or thrombopoietin-like therapies.
- Platelet transfusions.

Patients who receive prohibited therapy during Cycle 1 will be ineligible for DLT evaluation and will be replaced unless they experience a DLT event. See Appendix 9 for more information.

5.7.3 Concomitant Surgery or Radiation Therapy

The use of surgery to manage cancer lesions during study treatment is discouraged. The impact of sitravatinib on wound healing has not yet been characterized. For patients with bone involvement, any foreseeable need for palliative radiotherapy should be addressed before study entry, if possible and clinically appropriate (e.g., bone lesions at risk for spontaneous micro-fractures or painful lesions). However, these treatments may be used in cases where it is medically necessary.

In the event that major surgery is needed during study treatment, the patient should, if possible, interrupt dosing with sitravatinib 2 weeks in advance of the surgery and resume dosing 2 weeks after the surgery.

If radiotherapy is required, the Sponsor will provide guidance on duration of sitravatinib interruption.

5.7.4 Other Anticancer or Experimental Therapy

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

* Certain ongoing hormonal therapies taken to prevent recurrence of a malignancy not under study (e.g., tamoxifen/aromatase inhibitor for breast cancer) may be permitted after discussion with and agreement of the Sponsor's Medical Monitor.

6 STUDY ASSESSMENTS

6.1 Screening

Voluntary, written, dated, and signed informed consent must be obtained before any study specific procedures are performed. Patients who completed the informed consent process but did not enroll on the study will be considered as screen failures. Limited information will be recorded in the CRF for these patients.

6.2 Study Period

For details on procedures during the study period, see Schedule of Assessments as shown in Table 1 and Table 3.

6.3 End of Treatment Assessment

All patients will be followed for AEs for at least 28 days after the last dose of Study Treatment. See the Schedule of Assessments (Table 1 and Table 3) for evaluations to be performed at the End of Treatment visit.

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

Survival status and subsequent therapies will be collected during long term follow-up as outlined in the Schedule of Assessments (Table 1 and Table 3) until death or lost to follow-up. Follow-up may be performed by telephone contact or email. Treatments received following participation in the study will be collected in the CRF.

6.5 Patient Discontinuation/Withdrawal

Patients may discontinue from study treatment or from study follow-up at any time at their own request, or they may be discontinued at any time at the discretion of the Investigator or Sponsor for safety, behavioral reasons, or the inability of the patient to comply with the protocol required schedule of study visits or procedures at a given study site.

Criteria that may be used to discontinue patients from receipt of study medication will include, but will not be limited to:

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

Reasons for discontinuation from study follow-up may include:

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

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. At least 2 attempts should be made to contact the patient, and each attempt should be recorded in the source documents. In any circumstance, every effort should be made to document patient outcome, if possible. The Investigator should inquire about the

reason for withdrawal, request that the patient returns for a final visit, and if applicable, follow-up with the patient regarding any unresolved adverse events.

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

7 PROCEDURES

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

7.1 Efficacy

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

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

unless the method does not adequately depict the individual's disease, in which case CT without contrast is preferred.

For patients having effusions or ascites, cytological proof of malignancy should be obtained prior to selection of the effusion as a non-target lesion. Effusions that have not been evaluated using cytology or were found to be non-malignant should not be considered to be cancer lesions. New fluid collections identified on-study and existing non-malignant fluid collections that change in character require cytological proof of malignancy in order to be reported as a new lesion.

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

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

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

Central radiology review for disease response and progression may be implemented in this study for Cohorts 7 through 10 and would be introduced with a future amendment or an Administrative Letter. Radiographic documentation (either in digital format or original films) for independent review must be preserved and be readily available for all newly enrolled patients in these cohorts, and attempts should be made to collect and preserve such material for previously enrolled patients, for submission to a central vendor.

7.2 Safety Assessments

7.2.1 Medical History

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

7.2.2 Physical Examination and Vital Signs

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

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

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

7.2.3 Eye Examination (Only for Cohorts 9 and 10)

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.

7.2.4 Laboratory Safety Assessments

Laboratory safety assessments for which data will be collected in this study will include hematology, coagulation, thyroid tests, urinalysis and chemistry parameters presented in Table 11.

Laboratory tests will be drawn at the time points described in the Schedule of Assessments (Table 1 and Table 3) and analyzed at local laboratories. Additional laboratory tests may be performed per standard of care, at the Investigator's discretion for the purpose of planning treatment administration, dose modification, following adverse events, or as clinically indicated. Performance of an additional urinalysis prior to study-related collection of fresh tumor tissue from lesions involving the genitourinary tract is discussed in Section 7.3.4.

Table 11: Laboratory Safety Parameters

Hematology Panel	**Blood Chemistry Panel**
Hemoglobin	Aspartate aminotransferase (AST)
Platelet count	Alanine aminotransferase (ALT)
White blood cell count (WBC)	Alkaline phosphatase
Neutrophil count	Total bilirubin (if Total bilirubin is ≥2×ULN and no evidence of Gilbert's syndrome, then fractionate into direct and indirect bilirubin)
Lymphocyte count	Lipase
	Amylase
Coagulation	Sodium
International normalized ratio (INR)	Potassium
Partial thromboplastin time (PTT)	Chloride
	Bicarbonate or [CO^2]
Urinalysis (dip stick)	Blood urea nitrogen (BUN)
Blood	Creatinine
Protein	Albumin
	Total Calcium
Thyroid Function Test	Magnesium
Thyroid-stimulating hormone (TSH)	Uric acid
	Glucose (only for Cohorts 9 and 10)

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

7.2.5 Electrocardiogram (ECG)

Single and triplicate ECGs are to be performed as outlined in the Schedule of Assessments (Table 1, Table 2, Table 3, and Table 4). It is preferable that the machine used has a capacity to calculate the standard intervals automatically. In addition, QTc will be manually calculated using the Fridericia's formula. Assessments reported by automated read as prolongation of QTc should be over-read by a cardiologist to ensure accuracy of interpretation.

7.2.6 Echocardiogram (ECHO)

Echocardiograms will be performed at screening, and thereafter as in the Schedule of Assessments (Table 1 and Table 3). Additional assessments of LVEF may be performed as clinically indicated at the Investigator's discretion if there are signs or symptoms of cardiotoxicity.

7.3 Laboratory Studies

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

7.3.1 Pharmacokinetic Evaluation

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

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

7.3.2 Pharmacodynamic Evaluation in Blood

Pharmacodynamic parameters that may be investigated in this study include but are not limited to plasma levels of circulating PD-L1, flow cytometry assessment for NK-cells, Tregs, macrophages, MDSCs, TCR sequencing, T- and B-cells including CD4, CD8 and Ki67+ cells and selected cytokines including CD8A, GZMB, IFNγ, CXCL9, CXCL10, CXCL11, and TBX21, prior to and during treatment. Full details on sample collection, processing, storage and shipment will be provided in the Study Laboratory Manual.

7.3.3 Circulating Tumor DNA

Blood samples for ctDNA analysis will be collected at baseline/screening, at confirmation of response of PR or CR, and at the End of Treatment visit, as outlined in Table 1 and Table 3. At each ctDNA time point, blood samples will be collected into two 10 mL Streck brand Cell-Free DNA Blood Collection tubes allowing shipping and stability at ambient temperatures. Full details on sample collection, processing, storage and shipment will be provided in the Study Laboratory Manual.

7.3.4 Pharmacodynamic Evaluation in Tumor Tissue

Pharmacodynamic parameters in tumor tissue that may be investigated in this study include but are not limited to PD-L1 expression, CD8+ TILs, NK-cells, Tregs, macrophages, and MDSCs, prior to and during treatment. Gene expression signatures and mutational assessment may also be measured. Full details on sample collection, processing, storage and shipment will be provided in the Study Laboratory Manual.

Freshly biopsied tumor tissue collections at pre-treatment and on-treatment timepoints for analysis of PD-L1 expression, other immune cell populations and evaluation of tumor gene alterations are highly desirable; however, tumor biopsies having significant risk should not be performed and tumor lesions evaluated on-treatment as measurable lesions per RECIST 1.1 should not be disturbed for study biopsies. Prior to any study-related biopsy involving tumors in the genitourinary tract, a urinalysis should be performed. If the results are consistent with a urinary tract infection, tumor lesions in other anatomical sites should be selected, if present. Archival samples may be submitted as pre-treatment samples if more recent tumor specimens or fresh biopsies cannot be obtained. An on-treatment tumor biopsy on Cycle 2 Day 15 is desirable for all treated patients and is not dependent on the type of pre-treatment tumor tissue submitted (i.e., archival or freshly collected biopsy).

Tumor PD-L1 expression in freshly biopsied tumor tissue will be determined by the PD-L1 (28-8) companion diagnostics assay completed through the central laboratory. If tumor tissue from a patient has previously undergone PD-L1 testing, results to be collected in the Case Report Form (CRF) include the type of assay employed and percent tumor and/or immune cell staining.

Tumor gene expression in freshly biopsied tumor samples will be determined using next generation sequencing performed by a central laboratory. For patients in whom tumor tissue has previously been tested using next generation sequencing, presence of specific tumor gene mutations and estimation of total mutation burden will be collected in the CRF.

Samples should be collected via a core needle of 18 gauge or larger or be collected by an incisional or excisional tumor biopsy. Where institutional practice uses a smaller gauge needle, samples should be evaluated for tumor cell quantity (i.e., > 100 tumor cells) to allow for adequate PD-L1 immunohistochemistry analyses. Samples should be formalin fixed and embedded in paraffin. Samples from fine needle aspirates (FNA) or decalcified bone are not appropriate for study evaluations.

7.4 Post-treatment Follow-up

Survival status and subsequent therapies will be collected during long term follow-up as outlined in the Schedule of Assessments (Table 1 and Table 3) until death or lost to follow-up. Beyond 28 days after last treatment, follow-up may be performed by

telephone contact. Treatments received following participation in the study will be collected in the CRF.

8 ADVERSE EVENT REPORTING

8.1 Sponsor Medical Monitor Personnel

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

8.2 Adverse Events

An adverse event (AE) is any reaction, side effect or other undesirable medical event that occurs during participation in a clinical trial, regardless of treatment group or suspected causal relationship to study treatment. Assessment of adverse events will include type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE, Version 5.0]), timing, seriousness, and relatedness to study treatment. A treatment emergent AE (TEAE) is an AE that occurs after the first dose of any study treatment or any preexisting condition that increases in severity after the first dose of study treatment.

All observed or volunteered AEs will be recorded in source documents and reported in the CRF. The best available medical terminology should be used to describe AEs in source documents and CRFs. Terms describing the diagnosis are preferred over individual signs and symptoms of the diagnosis. If determination of the diagnosis is delayed, record signs and symptoms and add the diagnosis as an additional AE when available; follow all recorded AEs to resolution. The actual date of onset should be recorded in all cases. Ongoing AEs that change in attribution or severity should have the date of change entered as the “end date” and a new AE record should be opened with the changed details. Examples of AEs include but are not limited to:

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

- Extravasation;
- Exposure during pregnancy or via breastfeeding;
- Medication error; or
- Occupational exposure.

8.2.1 Laboratory Abnormalities

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

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

Hy's Law

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

Cases meeting Hy's Law should be reported as SAEs. Study treatments (sitravatinib, nivolumab, *or* sitravatinib, pembrolizumab and enfortumab) should be permanently discontinued for a Hy's Law case.

8.2.2 Severity Assessment

AEs occurring during this study will be graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0). Documentation of AE grading in the source documents and CRF should be consistent with provided definitions.

8.2.3 Causality

For each AE, the Investigator should determine and document whether there exists a reasonable possibility that the study treatment caused or contributed to the AE. The Investigator's assessment should be recorded in the source document. The CRF will provide the options for attribution to each study treatment as "related" or "not related." If the Investigator's causality assessment is "unknown but not related to investigational product," this should be recorded in the CRF as "not related." If the Investigator does not know whether or not the study treatment is causally related to the event, reporting for study purposes will be as "related" to study treatment.

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

8.3 Serious Adverse Events

8.3.1 Definition of a Serious Adverse Events

An SAE is any event that meets any of the following criteria:

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

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

Definition of Terms

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

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

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

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

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

8.3.2 Exposure During Pregnancy

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

- A female becomes or is found to be pregnant during treatment or within 6 months after discontinuing treatment or having been directly exposed to the investigational product;

- A male is exposed to the investigational product prior to or around the time of conception or during the pregnancy of his partner.

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

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

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

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

If the outcome of the pregnancy meets the criteria for an SAE (i.e., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), an SAE report should be submitted to the Sponsor.

8.4 Reporting of SAEs and AEs

8.4.1 Reporting Period

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

study drug. These SAEs should be followed until resolved or stabilized to a chronic condition.

The reporting period for non-serious AEs begins from the day of first dose of study treatment and continues until at least 28 days after last administration of study treatment. If a patient begins a subsequent anticancer therapy, the AE reporting period ends at the time the new treatment is started.

8.4.2 Reporting Requirements

All SAEs must be reported within 24 hours of Investigator/site knowledge of the event, irrespective of the extent of available AE information, by faxing the SAE report to the Sponsor's pharmacovigilance representative designated in the Study Manual. The 24-hour timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports and to the initial and follow-up reporting of exposure during pregnancy and exposure via breastfeeding. The need for an expedited report to regulatory authorities will be determined by the Sponsor and necessary reporting will be performed by the Sponsor. The Sponsor will notify study Investigators of all Suspected, Unexpected (as judged against the Investigator Brochure) Serious Adverse Reaction (SUSAR) reports. The Investigator is responsible for reporting all SUSARs to the IRB/EC.

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

9 STATISTICS

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

9.1 Hypothesis and Sample Size

This Phase 2 study will use Predictive Probability Designs (Lee-2008) for initial Cohorts 1 and 2. The design, hypothesis and sample size considerations for the initial Cohorts 1 and 2 are described below. Refer to Appendix 5, Appendix 6, Appendix 8 and Appendix 9 for study design and statistical considerations applicable to all contingent Cohorts 3 through 10. In summary, Cohorts 3 and 4 will also use Predictive Probability Designs with the same assumptions as the initial cohorts (Appendix 5), Cohorts 5 and 6 will use Predictive Probability Designs with revised assumptions (Appendix 6), Cohorts 7 and 8

will use confidence interval method with the revised assumptions (Appendix 8), the lead-in dose escalation portion of Cohort 9 will use the mTPI-2 design (Guo-2017; Appendix 9), and the dose expansion portion of Cohort 9 and Cohort 10 will use Simon 2-stage optimal designs (Simon-1989; Appendix 9).

In creating the statistical designs for initial Cohorts 1 and 2, the Type 1 error (α) is constrained to <0.05 and Power ($1-\beta$) is constrained to ≥ 0.90.

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% (p_0); thus this rate is considered uninteresting. The target ORR using sitravatinib in combination with nivolumab in this study population is 30% (p_1). 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 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 12 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 12: 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%

9.2 Data Handling

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

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

9.3 Analysis Populations

9.3.1 Full Analysis Population

The full analysis population (FAP) is defined as all patients who receive one dose of all study treatments (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 Cohorts 9 and 10).

The primary efficacy analyses of the primary and secondary efficacy endpoints will be performed in the FAP for all cohorts. In addition, the FAP population will be used 1) in making decisions to expand the study to the third stage of enrollment for Cohorts 1 through 4, and 2) for the interim futility analysis for Cohorts 7 and 8.

9.3.2 Clinical Activity Evaluable Population

The clinical activity evaluable population will include patients who receive at least one dose of both sitravatinib and nivolumab and 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.

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, and on the Simon 2-stage optimal design for Cohorts 9 (dose expansion portion) and 10.

9.3.3 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.

9.3.4 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.

9.3.5 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.

9.3.6 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.

9.3.7 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 (defined in Appendix 9). Patients who received prohibited therapy during Cycle 1 (refer to Section 5.7.2), 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.

9.4 Efficacy Endpoint Definitions and Analyses

9.4.1 Objective Response Rate

Objective disease response will be categorized in accordance with RECIST v1.1 (Appendix 4). Objective Response Rate (ORR) is defined as the percent of patients documented to have a confirmed Complete Response (CR) or Partial Response (PR).

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

9.4.2 Clinical Benefit Rate

Clinical Benefit Rate (CBR) is defined as the percent of patients documented to have a confirmed Complete Response (CR), Partial Response (PR), or Stable Disease (SD) documented during at least 1 on-study assessments.

9.4.3 Duration of Response

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

9.4.4 Progression-Free Survival

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

9.4.5 Overall Survival

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

9.4.6 Subgroup Analyses

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.

9.5 Safety Data Presentations and Summaries

9.5.1 Adverse Events

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

9.5.2 Prior and Concomitant Medications

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

9.5.3 Clinical and Laboratory Assessments

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

Clinical laboratory results will be listed by patient and, as appropriate, summarized descriptively, which will include a display of change from baseline. Selected parameters will be presented in shift tables of baseline against worst grade test result. Laboratory values outside of the normal ranges will be identified. Laboratory values that meet Grade 3 or 4 criteria according to NCI CTCAE v.5.0 will be listed and summarized.

ECG assessments will be evaluated for change of QTc from baseline as an exposure: response analysis. The Investigator's interpretation of QTc will be used in the clinical management of patients. The study analysis will use Fridericia's formula applied programmatically to the ECG data collected in CRFs using the QT interval and either the RR interval or the heart rate if the RR interval is not reported.

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

9.5.4 Patient Demographics, Baseline Characteristics and Disposition

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

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

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

9.5.5 Analysis of Study Treatment Dosing

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

9.6 Other Study Endpoints

9.6.1 Pharmacokinetic Analysis

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

9.6.2 Pharmacodynamic and Exploratory Analyses

No formal statistical analysis of PD or exploratory endpoints will be performed. Data from each assay will be listed by dose level and Phase 2 cohort. Possible relationships between correlative endpoints, PD variables, PK parameters, safety, and clinical activity may be examined if appropriate.

9.7 Interim Analysis

No interim statistical analysis is planned during this study. As detailed in 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.

9.8 Data Monitoring Committee

No Data Monitoring Committee is planned during this study.

10 ETHICS AND RESPONSIBILITIES

10.1 Ethical Conduct of the Study

This study will be conducted in accordance with International Ethical Guidelines for Biomedical Research Involving Human Patients (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (GCP) (International Council for Harmonisation [ICH] 1996), ICH E6 (R2) and concepts that have their origin

in the Declaration of Helsinki (World Medical Association 1996, 2008 & 2013). Specifically, this study is based on adequately performed laboratory and animal experimentation; the study will be conducted under a protocol reviewed and approved by an IRB/EC; the study will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the patients will be respected; the physicians conducting the study do not find the hazards to outweigh the potential benefits; and each patient will give his or her written informed consent before any protocol-driven tests or evaluations are performed.

10.2 Obligations of Investigators

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

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

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

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

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

Prior to the shipment of clinical supplies or initiation of the study, the clinical trial protocol along with the informed consent form (ICF), Investigator's Brochure, and any other written information or instructions for the patient must be submitted to the IRB/EC/REB for written approval. The Investigator will provide the Sponsor with a copy of the IRB/EC/REB's written approval, as well as the membership list or a compliance statement from the IRB/EC/REB. The Investigator is responsible for notifying the IRB/EC/REB of any Sponsor-approved amendments to the protocol or ICF, SAEs occurring in patients treated at the study site in accordance with local IRB/EC/REB practice, and all expedited safety reports from SAEs occurring at other study sites participating in the drug development program.

10.4 Informed Consent Form

The ICF must contain all elements required by the Food and Drug Administration (FDA) under 21 Code of Federal Regulations (CFR) Part 50 and the ICH GCP guidelines (ICH E6, 4.8) in addition to any other elements required by applicable national, state, provincial, and local regulations, or institutional policies.

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

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

10.5 Confidentiality

All information generated in this study is considered confidential, is subject to applicable privacy rules and regulations, and must not be disclosed to any person or entity not directly involved with the study without the Sponsor's prior written consent or in accordance with applicable law or regulations. Persons or entities involved with the study who may have access to the information will be subject to contractual confidentiality requirements. However, authorized regulatory officials, such as IRB/EC/REB, the Sponsor and its authorized representatives (as and to the extent authorized in the patient's ICF) are allowed access to the records.

Identification of patients in CRFs shall be by study assigned patient numbers only. If required, the patient's full name may be made known to authorized third-parties, to the extent permitted by applicable laws and regulations and mentioned in the ICF.

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

Records and documents which identify the individual patient will be stored securely for the length of time required by applicable clinical research, health information and data privacy laws, as described in Section 11.2 and in the ICF.

Regarding Privacy and Data Protection, the Sponsor ensures that personal data is collected and processed in accordance with all the applicable laws and regulations.

Detailed description of the conditions for the collection and processing of personal data is made available to the patient in the ICF and, if applicable, the relating Data Protection Privacy Policy.

The Sponsor, as data controller, collects and processes personal data related to (i) patient identity and health in order to conduct the study, and (ii) financial data and identification data for administrative tasks, under the conditions set forth in the ICF.

In accordance with all applicable data protection rules, the patient will have the right to access, rectify, delete, limit or oppose the processing of its personal data, the right to define guidelines for the storage, deletion and communication of the data after its death and the right to the portability of its personal data. The Investigator is in charge of the exercising of the rights. The Sponsor may also have appointed a Data Protection Officer to whom it will be permitted access to directly identifying personal data when necessary to answer a patient's request.

The Sponsor has implemented appropriate protocols and mechanisms in case of a breach of confidentiality.

10.6 Reporting of Serious Breaches of the Protocol or ICH GCP

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

11 RECORDS MANAGEMENT

11.1 Source Documentation

Source documents include hospital or clinical patient charts, pertinent historical medical records, laboratory test reports, ECG tracings, pathology reports, radiographs, etc. All source documents must be legible. Data reported in CRFs and evidence of patient's informed consent must be documented in source documents.

11.2 Study Files and Records Retention

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

CRFs must be signed by the Principal Investigator or by an authorized Sub-Investigator to attest that the information included is true.

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

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

12 QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Monitoring Procedures

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

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

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

12.2 Auditing and Inspection Procedures

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

13 CHANGES IN STUDY CONDUCT

13.1 Protocol Amendments

Changes to the study protocol, except those intended to reduce immediate risk to study patients, may be made only by the Sponsor. A protocol change intended to eliminate an

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

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

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

13.2 Protocol Deviations

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

14 END OF TRIAL

14.1 End of Trial in a European Union Member State

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

14.2 End of Trial in all other Participating Countries

End of Trial in all other participating countries is defined as the time at which all patients enrolled in the study have completed the last study visit and data from those visits have been reviewed by the Investigator or designee.

14.3 Premature Termination

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

15 STUDY REPORT AND PUBLICATION POLICY

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

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

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APPENDIX 1. ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair
5	Dead

APPENDIX 2. CALCULATION OF GLOMERULAR FILTRATION RATE AND RENAL IMPAIRMENT SCALE

During this study, renal function will be evaluated using the estimated glomerular filtration rate (eGFR). eGFR at study entry will be captured in the CRF to document patient eligibility. For reporting purposes, eGFR will be derived within the study database. The method to be used to calculate eGFR is the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI, Levey-2009) equation. The link to the on-line calculator, instructions for use and equation are presented below. In addition, a link to download the app or calculator are provided.

Severity of renal impairment will be categorized using the FDA Guidance for Industry dated March 2010. The scale for renal impairment is presented below.

Calculation of eGFR Using CKD-EPI Calculator

Link to CKD-EPI Calculator:

https://www.kidney.org/professionals/kdoqi/gfr_calculator

Link to Download CKD-EPI App or Calculator:

https://www.kidney.org/professionals/tools

When using the CKD-EPI calculator, ensure that height and weight are entered into the calculator. The result should present as mL/min rather than mL/min/1.73 m^2. Below are instructions on patient data entry.

Enter the following data (it is not necessary to enter data for cystatin C):

- serum creatinine (standardized mg/dl or µmol/L, traceable to IDMS);
- age;
- gender;
- race;
- standard assays – yes;
- remove body surface adjustment – yes;
- height;
- weight.

The following is the CKD-EPI equation used to calculate eGFR standardized to body surface area 1.73 m^2, without consideration of height or weight.

$$eGFR = 141 \times \min\left(\frac{Scr}{\kappa}, 1\right)^{\alpha} \times \max\left(\frac{Scr}{\kappa}, 1\right)^{-1.209} \times (0.993)^{Age} \times 1.018\,[if\ female] \times 1.159[if\ black]$$

Abbreviations / Units
eGFR (estimated glomerular filtration rate) = mL/min/1.73m^2
S_{Cr} (standardized serum creatinine) = mg/dL
κ = 0.7 (females) or 0.9 (males)
α = -0.329 (females) or -0.411 (males)
min = indicates the minimum of S_{Cr}/κ or 1
max = indicates the maximum of S_{Cr}/κ or 1
age = years

Classification of Renal Impairment Using FDA Guidance for Industry

The renal impairment classification scale provided in the guidance document considers eGFR and Estimated Creatinine Clearance (CLcr). It allows for the fact that equations to calculate eGFR are evolving. In this study, eGFR will be calculated using the CKD-EPI equation with substitution of individual body surface area based on height and weight rather than use of the standardized value of 1.73 m^2. The following scale is a reprint from the FDA Guidance for Industry and will be used to group patients in the renal impairment substudy described in Appendix 7 and in population pharmacokinetic analyses.

Classification of Renal Function Based on Estimated GFR or Estimated Creatinine Clearance			
Stage	**Description**	**eGFR (mL/min/1.73m²)**	**CLcr (mL/min)**
1	Control (Normal) GFR	≥ 90	≥ 90
2	Mild Decrease in GFR	60-89	60-89
3	Moderate Decrease in GFR	30-59	30-59
4	Severe Decrease in GFR	15-29	15-29
5	End Stage Renal Disease	<15 not on dialysis or requiring dialysis	<15 not on dialysis or requiring dialysis

APPENDIX 3. MEDICATIONS OR SUBSTANCES TO BE AVOIDED OR USED WITH CAUTION DURING TREATMENT WITH SITRAVATINIB

Examples of Drugs with a Known Risk of Torsades de Pointes*

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

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Domperidone (Only on Non US Market)	Motilium, Motillium, Motinorm Costi, Nomit	Antiemetic	Nausea, vomiting
Donepezil	Aricept	Cholinesterase inhibitor	Dementia (Alzheimer's Disease)
Dronedarone	Multaq	Antiarrhythmic	Arrhythmia
Droperidol	Inapsine, Droleptan, Dridol, Xomolix	Antipsychotic / Antiemetic	Anesthesia (adjunct), nausea
Erythromycin	E.E.S., Robimycin, EMycin, Erymax, Ery- Tab, Eryc Ranbaxy, Erypar, Eryped, Erythrocin Stearate Filmtab, Erythrocot, E-Base, Erythroped, Ilosone, MY-E, Pediamycin, Abboticin, Abboticin-ES, Erycin, PCE Dispertab, Stiemycine, Acnasol, Tiloryth	Antibiotic	Bacterial infection, increase GI motility
Escitalopram	Cipralex, Lexapro, Nexito, Anxiset-E, Exodus, Esto, Seroplex, Elicea, Lexamil, Lexam, Entact, Losita, Reposil, Animaxen, Esitalo, Lexamil	Antidepressant, SSRI	Depression (major), anxiety disorders
Flecainide	Tambocor, Almarytm, Apocard, Ecrinal, Flécaine	Antiarrhythmic	Arrhythmia
Fluconazole	Diflucan, Trican	Antifungal	Fungal infection
Gatifloxacin (Removed from US Market)	Tequin	Antibiotic	Bacterial infection
Grepafloxacin (Removed from US Market)	Raxar	Antibiotic	Bacterial infection
Halofantrine (Only on Non US Market)	Halfan	Antimalarial	Malaria
Haloperidol	Haldol, Aloperidin, Bioperidolo, Brotopon, Dozic, Duraperidol, Einalon S, Eukystol, Halosten, Keselan, Linton, Peluces, Serenace, Serenase, Sigaperidol	Antipsychotic	Schizophrenia, agitation
Hydroquinidine (Dihydroquinidine) (Only on Non US Market)	Serecor	Antiarrhythmic	Arrhythmia

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Hydroxychloroquine	Plaquenil, Quineprox	Antimalarial, Anti-inflammatory	Malaria, SLE, rheumatoid arthritis
Ibogaine (Only on Non US Market)		Psychedelic	Narcotic addiction, unproven
Ibutilide	Corvert	Antiarrhythmic	Arrhythmia
Levofloxacin	Levaquin, Tavanic	Antibiotic	Bacterial infection
Levomepromazine (Methotrimeprazine) (Only on Non US Market)	Nosinan, Nozinan, Levoprome	Antipsychotic	Schizophrenia
Levomethadyl acetate (Removed from US Market)	Orlaam	Opioid agonist	Narcotic dependence
Levosulpiride (Only on Non US Market)	Lesuride, Levazeo, Enliva	Antipsychotic	Schizophrenia
Mesoridazine (Removed from US Market)	Serentil	Antipsychotic	Schizophrenia
Methadone	Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadon	Opioid agonist	Narcotic dependence, pain
Moxifloxacin	Avelox, Avalox, Avelon	Antibiotic	Bacterial infection
Nifekalant (Only on Non US Market)	Shinbit	Antiarrhythmic	Arrhythmia
Ondansetron	Zofran, Anset, Ondemet, Zuplenz, Emetron, Ondavell, Emeset, Ondisolv, Setronax	Antiemetic	Nausea, vomiting
Oxaliplatin	Eloxatin	Anti-cancer	Cancer
Papaverine HCl (Intra- coronary)		Vasodilator, Coronary	Diagnostic adjunct
Pentamidine	Pentam	Antifungal	Fungal infection (Pneumocystis pneumonia)
Pimozide	Orap	Antipsychotic	Tourette's Disorder
Probucol (Removed from US Market)	Lorelco	Antilipemic	Hypercholesterolemia
Procainamide	Pronestyl, Procan	Antiarrhythmic	Arrhythmia
Propofol	Diprivan, Propoven	Anesthetic, general	Anesthesia
Quinidine	Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora	Antiarrhythmic	Arrhythmia

Generic Name	**Brand Names (Partial List)**	**Drug Class**	**Therapeutic Use**
Roxithromycin (Only on Non US Market)	Rulide, Xthrocin, Roxl-150, Roxo, Surlid, Rulide, Biaxsig, Roxar, Roximycinv, Roxomycin, Rulid, Tirabicin, Coroxin	Antibiotic	Bacterial infection
Sevoflurane	Ultane, Sojourn	Anesthetic, general	Anesthesia
Sotalol	Betapace, Sotalex, Sotacor	Antiarrhythmic	Arrhythmia
Sparfloxacin (Removed from US Market)	Zagam	Antibiotic	Bacterial infection
Sulpiride (Only on Non US Market)	Dogmatil, Dolmatil, Eglonyl, Espiride, Modal, Sulpor	Antipsychotic, atypical	Schizophrenia
Sultopride (Only on Non US Market)	Barnetil, Barnotil, Topral	Antipsychotic, atypical	Schizophrenia
Terfenadine (Removed from US Market)	Seldane	Antihistamine	Allergic rhinitis
Terlipressin (Only on Non US Market)	Teripress, Glypressin, Terlipin, Remestyp, Tresil, Teriss	Vasoconstrictor	Septic shock
Terodiline (Only on Non US Market)	Micturin, Mictrol	Muscle relaxant	Bladder spasm
Thioridazine	Mellaril, Novoridazine, Thioril	Antipsychotic	Schizophrenia
Vandetanib	Caprelsa	Anti-cancer	Cancer (thyroid)

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

Examples of Drugs with Conditional Risk of Torsades de Pointes*

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Abiraterone	Zytiga, Abiratas, Abretone, Abirapro	Anti-androgen	Cancer (Prostate)
Amantadine	Symmetrel, Symadine	Antiviral	Viral infection (Influenza), Parkinson's disease
Amisulpride	Barhemsys, Solian, Supitac, Soltus, Amitrex, Amazeo	Antiemetic, Antipsychotic	Nausea and vomiting, postoperative
Amitriptyline	Elavil (Discontinued 6/13), Tryptomer, Tryptizol, Laroxyl, Saroten, Sarotex Lentizol, Endep	Antidepressant, Tricyclic	Depression
Amphotericin B	Fungilin, Fungizone, Abelcet, AmBisome, Fungisome, Amphocil, Amphotec	Antifungal	Fungal infection
Amsacrine (Acridinyl anisidide) (Only on Non US Market)	Amsidine	Antineoplastic Agent	Cancer (Acute Lymphoblastic Leukemia)
Atazanavir	Reyataz, Evotaz	Antiviral	Viral infection (HIV/AIDS)
Bendroflumethiazide (Bendrofluazide)	Aprinox, Corzide	Diuretic, thiazide	Hypertension, diuresis
Chloral hydrate	Aquachloral, Novo-Chlorhydrate, Somnos, Noctec, Somnote	Sedative	Sedation, insomnia
Cimetidine	Tagamet	Antacid	Gastric hyperacidity, GERD
Clomipramine	Anafranil	Antidepressant, Tricyclic	Depression
Diphenhydramine	Benadryl, Nytol, Unisom, Sominex, Dimedrol, Daedalon, Banophen	Antihistamine	Allergic rhinitis, insomnia
Doxepin	Sinequan, Silenor, Aponal, Adapine, Doxal, Deptran, Sinquan	Antidepressant, Tricyclic	Depression
Eperisone (Only on Non US Market)	Myonal, Epry	Antispasmodic	Spasticity
Esomeprazole	Nexium, Nexum, Inexium	Proton Pump Inhibitor	Gastric hyperacidity, GERD
Famotidine	Pepcid, Fluxid, Quamatel	H2-receptor antagonist	Gastric hyperacidity, GERD

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Fluoxetine	Prozac, Sarafem, Fontex	Antidepressant, SSRI	Depression
Fluvoxamine	Faverin, Fevarin, Floxyfral, Dumyrox, Luvox	Selective Serotonin Reuptake Inhibitor	Depression, Obsessive Compulsive Disorder
Furosemide (frusemide)	Lasix, Fusid, Frumex, Lasilix	Diuretic	Hypertension, diuresis
Galantamine	Reminyl, Nivalin, Razadyne-ER, Lycoremine	Cholinesterase inhibitor	Dementia (Alzheimer's Disease)
Garenoxacin (Only on Non US Market)	Geninax	Antibiotic	Bacterial infection
Hydrochlorothiazide	Apo-Hydro, Aquazide H, BP Zide, Dichlotride, Hydrodiuril, HydroSaluric, Microzide, Esidrex, Oretic	Diuretic	Hypertension, diuresis
Hydroxyzine	Atarax, Vistaril, Aterax, Alamon, Durrax, Equipose, Masmoran, Orgatrax, Paxistil Quiess, Tran-Q, Tranquizine	Antihistamine	Allergic reaction, anxiety disorders
Indapamide	Lozol, Natrilix, Insig	Diuretic	Hypertension, diuresis
Itraconazole	Sporanox, Onmel	Antifungal	Fungal infection
Ivabradine	Procoralan, Coralan, Corlentor, Coraxan, Ivabid, Bradia	Antianginal	Angina Pectoris (heart pain)
Ketoconazole	Nizoral, Sebizole, Ketomed, Keton	Antifungal	Fungal infection
Lansoprazole	Prevacid, Ogast	Proton Pump Inhibitor	Gastric hyperacidity, GERD
Loperamide	Imodium	Opioid agonist	Diarrhea
Metoclopramide	Reglan, Afipran, Maxolon, Cerucal, Clopamon, Clopra, Maxeran, Maxolon, Metozolv, Plasil, Pramin, Primperan, Perinorm	Antiemetic	Nausea, vomiting
Metolazone	Zytanix, Zaroxolyn, Mykrox	Diuretic	Hypertension, diuresis
Metronidazole	Flagyl	Antibiotic	Trichomoniasis, amebiasis, bacterial infection
Nelfinavir	Viracept	Antiviral	Viral infection (HIV/AIDS)
Olanzapine	Zyprexa, Zydis, Relprevv	Antipsychotic, atypical	Schizophrenia, bipolar disorder

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

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

Examples of Sensitive Substrates and Substrates with Narrow Therapeutic Index for P-gp and BCRP Transporters

Enzyme	
P-gp	Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus, fexofenadine, imatinib, lapatinib, maraviroc, nilotinib, posaconazole, ranolazine, saxagliptin, sirolimus, sitagliptin, talinolol, tolvaptan, topotecan
BCRP	Methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan

Examples of Sensitive Substrates and Substrates with Narrow Therapeutic Index for the Indicated CYP3A4 Enzymes

Enzyme	
CYP3A4	Alfentanil, avanafil, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib dronedarone, ebastine, eletriptan, eplerenone, everolimus, felodipine, ibrutinib, indinavir, lomitapide, lovastatin, lurasidone, maraviroc, midazolam, naloxegol, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, ticagrelor, tolvaptan, triazolam, vardenafil

APPENDIX 4. ABBREVIATED PRESENTATION OF RECIST VERSION 1.1 GUIDELINES

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

Categorizing Lesions at Baseline

Measurable Lesions

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

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

Non-Measurable Disease

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

APPENDIX 5. CONTINGENT STUDY COHORTS IN PATIENTS PREVIOUSLY RECEIVING TREATMENT WITH SELECTED IMMUNOTHERAPIES

In the event that results in of 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 following lists sections of the main protocol and describes any changes to be implemented in cohorts of patients that have received selected immunotherapies and checkpoint inhibitor therapy.

Study Objectives – See main protocol.

Study Endpoints – See main protocol.

Study Design – Unchanged with the exception of the description of the populations to be enrolled into new cohorts. The population will be stratified into 2 cohorts:

- 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.

Enrollment Criteria – See main protocol (inclusion and exclusion criteria changes specific to Cohorts 3 and 4 under Appendix 5 are noted as such in Section 4.1 and Section 4.2).

Study Assessments and Procedures – See main protocol.

Statistical Design – See main protocol.

APPENDIX 6. CONTINGENT STUDY COHORTS IN CHECKPOINT INHIBITOR THERAPY NAÏVE POPULATIONS

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 appendix were implemented by an Administrative Letter dated May 2019.

The following lists sections of the main protocol and describes any changes to be implemented in cohorts of CIT-naïve patients.

Study Objectives – See main protocol.

Study Endpoints – See main protocol.

Study Design – Unchanged with the exception of the description of the populations to be enrolled into new cohorts. The population will be stratified into 2 cohorts:

- 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.

Enrollment Criteria – See main protocol (inclusion and exclusion criteria changes specific to Cohorts 5 and 6 under Appendix 6 are noted as such in Section 4.1 and Section 4.2).

Study Assessments and Procedures – See main protocol.

Statistical Design – Changes to hypothesis and sample size.

Hypothesis and Sample Size

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% (p_0); thus, this rate is considered uninteresting. The target ORR using sitravatinib in combination with nivolumab in this study population is 40% (p_1). 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 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.

APPENDIX 7. EVALUATION OF THE PHARMACOKINETICS OF SITRAVATINIB 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, this evaluation of the pharmacokinetics of sitravatinib in patients with renal impairment may be implemented. These data are a necessary component in the successful development of a new cancer therapy. The fact that many patients with advanced or metastatic urothelial carcinoma have or will develop renal impairment identifies this study as an appropriate situation in which to gather these data. A subset of study sites will participate in this evaluation; it is optional for both study sites and individual patients. The decision to implement this aspect of the study will be documented for Regulators and Institutional Review Boards by an Administrative Letter to Investigators.

The evaluation of the PK of sitravatinib in patients with renal impairment was implemented by an Administrative Letter dated December 2018.

With the introduction of cohorts evaluating sitravatinib in combination with pembrolizumab and enfortumab with protocol Version 4.0, and in an effort to control for confounders, the evaluation of the PK of sitravatinib in patients with renal impairment will only to apply to Cohorts 1 through 8 where the study treatment is sitravatinib in combination with nivolumab.

The eligibility criteria for this study allow enrollment of patients having renal impairment categorized as mild or moderate, defined as estimated GFR 30-59 mL/min and 60-89 mL/min, respectively, using the CKD-EPI equation (Appendix 2). Upon implementation of this study appendix, the evaluation of the PK of sitravatinib in at least 6 patients each having no renal impairment, mild renal impairment or moderate renal impairment at enrollment will be undertaken. Consenting patients with no, mild or moderate renal impairment enrolling at selected study sites will substitute blood sample collection over a 24-hour period following sitravatinib dosing on Day 1 and Day 15 (± 2 days) of treatment as described in Table 13, rather than the sparse PK sampling schedule described for Day 1 and Day 15 in Table 2. All other PD biomarker and ECG assessments described in Table 2, as well as sparse PK sampling after Cycle 1, will be performed in the sub-study population. On the days of PK sampling, patients should delay taking the daily sitravatinib dose until the pre-dose PK sample has been collected in the clinic. PK blood samples will each collect 4 mL of blood.

Table 13: Substitute Day 1 and 15 Sitravatinib PK Sample Schedule During Renal Impairment Sub-study[3]

	Cycle 1 Day 1 and Again Cycle 1 Day 15 (± 2 days)						
Collection Time and Allowable Window	**Pre-dose (-0.5-0 hour)**	**30 min (± 10 min)**	**2 hour (±15 min)**	**4 hour (±30 min)**	**6 hour (±30 min)**	**8 hour (±30 min)**	**24 hour (±2 hours)**
PK Sample[1, 2]	X	X	X	X	X	X	X

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

2 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, if the patient continues study treatment.

3 See Table 2 for all other PD biomarker and ECG assessments, as well as sparse PK sampling after Cycle 1, that must also be performed.

PK concentration and parameter data will be descriptively derived and displayed. A descriptive comparison to data collected in other patients within this study and other studies within the sitravatinib program will be conducted using $AUC_{0\text{-}t}$, $AUC_{(0\text{-}\infty)}$, C_{max}, T_{max}, $t_{1/2}$, and steady state PK exposure parameters. Descriptive statistics will be used to summarize patient characteristics, treatment administration and safety variables. Details of this analysis will be provided in the PKAP.

APPENDIX 8. CONTINGENT STUDY COHORTS IN PATIENTS PREVIOUSLY RECEIVING TREATMENT WITH AN ANTIBODY-DRUG CONJUGATE

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 appendix were implemented by an Administrative Letter dated September 2019.

The following lists sections of the main protocol and describes any changes to be implemented in cohorts of patients that have received checkpoint inhibitor and ADC therapy.

Study Objectives – See main protocol.

Study Endpoints – See main protocol.

Study Design – Unchanged with the exception of the description of the populations to be enrolled into new cohorts. The population will be stratified into 2 cohorts:

- 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.

Enrollment Criteria – See main protocol (inclusion and exclusion criteria changes specific to Cohorts 7 and 8 under Appendix 8 are noted as such in Section 4.1 and Section 4.2).

Study Assessments and Procedures – See main protocol.

Statistical Design – Changes to statistical design, hypothesis and sample size.

Hypothesis and Sample Size

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.

APPENDIX 9. CONTINGENT STUDY COHORTS EVALUATING SITRAVATINIB COMBINATION WITH A CHECKPOINT INHIBITOR AND AN ANTIBODY-DRUG CONJUGATE

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. Cohort 10 also described in this appendix is pending implementation.

The following lists sections of the main protocol and describes any changes to be implemented in cohorts of patients that will receive treatment with sitravatinib in combination with pembrolizumab and enfortumab.

Background and Rationale – See main protocol.

Study Objectives – See main protocol.

Study Endpoints – See main protocol.

Study Design – Design details specific to Cohort 9 (including lead-in dose escalation and dose expansion portions) and Cohort 10 under Appendix 9 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 and a platinum-based chemotherapy (dose expansion portion of Cohort 9), and in patients with previously untreated locally advanced or metastatic urothelial cancer (Cohort 10). Depending on the results in previous cohorts, only one or more of Cohort 9 and Cohort 10 may be implemented. Description of the populations to be enrolled into Cohort 9 and Cohort 10 evaluating the triple combination of sitravatinib, pembrolizumab and enfortumab are described below.

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

- Cohort 10: Patients with previously untreated unresectable, locally advanced or metastatic urothelial cancer.

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 14, whereas the starting doses for pembrolizumab and enfortumab are shown in Table 15. 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 14 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 15) 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 15). 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 14: 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 15: 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	1.25mg/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 5.7.2), 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 level expansion and dose escalation or de-escalation will be in accordance with the mTPI-2 method (Dose-Finding Spreadsheet presented in Appendix 11), and will be made in collaboration with the Investigators and documented for Regulators and Institutional Review Boards by an Administrative Letter to Investigators. To ensure sufficient patient experience at the dose regimen to be used in the dose expansion portion of Cohort 9 and contingent Cohort 10, enrollment at any dose regimen under consideration may be expanded to include at least 6 patients.

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

Selection of Phase 2 Dose Regimen for Sitravatinib Combination with Pembrolizumab and Enfortumab (for Dose Expansion Portion of Cohorts 9 and for Cohort 10)

The RP2Ds identified in lead-in dose escalation portion of Cohort 9 will be selected for the dose expansion portion of Cohort 9 and the contingent Cohort 10. A dose regimen below the MTD may be selected.

Once RP2Ds are identified, patients from lower dose levels who continue to receive study treatment may be permitted to dose escalate to the recommended dose regimen.

Dose Expansion Portion of Cohort 9 and Contingent Cohort 10

Following completion of the lead-in dose escalation portion of Cohort 9, and in the event that a tolerable dose regimen is identified for sitravatinib in combination with pembrolizumab and enfortumab, as many as 2 cohorts will evaluate the recommended dose regimen of sitravatinib in combination with pembrolizumab and enfortumab in patients who have previously received a PD-(L)1 checkpoint inhibitor and a platinum-based chemotherapy (dose expansion portion of Cohort 9), and in patients with previously untreated locally advanced or metastatic urothelial cancer (Cohort 10).

Enrollment Criteria – See main protocol (inclusion and exclusion criteria changes specific to Cohorts 9 and 10 under Appendix 9 are noted as such in Section 4.1 and Section 4.2).

Study Assessments and Procedures – See main protocol.

Statistical Design – Changes to statistical design, hypothesis and sample size.

Hypothesis and Sample Size

Lead-In Dose Escalation Evaluation for Sitravatinib 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 Appendix 11 for the dose escalation decision table using the mTPI-2 method.

Dose Expansion Portion of Cohort 9 and Cohort 10

Simon 2-stage optimal designs (Simon-1989) will be used to establish stopping rules for futility for the dose expansion portion of Cohort 9 and for Cohort 10. The dose expansion portion for Cohort 9 will also include patients from the lead-in dose escalation portion of Cohort 9 who had similar starting doses to the recommended starting doses for the sitravatinib combination with pembrolizumab and enfortumab.

- For the dose expansion portion of Cohort 9, the null hypothesis for ORR is 45%; the alternative hypothesis for ORR is 70%. The first stage of patient enrollment will include 15 patients evaluable for response. If 8 or more patients achieve an objective response, enrollment will continue to approximately 35 patients; if at least 21 objective responses are observed from both stages, further investigation will be considered warranted. If the true ORR is 45% (null hypothesis), the probability of early termination during the study is 65.4%; the Type 1 error is 0.048, and the power is 90.0%.
- For Cohort 10, the null hypothesis for ORR is 45%; the alternative hypothesis for ORR is 65%. The first stage of patient enrollment will include 19 patients evaluable for response. If 10 or more patients achieve an objective response, enrollment will continue to approximately 49 patients; if at least 28 objective responses are observed from both stages, further investigation will be considered warranted. If the true ORR is 45% (null hypothesis), the probability of early termination during the study is 67.1%; the Type 1 error is 0.05, and the power is 85%.

APPENDIX 10. EXAMPLES OF PROHIBITED P-GP INHIBITORS AND STRONG CYP3A4 INHIBITORS DURING TREATMENT WITH ENFORTUMAB

Patients must have discontinued treatment with any of the following for at least 2 weeks prior to the first dose date of enfortumab. There could also be additional new drugs and marketed drugs that could be identified as inducers/inhibitors with continued research. Use of any concomitant medication known to be a P-gp inducer/inhibitor and/or a strong CYP3A4 inhibitor with enfortumab is not permitted.

Strong CYP3A4 Inhibitors	Boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, diltiazem, elvitegravir/ritonavir, grapefruit juice, idelalisib, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, paritaprevir/ritonavir/ombitasvir plus dasabuvir, posaconazole, ritonavir, saquinavir/ritonavir, telaprevir, tipranavir/ritonavir, telithromycin, troleandomycin, voriconazole.
P-gp Inhibitors	Azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir, ritonavir, quercetin, quinidine, ranolazine, ticagrelor, verapamil.
P-gp Inducers	Avasimibe, carbamazepine, phenytoin, rifampin, St John's wort, tipranavir/ritonavir.

Note: Any additional P-gp inducers/inhibitors or strong CYP3A4 inhibitors that are identified or become commercially available while the clinical trial is ongoing are also prohibited.

APPENDIX 11. 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 Appendix 9 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 Toxicities	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
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
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	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
10										DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D	D	D	D	D	D	D	D	D
11											DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D	D	D	D	D	D
12												DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D	D	D
13													DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	D
14														DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
15															DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
16																DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
17																	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
18																		DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
19		E = Escalate to the next higher dose																	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
20		S = Stay at the current dose																		DU	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
21		D = De-escalate to the next lower dose																			DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
22		U = The current dose is unacceptable toxic																				DU	DU	DU	DU	DU	DU	DU	DU	DU
23		MTD = 0.30																					DU	DU	DU	DU	DU	DU	DU	DU
24		Sample size = 30																						DU	DU	DU	DU	DU	DU	DU
25		Epsilon1 (ε1) = 0.05																							DU	DU	DU	DU	DU	DU
26		Epsilon1 (ε2) = 0.03																								DU	DU	DU	DU	DU
27																											DU	DU	DU	DU
28																												DU	DU	DU
29																													DU	DU
30																														DU

APPENDIX 12. COVID-19 PANDEMIC CHANGES TO STUDY CONDUCT

The table 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.

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. • Visit windows of +/- 3 days are allowed for Day 8 clinic visits (for dose expansion portion of Cohort 9 and Cohort 10).
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.

Assessment/Procedure	Change During COVID-19 Pandemic
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. For dose expansion portion of Cohort 9 and Cohort 10: • The PK collection required post-dose at 7 hours (5-9 hours) on C1D1 and C2D1 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.