Official Title of Study:

A Randomized Phase 3 Study of Sitravatinib in Combination with Nivolumab Versus Docetaxel in Patients with Advanced Non-Squamous Non-Small Cell Lung Cancer with Disease Progression On or After Platinum-Based Chemotherapy and Checkpoint Inhibitor Therapy (SAPPHIRE)

PROTOCOL(S) 516-005

NCT Number: NCT03906071

Document Date (Date in which document was last revised): 07 October 2021

MIRATI THERAPEUTICS

CLINICAL RESEARCH PROTOCOL

DRUG(S):	Sitravatinib (MGCD516) Nivolumab (OPDIVO®) Docetaxel
STUDY NUMBER:	516-005
PROTOCOL TITLE:	A Randomized Phase 3 Study of Sitravatinib in Combination with Nivolumab Versus Docetaxel in Patients with Advanced Non-Squamous Non-Small Cell Lung Cancer with Disease Progression On or After Platinum-Based Chemotherapy and Checkpoint Inhibitor Therapy (SAPPHIRE)
IND NUMBER:	141664
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SPONSOR:	Mirati Therapeutics, Inc. 3545 Cray Court San Diego, California, 92121, USA
ORIGINAL PROTOCOL DATE:	21 November 2018
VERSION NUMBER:	V5.0
VERSION DATE:	07 October 2021

DOCUMENT HISTORY

Document	Version Date	Summary of Changes
Original Protocol, Version 1.0	21 November 2018	NA
Version 2.0	30 January 2020	Title: • Protocol title updated to reflect the patient population to be enrolled in the study. Study Summary: • Revised the target population to include patients in the third-line treatment setting, post-CIT in addition to patients in the second line treatment setting based on feedback from investigators, review of treatment and clinical trial landscape and data from our ongoing Phase 2 study (MRTX-500). • Added background information on the mOS with docetaxel in the third-line treatment setting, post-CIT as per the expanded patient population to be enrolled in the study. • Replaced stratification factor of 'duration of previous CIT treatment (< 9 months vs ≥ 9 months)' with 'prior lines of therapy in the advanced setting (1 vs 2)' to align with the change in eligibility criteria allowing patients to enroll after 1st and 2nd line treatment. • Revised statistical considerations from an adaptive sample size re-estimation design to a group sequential design with one interim OS analysis for efficacy and futility and removed the interim ORR analysis resulting in a decrease in total number of patients for the study. • Added an exploratory objective to characterize the immunogenicity of nivolumab in combination with sitravatinib. Schedule of Assessments (Table 1): • Added clarification around the screening window. • Added clarification around the allowable window for Day 1 visits beyond Cycle 1 Day 1. • Added clarification around the Investigator Evaluation of Progression on most recent CIT regimen.

Document	Version Date	Summary of Changes
		• Added clarification on timepoint for Nivolumab ADA sample collection in the table and footnote #10 (per Protocol Administrative Letter dated 08 October 2019). • Added clarification on allowable window around Cycle 3 Day 1 ECHO or MUGA. • Added clarification on the collection timepoint for PRO Questionnaires in the table and footnote #13 (per Protocol Administrative Letter dated 08 October 2019). • Footnote #1: clarified timing of treatment start in relation to date of randomization. • Footnote #3: revised to indicate that the ctDNA blood sample is optional and not a mandatory assessment. • Footnote #7 and #8: clarified allowable window around the timing of safety lab assessments. • Footnote #12: clarified the timing of on-study disease evaluations to be calculated based on the calendar from the date of randomization (per Protocol Administrative Letter dated 08 October 2019). • Footnote #14: revised the reporting period for serious and non-serious immune-related AEs, the reporting period for irAES will continue until at least 100 days after the last administration of nivolumab or until subsequent immunotherapy is administered, whichever occurs earlier. Schedule of PK sample collections for Sitravatinib and triplicate ECG Assessments (Table 2) and Section 5.2.3 Nivolumab administration: • Footnote #1: clarified timing of the PK and ECG assessments in relation to dosing with sitravatinib and nivolumab on days when these are required. Section 1.1.3 Second- and Third-Line Chemotherapy for Non-Small Cell Lung Cancer: • Added background information on the mOS with docetaxel in the third-line treatment setting, post-CIT as per the expanded patient population to be enrolled in the study.

Document	Version Date	Summary of Changes
		Section 1.3.1 Sitravatinib Drug Substance: • Removed the word "salt" from the sitravatinib malate name. Sections 1.3.2 Non-clinical Data, 1.3.3 Sitravatinib Clinical Experience: • Added guidance, throughout, that the Investigator's Brochure should be referenced for current data. Section 1.3.3.3 Sitravatinib Clinical Efficacy: • Added update on preliminary efficacy data in the ongoing Phase 2 study (MRTX-500) which continues to demonstrate a robust median overall survival in a similar patient population to the population being enrolled into this study. Section 1.3.3.4 Sitravatinib Capsule Formulation Study and 5.1.1 Sitravatinib Formulation, packaging and Storage: • Removed specifics around the sitravatinib capsule properties, these will be added to the Pharmacy Manual. Section 1.3.3.5 Sitravatinib Dosing with Food: • Simplified the details around the food effect sub-study being conducted in the ongoing Phase 2 study (MRTX-500). Section 1.4 Nivolumab: • Added guidance, throughout protocol, that the current OPDIVO USPI and SmPC should be referenced for current data. Section 1.6 Docetaxel: • Added guidance, throughout protocol, that the current TAXOTERE USPI and SmPC should be referenced for current data. • Added guidance that TAXOTERE or generic equivalent (docetaxel) are acceptable for use in this study. Section 2.1.3 Exploratory Objective and 2.1.6 Exploratory Endpoints: • Addition of exploratory objective to characterize the immunogenicity of nivolumab in combination with sitravatinib.

Document	Version Date	Summary of Changes
		Section 3 Study Design: • Revised the target population to include patients in the third-line treatment setting, post-CIT in addition to patients in the second line treatment setting based on feedback from investigators, review of treatment and clinical trial landscape and data from the ongoing Phase 2 study (MRTX-500). • Replaced stratification factor of 'duration of previous CIT treatment (< 9 months vs ≥ 9 months)' with 'prior lines of therapy in the advanced setting (1 vs 2)' to align with the change in eligibility criteria allowing patients to enroll after 1st and 2nd line treatment. • Revised statistical considerations from an adaptive sample size re-estimation design to a group sequential design with one interim OS analysis for efficacy and futility and removed the interim ORR analysis resulting in a decrease in total number of patients for the study. Section 4.1 Inclusion Criteria: • Inclusion Criterion #1: added staging for metastatic and locally advanced disease for clarity. • Inclusion Criterion #2: Revised to include patients that have received 2 lines of treatment in the advanced disease setting and guidance around acceptable first and second lines of treatment in order to meet eligibility. • Inclusion Criterion #3 and #4: clarified refences to the CIT are to the most recent CIT prior to coming on study and duration of prior CIT. Section 4.2 Exclusion Criteria: • Throughout: clarified that timing for certain exclusions is in reference to date of randomization and not from treatment start for consistency. • Exclusion Criterion #9: Revised to clarify exceptions to current or prior use of immunosuppressive medications for non-immune conditions within 28 days of randomization. • Exclusion Criterion #11: Revised to clarify that treatment with antacids and /or H2 antagonist are permitted.

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		• Exclusion Criterion #16: Revised to add timeframes after each sub-criterion. • Exclusion Criterion #23: Revised to align with OPDIVO USPI guidance that breastfeeding or planning to breastfeed within 5 months following the last dose of nivolumab is exclusionary. Section 4.4 Randomization: • Revised to actual process being followed. Section 5.1.4 Sitravatinib Dose Modification or Discontinuation: • Removed language that indicated that following sitravatinib dose reduction and control of adverse event, re-challenge at a higher sitravatinib dose is permitted at the discretion of the Investigator. Section 5.2 Nivolumab Study Drug: • Revised language to indicate that nivolumab will be provided by Sponsor. Section 5.3 Docetaxel Study Drug: • Revised language to add that Docetaxel will be provided by Sponsor depending on local country requirements. • Added guidance that TAXOTERE or generic equivalent (docetaxel) are acceptable for use in this study. Section 5.3.3 Docetaxel Administration and 5.3.4 Docetaxel Dose Modification: • Added language to clarify that the initial dose (Cycle 1) of docetaxel should remain at 75 mg/m^2. Section 5.4.1.1 General Management of Non-Hematological Toxicities: • Clarified guidance for sitravatinib dose management: – Symptomatic Grade 2 sitravatinib-related non-hematological adverse events occurring any time on study, particularly early in treatment (e.g., Cycle 1 Day 15 or Cycle 2 Day 1), are recommended to be managed using dose reduction to the next lower dose level, per the reduction schedule outlined in

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		Table 3, rather than continued dosing until interruption becomes necessary. – Treatment with sitravatinib may continue without dose modification (e.g., interruption or reduction) in cases of asymptomatic amylase and/or lipase increases in the absence of other clinical evidence of pancreatitis (eg, symptoms, electrolyte abnormalities, radiographic changes) at the investigator's discretion. – Table 5 and related footnotes were updated. Section 5.4.4 Management of Hy's Law Cases: • Added clarifications with regards to when sitravatinib and nivolumab should be permanently discontinued and steroids administered. Section 5.6.1 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 antacids and /or H2 antagonist administration in relation to sitravatinib dosing. • Supportive Care/Palliative Care: added language to indicate that bisphosphonates (eg, zoledronic acid) and RANK-L inhibitors (eg, denosumab) should be initiated prior to first dose of study therapy. • Vaccines: added language to clarify that live attenuated vaccines are to be avoided within 100 days of nivolumab dosing. Section 5.6.3 Other Anticancer or Experimental Therapy: • Added language indicating that certain ongoing hormonal therapies taken to prevent recurrence of a malignancy not under study (eg, tamoxifen/aromatase inhibitor for breast cancer) may be permitted after discussion with and agreement of the Sponsor's Medical Monitor. Sections 6.3 End of Treatment Assessments, 8.4.1 Reporting Period and 9.5.1 Adverse Events: • Added language with regards to the reporting period for serious and non-serious immune-related AEs, the reporting period for irAES will continue

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		until at least 100 days after the last administration of nivolumab or until subsequent immunotherapy is administered, whichever occurs earlier. Section 7.1 Documentation of Disease Progression On or After Prior Chemotherapy and Checkpoint Inhibitor Therapy: • Clarified that refences to the CIT are to the most recent CIT prior to coming on study. Section 7.2.2 Radiographic Disease Assessments: • Removed language indicating that central radiology review would only be conducted until completion of the interim analysis for ORR based on the change in study design there will only be one interim analysis and a final analysis of the primary endpoint of overall survival, including a futility analysis. The previously planned ORR endpoint will remain as a secondary endpoint and central radiology review will continue until the completion of the study. • Per FDAs request, removed language referencing modifications to RECIST 1.1 to address potential temporary treatment effects including tumor necrosis, cavitation, flare response and pseudoprogression (per Protocol Administrative Letter dated 08 October 2019). Section 7.3.4 Electrocardiograms: • Removed language that that QTc will be manually calculated using the Fridericia's formula. Section 7.4.3.1 Circulating Tumor DNA: • Revised to indicate that the ctDNA blood sample is optional and not a mandatory assessment. Section 8.3.2 Exposure During Pregnancy: • Clarified timing around male exposure to investigational product for consistency. Section 9.1.1 Primary Efficacy Hypothesis and Section 9.1.1.1 Sample Size Determination: • Revised per revision in the study design from adaptive design to a group sequential design with one interim analysis and one final analysis, without a sample size re-estimation. Approximately 372 total OS events will be required to detect the

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		assumed HR at a 2-sided alpha 0.05 and a power of 85%. Assuming an enrollment duration of approximately 25 months and an additional 13 months of follow-up, a sample size of approximately 532 patients is planned to achieve the required number of events. Removal of Section 9.1.1.2 Interim Analysis based on OS for futility and Sample Size Readjustment and Section 9.1.2 Secondary Efficacy Hypothesis: • Per revision in the study design from adaptive design to a group sequential design with one interim analysis and one final analysis, without a sample size re-estimation. Section 9.4.2 Objective Response Rate: • Revised per revision in the study design from adaptive design to a group sequential design with one interim analysis and one final analysis, without a sample size re-estimation. Section 9.4.3 Clinical Benefit Rate: • Updated definition of Clinical Benefit Rate to align with RECIST 1.1. guidance on Stable Disease. Section 9.4.4 Duration of Response: • Updated to include censoring rules. Section 9.4.6 Subgroup Analyses: • Updated based on changes to the stratification factors and added analysis for geographic regions. Section 9.7 Interim Analysis: • Revised to reflect the change in study design. There will only be one interim analysis and a final analysis of the primary endpoint of overall survival, including a futility analysis. The previously planned ORR endpoint will remain as a secondary endpoint and central radiology review will continue until the completion of the study. Section 16 References: • Updated accordingly based on changes throughout the protocol. Appendix 4 Abbreviated Presentation of RECIST Version 1.1 Guidelines:

Document	Version Date	Summary of Changes
		• Per FDAs request, removed language referencing modifications to RECIST 1.1 to address potential temporary treatment effects including tumor necrosis, cavitation, flare response and pseudoprogression (per Protocol Administrative Letter dated 08 October 2019). Addressed clerical errors and made minor clarifications.
Version 3.0	20 April 2020	Throughout: • Addressed clerical errors and made minor clarifications. • Deletion of reference to region specific approved product labels and replaced with broader non-region specific reference to approved product labels. • Addition of sitravatinib malate capsule formulation. [Note that the free base capsule formulation will remain available in the USA; patients who start the study on the free base capsule formulation 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. Schedule of Assessments (Table 1): • Revision of "Long Term Follow Up" row to "Follow-Up" to clarify and confirm that the assessment is follow-up and an "X" added to the Initial Follow-up column. Removal of reference to footnote #17 under the Assessment column as the reference is captured in the Long Term Follow-Up column. Section 1.3.3.1 Sitravatinib Pharmacokinetics: • Addition of 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:

Document	Version Date	Summary of Changes
		• Addition of relevant studies contributing to sitravatinib's clinical safety data and update to the safety data per sitravatinib's current Investigators Brochure. Section 1.3.3.3 Sitravatinib Clinical Efficacy: • Removed outdated information. Section 1.3.3.4 Sitravatinib Capsule Formulation Study: • Addition of interim results from Study 516-006, a healthy volunteer study evaluating the bioavailability and PK of sitravatinib free base and sitravatinib malate capsule formulations. • Removal of excess information from the MRTX-500 PK sub-study in order to focus on pertinent information and streamline the document. Section 1.4.3 Nivolumab Clinical Data: • OPDIVO information updated based on USPI dated March 2020. Section 1.5.2 Evaluation of Potential for Increased Toxicity with Combination Use of Sitravatinib and Nivolumab: • Information updated based on OPDIVO USPI dated March 2020 and sitravatinib Investigator's Brochure v6.0, dated 01 November 2019. Section 1.6.3 Docetaxel Clinical Data: • TAXOTERE information updated based on TAXOTERE USPI dated December 2019. Section 1.7 Study Rationale: • Addition of starting dose information for sitravatinib malate capsule formulation. Section 3 Study Design: • Clarification around allowable window for nivolumab infusion. • Clarification regarding availability of sitravatinib free base capsule formulation only being available in the USA and addition of sitravatinib malate capsule formulation daily dose. • Clarification that patients in the USA who initiate study treatment with sitravatinib free base capsule

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		formulation will continue the study with the free base capsule formulation until study treatment discontinuation. • Addition of language defining End of Trial. Section 4.1 Inclusion Criteria: • Inclusion Criterion #11d: Clarification of ALT and AST parameters for patients with documented liver metastases Section 4.3 Live Style Guidelines: • Addition of language requiring at least 2 acceptable methods of birth control and clarification on what constitutes acceptable methods of birth control considered highly effective. Section 5 Study Treatments: • Addition of language to clarify investigational products versus non-investigational products used in this study. Section 5.1 Sitravatinib: • Introduction of the sitravatinib malate capsule formulation product. The malate formulation is more stable and has properties that are improved for future commercialization. Section 5.1.3 Sitravatinib Administration: • Addition of sitravatinib malate capsule formulation daily dose as supported by the data from study 516-006. Section 5.1.4 Sitravatinib Dose Modification or Discontinuation: • Addition of sitravatinib malate capsule formulation dose modification guidelines as supported by the data from study 516-006 and in alignment with the dose modification guidelines of the sitravatinib free base formulation. Section 5.6.1 Concomitant Medication(s): • Addition of information regarding P-gp and BCRP transporters and CYP3A4 substrates with sitravatinib to clarify information provided in Appendix 2.

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		• Addition of information regarding strong and moderate CYP3A4 inhibitors with docetaxel to clarify information provided in Appendix 3. Section 10.5 Confidentiality and Privacy Protection: • Addition of data privacy protection language for compliance with European Union General Data Protection Regulation (GDPR) data privacy regulations. Appendix 2 Medication 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. • 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 3 Examples of Strong and Moderate CYP3A4 Inhibitors: • Changed title to clarify that the lists in this section are examples and not a complete list. • Removed bold and italic font since medications listed are examples only; information regarding avoidance and use with caution of medications that are strong or moderate CYP3A4 inhibitors is provided in Section 5.6.1 Concomitant Medication(s). Appendix 5 COVID-19 Pandemic Changes to Study Conduct: • Addition of appendix allowing temporary changes to specific protocol assessments and procedures that are allowable only during the COVID-19 pandemic.
Version: 3.1(Canada) 3.2 (Spain) 3.3 (France) 3.4 (Italy) 3.5 (Belgium) 3.6 (Germany)	17 June 2020 07 July 2020 20 July 2020 20 August 2020 12 August 2020 23 September 2020	Country specific protocol amendments submitted to individual countries during the Clinical Trial Application process.

Document	Version Date	Summary of Changes
3.7 (United Kingdom)	22 September 2020	
Version 4.0	06 January 2021	This protocol amendment is intended to harmonize the country specific amendments where possible. Throughout: • Link to reference added for SmPC wherever the Opdivo and Taxotere approved product label is referenced. Section 3 Study Design • Removed "receipt of maximum number of cycles per local standard of care" as reason for discontinuation of administering treatment to patients. Section 4.1 Inclusion Criteria • Inclusion criterion #1: Added language to clarify that patients, who are eligible for concurrent radiochemotherapy are excluded • Inclusion criterion#2: clarified that for patients who received platinum-based adjuvant, neoadjuvant, or definitive chemoradiation therapy, given for locally advanced disease followed by recurrent or metastatic disease within 6 months of completing chemotherapy may be considered treatment in the advanced disease setting. • Inclusion criterion #11e: clarified the required serum bilirubin value Section 4.2 Exclusion Criteria • Exclusion criterion #6: Prior Therapies: revised to allow for prior anti-CTLA-4 administered in combination with an anti-PD-(L)1. • Exclusion criterion #24: revised to exclude patients who are unable to give consent Section 4.3 Life Style Guidelines • Added language to clarify that men with WOCBP partners must also use highly effective methods of contraception Section 5.6.1 Concomitant Medication(s) • Revised guidance for Gastric Acid Medications with Sitravatinib. Schedule of Assessments (Table 1):

Document	Version Date	Summary of Changes
		• Added pregnancy testing for women of childbearing potential, at the beginning of every cycle and maintained pregnancy testing for at least 1 month after the last dose of sitravatinib, 5 months after the last dose of nivolumab and for 1 month after the last dose of docetaxel. • Revised footnote #6, #15 and #16 to reflect the additional pregnancy testing • Revised footnote #15 to clarify the occurrence of the EOT visit Section 7.3.3 Laboratory Safety Assessments • Added language regarding the additional pregnancy testing Section 14.1 End of Trial in a European Union Member State • Revised language to clarify that End of Trial is defined as the last visit of the last patient, or at a later time point as defined in the protocol, in a Member State of the European Union. <u>For sites in Germany and Switzerland the following information was modified:</u> Schedule of Assessments (Table 1): • Added HIV, Hepatitis B, and Hepatitis C testing at screening. Section 4.2 Exclusion Criteria • Revised Exclusion Criterion 9b to exclude patients testing positive for HIV infection at screening. • Revised Exclusion Criterion 13 to exclude patients testing positive for hepatitis B or hepatitis C infection at screening. Section 7.3.3 Laboratory Safety Assessments • Added details for hepatitis B, hepatitis C, and HIV infection testing. For sites in Germany only, the following information was modified: Schedule of Assessments (Table 1): • Removed the performance of MUGA scan at screening and on study

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		Section 7.3.5 Echocardiogram or Multigated Acquisition Scan • Deleted the option of MUGA scans and revised the section heading accordingly.
Version 5.0	07 October 2021	Cover Page: • Sponsor Address updated Schedule of Assessments (Table 1): • Footnote 11 updated to reference (Table 8) Throughout: Sections 1.4.3, 1.4.3.4, 1.5.2, 1.6.3, 1.6.3.2, 5.2, 5.3, and 5.4 were updated to reflect Investigators Brochure v8.1 dated August 2021, OPDIVO USPI dated September 2021, and Docetaxel USPI dated May 2021, as applicable Section 1.4.3.3 Nivolumab Adverse Reactions in Clinical Trials • Urinary tract infection added to the list of most common adverse reactions (≥ 20%) as of September 2021 Section 1.4.3.5 Safety Reported Non-Small Cell Lung Cancer Trials Clinical Trials • The description of the patient population in the Checkmate-017 and Checkmate-057 trials was updated Section 4.2 Exclusion Criterion • Exclusion criterion 11 (need for treatment with a protocol pump inhibitor: antacids and/or H2 antagonists permitted) deleted. The numbering of the list of exclusion criteria was maintained Section 5.6.1 Concomitant Medications (s) • Language describing use of Gastric Acid Medications with Sitravatinib was deleted • Language describing the use of P-gp Inhibitors and Inducers with Sitravatinib was added Section 7.1 Documentation of Disease Progression on or After Prior Chemotherapy and Checkpoint Inhibitor Therapy

Document	Version Date	Summary of Changes
		• Clarified that radiology reports are appended to the CRF in countries where permitted by applicable laws and regulations Section 7.4.3.2 Markers in Tumor Tissue • Clarified that tumor burden reports are appended to the CRF in countries where permitted by applicable laws and regulations Section 9.4.1 Overall Survival • Language clarifying the analysis of overall survival was added Section 9.4.2 Objective Response Rate • Language clarifying the analysis of the objective response rate was added Section 9.4.4 Duration of Response Language regarding censoring of subjects in the analysis of duration of response was deleted Section 9.4.5 Progression Free Survival Language regarding censoring of subjects in the analysis of duration of response was deleted • The Language was updated for clarification Section 10.5 Confidentiality and Privacy Protection • Language justifying the collection of race and ethnicity data to support population PK analysis was added

STUDY SUMMARY

Title: A Randomized Phase 3 Study of Sitravatinib in Combination with Nivolumab Versus Docetaxel in Patients with Advanced Non-Squamous Non-Small Cell Lung Cancer with Disease Progression On or After Platinum-Based Chemotherapy and Checkpoint Inhibitor Therapy

(**SAPPHIRE**: **S**itr**A**vatinib **P**lus Nivolumab in **P**atients Refractory to C**H**emo and Checkpoint **I**nhibito**R** Th**E**rapy)

Rationale: Combining an immunotherapeutic Programmed Cell Death 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). In addition, M2 macrophages express checkpoint ligands such as PD-L1, PD-L2, B7- H1 and B7-H2 that further inhibit T effector cell function. Given that anti-tumor host defense is usually mediated by cytotoxic T lymphocytes whose activation and stimulation is supported by Th1 type cytokines, the inhibition of Axl and MERTK are predicted to enhance an anti-tumor immune response. Furthermore, both Axl and MERTK are expressed by natural killer (NK) cells and negatively regulate NK cell activity in the TME as part of a feedback regulatory mechanism resulting in decreased NK cell anti-tumor activity and enhanced tumor progression and metastasis. Given the immunosuppressive function of TAM RTKs in the TME, inhibition of Axl

and MERTK may complement PD-1/PD-L1 checkpoint inhibition to unleash the host anti-cancer immune response.

The MET (Mesenchymal-Epithelial Transition) RTK is implicated in modification of tumor immune responses based on its role in mediating an immunosuppressive TME as well as its role in regulating antigen presenting cell (APC) function. MET is expressed by immature CD14-positive monocytes and can induce an immunosuppressive phenotype when its ligand, 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 (ie, 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 T regulatory cells (Tregs) and MDSCs. Tregs express VEGFR2 and the inhibition of VEGFR2 utilizing a specific VEGFR2 antibody antagonist or VEGFA neutralizing antibody (but not a VEGFR1 antagonist) inhibited Treg cell 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 a spectrum-selective RTK inhibitor that inhibits several closely related RTKs including the TAM family (Tyro3/Axl/MERTK), VEGFR2, KIT, and MET. Based on the role of these receptors in key immune cell types, sitravatinib and checkpoint inhibitor therapy (CIT) are predicted to have complementary effects in triggering a tumor-directed immune response.

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 NSCLC who have disease progression during or following platinum-containing chemotherapy. While anti-PD-1/PD-L1 antibodies, including nivolumab, produce durable responses in some patients with NSCLC and other cancers, the majority of patients do not respond to single agent CIT or eventually progress. The mechanism of action of PD-1 inhibitors has been an area of intense research and multiple factors have emerged that correlate with resistance, including both factors intrinsic to tumor cells as well as an immunosuppressive tumor microenvironment. Combining an immunotherapeutic PD-1/PD-L1 checkpoint inhibitor with an agent that has both immune modulatory and antitumor properties could enhance the antitumor efficacy observed with either agent alone. Docetaxel is approved as a single-agent chemotherapy option for the treatment of patients with advanced NSCLC previously treated with platinum-based chemotherapy. Median overall survival reported in randomized clinical trials using docetaxel in the second-line treatment setting has varied between approximately 5.7 and 9.5 months. Median overall survival with docetaxel in the third-line treatment setting, post-CIT, is not expected to be significantly different than in the second-line setting with median overall survival of approximately 6.8 to 9.0 months reported in retrospective analyses. This study will compare the efficacy of sitravatinib in combination with nivolumab versus docetaxel in patients with advanced non-squamous NSCLC who have previously experienced radiographic disease progression on or after platinum-based chemotherapy and checkpoint inhibitor therapy.
Target Population:	Patients with non-squamous NSCLC with no known oncogenic *EGFR, ALK, or ROS-1* genomic tumor aberrations, who have radiographic disease progression on or after CIT either administered in combination with platinum-based chemotherapy or following platinum-based chemotherapy in the advanced disease setting.
Number in Trial:	Approximately 532 patients will be randomized into the study.
Primary Objective:	To compare Overall Survival (OS) in patients with non-squamous NSCLC who have experienced disease progression on or after platinum-based

	chemotherapy and CIT, treated with sitravatinib and nivolumab versus docetaxel.
Secondary Objectives:	• To evaluate the safety of sitravatinib in combination with nivolumab in the study population. • To evaluate the relative tolerability of sitravatinib and nivolumab versus docetaxel. • To evaluate secondary efficacy endpoints in the study population. • To evaluate the pharmacokinetics (PK) of sitravatinib (MGCD516) administered in combination with nivolumab. • To evaluate health-related quality of life and lung cancer-specific symptoms in the study population.
Exploratory Objective:	• To assess correlations between baseline tumor immune biomarkers and gene mutations and treatment-related outcomes. • To evaluate efficacy endpoints using exploratory disease response criteria. • To characterize the immunogenicity of nivolumab in combination with sitravatinib.
Primary Endpoint:	Overall Survival (OS)
Secondary Endpoints:	• Safety characterized by type, incidence, severity, timing, seriousness and relationship to study treatment of adverse events, laboratory abnormalities, and number of patients discontinuing study treatment due to an adverse event. • Secondary efficacy endpoints: – Objective Response Rate (ORR) as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). – Duration of Response (DOR); – Clinical Benefit Rate (CBR); – Progression-Free Survival (PFS); and – 1-Year Survival Rate. • Blood plasma concentrations of MGCD516. • Patient reported outcome (PROs): – Lung Cancer Symptom Scale (LCSS); and – European Quality of Life Five Dimensions Questionnaire (EQ-5D-5L).
Exploratory Endpoints:	• Tumor PD-L1 expression. Tumor gene alterations. • Circulating tumor deoxyribonucleic acid (ctDNA).

- Efficacy parameters as evaluated per iRECIST.
- Nivolumab anti-drug antibody (ADA)

Study Design: Study 516-005 is an open-label, randomized (1:1), multicenter, Phase 3 clinical trial evaluating the efficacy and safety of nivolumab in combination with the investigational agent sitravatinib compared to docetaxel in patients with advanced non-squamous NSCLC who have previously experienced radiographic disease progression on or after treatment with CIT either administered in combination with platinum-based chemotherapy or following platinum-based chemotherapy. The primary objective is to compare OS in the two treatment arms. Secondary objectives include evaluation of safety and tolerability, secondary efficacy endpoints, PK of sitravatinib, and patient reported outcomes. Correlative science endpoints include tumor PD-L1 expression, tumor gene mutations, nivolumab ADA and ctDNA. The Schedule of Assessments to be performed in the study is presented in Table 1.

Patient eligibility for study enrollment based on radiographic disease progression on or after treatment with CIT and platinum-based chemotherapy will be evaluated by the Investigator. Data entered into the case report form (CRF) are to include the date of at least one radiographic evaluation prior to the occurrence of disease progression on most recent CIT treatment and the date the radiographic evaluation demonstrating disease progression, as well as specifics about organ systems (eg, lung, liver, lymph node, bone and/or brain) having tumors that increase in size or are new.

Patient randomization will be stratified based on:

1. Prior treatment regimens in the advanced setting (1 versus 2);
2. ECOG Performance Status at baseline (0 versus 1); and
3. Presence of brain metastasis at baseline (presence versus absence).

Patients randomized to the experimental arm will receive treatment with nivolumab in combination with sitravatinib, delivered in 28-day cycles. Nivolumab will be administered as an infusion over approximately 30 minutes at 240 mg every 2 weeks or 480 mg every 4 weeks, at the discretion of the Investigator. Patients that are randomized under this protocol version will receive sitravatinib malate capsule formulation administered orally at starting dose of 100 mg once daily (QD). Patients enrolled in the USA who began treatment with the sitravatinib free base capsule formulation will remain on the free base capsule formulation

throughout the duration of the study; the starting dose of sitravatinib free base capsule formulation is 120 mg QD.

Patients randomized to the comparator arm will receive treatment with docetaxel, delivered in 21-day cycles. Docetaxel will be administered by intravenous infusion at 75 mg/m^2 over 1 hour or according to institutional practices, every 3 weeks. Premedication with dexamethasone (or institutional equivalent) will be required in accordance with regional standards.

Disease assessments and patient-reported outcomes questionnaires must be performed as scheduled according to the calendar to prevent the introduction of bias based on toxicity into the assessment of efficacy. Disease response and progression per RECIST 1.1 as documented by the Investigator in the CRF will be the basis for patient management and supportive statistical analyses of radiology-based study endpoints.

Central radiology review for disease response and progression will be conducted. Timely and complete disease assessments and transfer of radiographic documentation to the Central Radiology Laboratory is critical to the integrity of this clinical trial.

Patients will receive study treatment as assigned at randomization until disease progression, unacceptable adverse events, investigator decision, 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 1.1 defined disease progression must be provided with and sign an informed consent detailing any available therapies and potential clinical benefit that the patient may be foregoing by continuing study treatment. Patients remaining on study treatment beyond RECIST 1.1. defined progression will continue to undergo disease assessments until study treatment is discontinued. Post- treatment disease assessment will continue until objective disease progression and PRO assessments will continue until start of subsequent anti-cancer therapy. No crossover to the alternative treatment assignment is provided in this study.

A sample size of approximately 532 patients is planned for this study; a total of 372 OS events will be required to detect the hypothesized HR. The study will employ a group sequential design with one planned interim analysis and a final analysis for the primary endpoint of OS.

Table 1: Schedule of Assessments

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	Nivo/Sitra Arm Cycles 1 and 2 Doce Arm Cycles 1, 2 and 3		Nivo/Sitra Arm ≥Cycle 3 Doce Arm ≥Cycle 4		Post Treatment		
	Within 28 days of randomization	Day 1 (± 2 days beyond C1)	N/S Arm Day 15 Doce Arm Day 8 (± 2 days)	Day 1 (± 2 days)	N/S Arm Day 15 (± 2 days) Necessary only if Nivolumab Q2W	End of Treatment[1] (28-35 days after last dose)	Initial Follow-up[2]	Long Term Follow-up[3]
Study Participation Informed Consent[4]	Before study specific assessments							
Randomization[4]	X							
Medical History, Disease History, Prior Therapy	X							
Investigator Evaluation of Radiographic Progression on most recent CIT regimen	X							
Tumor Tissue Collection for PD-L1 Expression and Tumor Gene Alterations[5]	X							
ctDNA Blood Sample[6]	X							
ECOG Performance Status	X	Cycle 3 only		Cycle 3 only		X		
Physical Exam[7]	X					X		
Abbreviated Physical Exam[7]		X	X	X	X			

Table 1: Schedule of Assessments (Continued)

Assessments	Screen/ Baseline	Nivo/Sitra Arm Cycles 1 and 2 Doce Arm Cycles 1, 2 and 3		Nivo/Sitra Arm ≥Cycle 3 Doce Arm ≥Cycle 4		Post Treatment		
	Within 28 days of randomization	Day 1 (± 2 days beyond C1)	N/S Arm Day 15 Doce Arm Day 8 (± 2 days)	Day 1 (± 2 days)	N/S Arm Day 15 (± 2 days) Necessary only if Nivolumab Q2W	End of Treatment[1] (28-35 days after last dose)	Initial Follow-up[2]	Long Term Follow-up[3]
Vital Signs[8]	X	X	X	X	X	X		
Pregnancy Test[9]	X	X		X		X	X	
Hematology[10,11]	X	X	X	X		X		
Urinalysis[10,11]	X	As clinically indicated						
Serum Chemistry[10,11]	X	X	X	X		X		
Thyroid Function Test[10,11]		X		X		X		
HIV, HBV, HCV serology[12]	X							
Blood for Sitravatinib PK[13]		See Table 2						
Blood for Nivolumab ADA[14]		X (Cycle 1 Day 1)		Coincide with disease evaluations and continue at the same intervals until either at least 80 days after last dose of nivolumab or start of subsequent therapy, whichever is sooner				
Single 12-Lead ECG[15]	X	As clinically indicated				X		
Triplicate 12-Lead ECG[15]		See Table 2						
ECHO (preferred) or MUGA[16]	X (-35 Day Window)	Cycle 3 Day 1 only (± 7 days) As clinically indicated after C3				X		
Disease Evaluation[17]	X	Every 8 weeks (± 10 days) for ~12 months and then every 16 weeks until disease progression or start of subsequent therapy, whichever is sooner						

Table 1: Schedule of Assessments (Continued)

Assessments	Screen/ Baseline	Nivo/Sitra Arm Cycles 1 and 2 Doce Arm Cycles 1, 2 and 3		Nivo/Sitra Arm ≥Cycle 3 Doce Arm ≥Cycle 4		Post Treatment		
	Within 28 days of randomization	Day 1 (± 2 days beyond C1)	N/S Arm Day 15 Doce Arm Day 8 (± 2 days)	Day 1 (± 2 days)	N/S Arm Day 15 (± 2 days) Necessary only if Nivolumab Q2W	End of Treatment[1] (28-35 days after last dose)	Initial Follow-up[2]	Long Term Follow-up[3]
PRO Questionnaires[18]		X (Cycle 1 Day 1)	Coincide with disease evaluations and continue at the same intervals until start of subsequent therapy					
Sitravatinib Dispensing and/or Reconciliation		X		X		Reconciliation		
Nivolumab Administration		Throughout as directed in product label and protocol						
Docetaxel Administration		Throughout as directed in product label and protocol, including standard-of-care pre-medication						
Adverse Events[19] and Concomitant Medications	SAEs only	Throughout						
Follow-Up							X	X

[1] End of Treatment: Visit occurs prior to the beginning of subsequent anticancer therapy or 28-35 days after last dose of study treatment (sitravatinib, nivolumab or docetaxel), whichever is earlier. Assessments completed in the previous 4 weeks do not need to be repeated with the exception of assessment of AEs, hematology and chemistry.

[2] Initial Follow-up: If study treatment is discontinued prior to disease progression, disease assessments should continue every 8 weeks ± 10 days (or 16 weeks ± 10 days if on treatment more than 1 year) until either progression of disease or start of subsequent therapy, whichever occurs earlier. PRO assessments should continue every 8 weeks ± 10 days (or 16 weeks ± 10 days if on treatment more than 1 year) until start of subsequent therapy. For patients randomized to sitravatinib/nivolumab, blood sampling for ADA assessment should be collected either at least 80 days after the last dose of nivolumab or immediately before start of subsequent therapy, whichever occurs earlier. Survival status and subsequent therapies will be collected. Women of childbearing potential will complete pregnancy testing at a monthly frequency, which will be maintained for at least 1 month after the last dose of sitravatinib, 5 months after the last dose of nivolumab and for 1 month after the last dose of docetaxel.

[3] 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. Long-term follow-up may be performed by telephone contact or email.

[4] Study Participation Informed Consent: May be performed more than 28 days prior to randomization and must be completed prior to initiation of any study specific assessments. Treatment should start within 3 business days of randomization.

[5] Tumor Testing for PD-L1 Expression and Tumor Gene Alterations: Submission of pre-study tumor samples is highly desirable but not mandatory for study participation. 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.

[6] Blood samples for ctDNA analysis is highly desirable but not mandatory for study participation: Blood will be collected in two 10 mL Streck brand Cell-Free DNA Blood Collection tubes allowing shipping and stability at ambient temperatures.

[7] 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.

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

[9] 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. Pregnancy testing will also be performed at the beginning of every treatment cycle and the same frequency (approximately monthly) will be maintained for at least 1 month after the last dose of sitravatinib, 5 months after the last dose of nivolumab and for 1 month after the last dose of docetaxel. 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.

[10] Selected Day 1 Assessments: Repeat assessment not required if screening assessment performed within 7 days before the first dose. Thyroid function test can also be performed within 7 days before first dose.

[11] Safety Laboratory Assessments: Hematology, chemistry, thyroid function and urinalysis evaluations (see Table 8) will be performed by local laboratories. Lab assessments may be performed up to 3 days prior to clinic visits.

[12] Sites in Germany and Switzerland only: Patients must be tested for HIV, hepatitis B virus (HBV) and hepatitis C virus (HCV) infection (by local laboratory) at screening. Patients testing positive for HIV infection are excluded from study. Patients with active hepatitis B (acute or chronic) defined as a positive HBsAg test result are excluded from study; patients with past or resolved HBV infection (defined as HBsAg negative and HBcAb positive) are eligible only if their HBV DNA test is negative. Patients with positive hepatitis C antibody test during screening are excluded from study unless HCV RNA is negative.

[13] Pharmacokinetic Samples: In patients randomized to sitravatinib/nivolumab, blood samples to be collected following ECGs and assessment of vital signs as scheduled in Table 2. In addition, unscheduled PK blood samples should be drawn before a daily sitravatinib dose (trough sample) in association with two kinds of safety events: 1) as soon as possible after a Serious Adverse Event (SAE), and 2) at a clinic visit at least one week following a dose modification of sitravatinib.

[14] Nivolumab Anti-Drug Antibody (ADA) Samples: In patients randomized to sitravatinib/nivolumab, blood sampling for ADA assessment will occur on C1D1 prior to the first dose of nivolumab on study, during study treatment to coincide with disease assessments, and continue at the same intervals until at least 80 days after last dose of nivolumab or start of subsequent therapy, whichever is sooner.

[15]12-Lead ECGs: In patients randomized to sitravatinib/nivolumab, 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.

[16]MUGA option is not available for sites in Germany.

[17]Disease Evaluations: To be performed at screening (28-day window allowed) and every 8 weeks from Randomization (± 10-day window for all other assessments except screening) until week 49 (~12 months) and then every 16 weeks until objective disease progression or start of subsequent therapy. All on-study disease evaluations should be based on a calendar beginning from the date of randomization. At screening/baseline, assessments are to include Computed Tomography Scan (CT) with contrast of the chest, CT or Magnetic Resonance Imaging (MRI) of the abdomen and pelvis, as well as brain MRI with and without gadolinium or CT with contrast, a whole-body bone scan (or Positron Emission Tomography (PET) or PET/CT if local standard for clinical trials) and evaluation of any superficial lesions. Subsequent disease assessments should include CT of the chest, CT or MRI of the abdomen and all sites of disease identified at baseline by the investigator or central review laboratory or, suspected to have developed; bone scans may be performed half as often (every 16 weeks) as other radiology evaluations and, in patients having lesions at baseline, should be performed during assessment for confirmation of disease response. Materials to be forwarded for independent central radiology review will include all imaging studies performed at screening/baseline and on-study until notified otherwise by the Sponsor. More detailed guidance on exceptional circumstances is provided in Section 8.2 and Appendix 4.

[18]Patient Reported Outcomes: EQ-5D-5L should always be completed before LCSS and both should be completed prior to other assessments performed during a visit. PRO assessments are to be completed on C1D1 prior to any assessments, then coincide with disease evaluations and continue at the same intervals until start of subsequent therapy; if the disease evaluation does not coincide with a clinic visit, the PRO should be completed at the clinic visit closest to the disease evaluation.

[19]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. The reporting period for serious and non-serious immune-related AEs (irAEs) will continue until at least 100 days after the last administration of nivolumab or until subsequent immunotherapy is administered, whichever is earlier.

Table 2: Schedule of PK Sample Collection for Sitravatinib and Triplicate ECG Assessments

	Screen/ Baseline	**Cycle 1 Day 1**				**Cycle 1 Day 15 (± 2 days)**		**Cycle 2, 3, 5 Day 1 only (± 2 days)**
Collection Time and Allowable Window	**Within 28 days of randomization**	**Pre-dose (-0.5-0 hour)**		**30 min (± 10 min)**	**5 hours[1] (± 2 hours)**	**Pre-dose (-0.5-0 hour)**	**5 hours (± 2 hours)**	**Pre-dose (-0.5-0 hour)**
PK Sample[2,3]		X		X	X	X	X	X
Triplicate ECG[1]		X (-1 hour)	X (-0.5 hour)		X	X	X	X

[1] 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 (eg, 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)

[2] Scheduled vital signs and triplicate ECGs precede PK sample collection. Sitravatinib dosing should precede nivolumab infusion. Nivolumab infusion can be administered any time after oral dose of sitravatinib is administered, except on C1D1 where the 30 min post sitravatinib dose PK sample has to be collected before the nivolumab infusion.

[3] In addition to the scheduled samples, an unscheduled PK blood sample should be drawn before a daily sitravatinib dose (trough sample) as soon as possible after a Serious Adverse Event (SAE), and at a clinic visit at least one week following a dose modification of sitravatinib.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
APC	Antigen Presenting Cells
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BCRP	Breast Cancer Resistance Protein
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
Ctrough	Trough Concentration
ctDNA	Circulating Tumor Deoxyribonucleic Acid
DDI	Drug-Drug Interaction
DLT	Dose Limiting Toxicity
DR	Duration of Response
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EIU	Exposure In-Utero
EQ-5D-5L	European Quality of Life Five Dimensions Questionnaire
FDA	Food and Drug Administration

LIST OF ABBREVIATIONS (Continued)

Abbreviation	Definition
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HDPE	High-Density Polyethylene
hERG	human Ether-a-go-go Related Gene
HGF	Hepatocyte Growth Factor
hr	Hour
HR	Hazard Ratio
IB	Investigator's Brochure
IC_{50}	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IFN-γ	Interferon Gamma
IgG4	Immunoglobulin G4
IND	Investigational New Drug
irAE	Immune-related Adverse Event
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine Device
kg	Kilogram
LCSS	Lung Cancer Symptom Scale
LVEF	Left Ventricular Ejection Fraction
mAb	Monoclonal Antibody
MDSC	Myeloid-Derived Suppressor Cell
MedDRA	Medical Dictionary for Regulatory Activities
MET	Mesenchymal-Epithelial Transition
mg	Milligram
mins	Minutes
mL	Milliliter
MMRM	Mixed Effect Model Repeated Measurement

LIST OF ABBREVIATIONS (Continued)

Abbreviation	Definition
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MSCs	Mesenchymal Stem Cells
MUGA	Multigated Acquisition Scan
NCI	National Cancer Institute
NE	Not Evaluable
NGS	Next Generation Sequencing
NK	Natural Killer
NPCB	No Prior Clinical Benefit
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
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
PET	Positron Emission Tomography
PFS	Progression-Free Survival
P-gp	P-glycoprotein
PK	Pharmacokinetics
PKAP	Pharmacokinetic Analysis Plan
PK/PD	Pharmacokinetic/Pharmacodynamic
PR	Partial Response
PRO	Patient Reported Outcome
Q2W	Every 2 Weeks
QD	Once Daily
QTc	Corrected QT Interval
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
RTKs	Receptor Tyrosine Kinases

LIST OF ABBREVIATIONS (Continued)

Abbreviation	Definition
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	System Organ Class
SUSAR	Suspected, Unexpected Serious Adverse Reaction
TAM	Tyro3, Axl and MERTK
TB	Total Bilirubin
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
TKIs	Tyrosine Kinase Inhibitors
TMB	Tumor Mutation Burden
TME	Tumor Microenvironment
Tregs	T Regulatory Cells
ULN	Upper Limit of Normal
WHO	World Health Organization
WOCBP	Women of Child Bearing Potential
µg	Microgram
µM	Micromolar
USA	United States of America
USPI	US Prescribing Information

1. INTRODUCTION AND RATIONALE

1.1. Disease and Therapeutic Strategy

1.1.1. Non-Small Cell Lung Cancer

Lung cancer remains the leading cause of cancer-related death worldwide, with GLOBOCAN estimating approximately 2.1 million new cases diagnosed in 2018 and approximately 1.76 million deaths attributed to lung cancer (Bray, 2018). Non-small cell lung cancer accounts for approximately 83% of lung cancer cases (Noone, 2018), of which approximately half are classified as adenocarcinoma of the lung; squamous cell carcinoma accounts for approximately one-quarter of NSCLC cases and large cell carcinoma is infrequently diagnosed.

1.1.2. First-Line Chemotherapy for Non-Small Cell Lung Cancer

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

1.1.3. Second- and Third-Line Chemotherapy for Non-Small Cell Lung Cancer

Docetaxel and pemetrexed are approved chemotherapy options in patients previously treated with platinum-based chemotherapy. Median OS reported in randomized clinical trials using these single agents as experimental or comparator therapies has varied between approximately 5.7 and 9.5 months and ORR between 5.5 and 12% (Shepherd, 2000), (Hanna, 2004), (Krzakowski, 2010), (Al-Saleh, 2012), (Scagliotti, 2009), (Tomasini, 2016). The benefits of docetaxel in particular are associated with considerable toxicity. Several studies evaluating docetaxel and pemetrexed within clinical trials of CITs are discussed in the Section 1.1.5.

Landmark clinical trials established docetaxel and pemetrexed as standard-of-care single-agent chemotherapy regimens for patients with NSCLC previously treated with platinum-based

chemotherapy. In a Phase 3 trial in patients with advanced or metastatic NSCLC who had previously been treated with platinum-based chemotherapy, 1:1 randomization to docetaxel or best supportive care was planned; the dose of docetaxel was decreased during the study, resulting in groups treated with docetaxel 100 mg/m^2 (n=49), docetaxel 75 mg/m^2 (n=55) or best supportive care (n=100) (Shepherd, 2000). Median survival was 7.0 months in the combined docetaxel arms versus 4.6 months for the control arm (p= 0.047); the difference in OS was more significant for docetaxel 75 mg/m^2 (7.5 versus 4.6 months; p=0.010). Among 84 patients with measurable disease treated with docetaxel, the ORR was 7.1%, with 3 patients having a response at each dose level. Median DOR was approximately 6 months. Febrile neutropenia occurred in 11 patients treated with docetaxel 100 mg/m^2, three of whom died, and in one patient treated with docetaxel 75 mg/m^2. With the exception of diarrhea, Grade 3 or 4 nonhematologic toxicity occurred at a similar rate in the 3 study arms. A Phase 3 trial comparing docetaxel 100 mg/m^2 (n=125), or docetaxel 75 mg/m^2 (n=125), to control single agent chemotherapy (vinorelbine or ifosfamide) (n=123) reported ORR of 10.8, 6.7%, and 0.8% in the treatment arms, respectively, and median DOR of 7.5 and 9.1 months, in the docetaxel arms, respectively (Fossella, 2000).

In a Phase 3 study evaluating the efficacy and toxicity of pemetrexed versus docetaxel in patients with advanced NSCLC previously treated with chemotherapy, patients received treatment with pemetrexed 500 mg/m^2 (n=283) or docetaxel 75 mg/m^2 (n-288) (Hanna, 2004). OS was 8.3 versus 7.9 months (not significant) for pemetrexed and docetaxel, respectively, and ORR was 9.1% versus 8.8%. Median PFS was 2.9 months in both arms. Grade 3 or 4 neutropenia was more common in the docetaxel group (40.2% v 5.3%), as were SAEs related to neutropenia. Treatment with pemetrexed resulted in similar efficacy outcomes, but with significantly fewer side effects compared with docetaxel, particularly AEs related to neutropenia. Based on comparable results in efficacy endpoints and a more favorable safety profile, pemetrexed received accelerated approval as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC who had received prior chemotherapy (Cohen, 2005), which was subsequently limited to NSCLC with non-squamous histology (Cohen, 2009).

Based on emerging evidence of differential expression of thymidylate synthase, the primary target of pemetrexed, between adenocarcinoma and squamous cell carcinoma of the lung, a retrospective analysis based on tumor histology was conducted (Scagliotti, 2009). The study included 399 patients with non-squamous cell NSCLC and 172 patients with squamous-cell NSCLC. In patients with non-squamous histology, the median OS was 9.3 months with pemetrexed versus 8.0 months for docetaxel (adjusted HR 0.78).

On the contrary, in patients with squamous-cell histology, the median OS was 6.2 months with pemetrexed versus 7.4 months for docetaxel (adjusted HR 1.56). ORR with pemetrexed was 11.5% versus 9.0% for patients with non-squamous cell NSCLC versus squamous-cell carcinoma.

The treatment landscape of NSCLC is rapidly changing with the approvals of CIT in the first- and second-line settings (see Section 1.1.5). Consensus on the appropriate treatment of NSCLC in the third-line setting is lacking (Planchard, 2019), (NCCN, 2019). However, single-agent

chemotherapy is commonly used in the third-line, with docetaxel, gemcitabine, vinorelbine, and pemetrexed most frequently administered (Davies, 2017). Median overall survival for docetaxel administered as third-line treatment of NSCLC has been reported as approximately 6.8 to 9.0 months based on retrospective analyses (Costantini, 2018), (Park, 2018), (Schvartsman, 2017).

1.1.4. 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 interferon gamma (IFN-γ). 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. PD-L1 expression in tumor, including in lung cancer, has been associated with poor survival motivating the development of PD-1 pathway inhibitors (Mu, 2011).

1.1.5. Checkpoint Inhibitor Therapy in Non-Small Cell Lung Cancer

Three CITs have been proven to be effective in the treatment of advanced NSCLC, nivolumab, pembrolizumab and atezolizumab.

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. Nivolumab is approved by the US Food and Drug Administration (FDA) for the treatment of patients with metastatic NSCLC with progression during or after platinum-based chemotherapy. A randomized Phase 3 trial (CHECKMATE-057) of nivolumab versus docetaxel was conducted in patients with non-squamous NSCLC that had progressed during or after platinum-based doublet chemotherapy. The primary endpoint was OS. Patients received 3 mg/kg of nivolumab (n=292) by intravenous infusion Q2W or docetaxel (n=290) administered intravenously at 75 mg/m^2 every 3 weeks (Q3W). Median survival was 12.2 months for nivolumab as compared to 9.4 months for docetaxel (HR 0.73, p-value 0.002). Progression-free survival was longer for docetaxel compared to nivolumab, median 4.2 months vs 2.3 months, respectively (HR 0.92, p-value 0.39). ORR was 19% for nivolumab and 12% for docetaxel, with median DOR of 17.2 months for nivolumab and 5.6 months for docetaxel (Borghaei, 2015). Nivolumab was also evaluated in a Phase 3 clinical trial (CHECKMATE-017) in patients with squamous NSCLC that had progressed during or after one prior platinum-based doublet chemotherapy regimen. The primary endpoint was OS. Patients received 3 mg/kg of nivolumab (n=135) by intravenous infusion Q2W or docetaxel (n=137) administered intravenously at 75 mg/m^2 Q3W. Median survival was 9.2 months for nivolumab as compared to 6.0 months for docetaxel (HR 0.59, p-value 0.0002) (Brahmer, 2015). Nivolumab was approved in the US in March 2015 for squamous NSCLC and October 2015 for non-squamous NSCLC.

Pembrolizumab is a humanized mAb that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. In a large Phase 1 clinical trial, pembrolizumab was given to 495 patients

with advanced NSCLC to evaluate safety, side-effect profile, and antitumor activity (Garon, 2015). Patients (some of whom had received previous therapy and some of whom had not) were treated with various doses and regimens of pembrolizumab. Pembrolizumab had an acceptable side-effect profile and showed anti-tumor activity. Among all patients, the objective response rate was 19.4%, and the median DOR was 12.5 months. The median duration of PFS was 3.7 months, and the median duration of OS was 12.0 months. A Phase 2/3 study randomized patients with advanced or metastatic NSCLC previously treated with a platinum-based chemotherapy and PD-L1 expression tumor proportion score of 1% or greater into three treatment arms: pembrolizumab 2 mg/kg (n=345), pembrolizumab 10 mg/kg (n = 346) or, docetaxel 75 mg/m^2 (n=343). Median OS was 10.4, 12.7 and 8·5 months in the three arms, respectively. The hazard ratio (HR) for pembrolizumab 2 mg/kg versus docetaxel was 0.71 (p-value 0.0008), and for 10 mg/kg versus docetaxel was 0.61 (p-value < 0·0001). Median PFS was approximately 4 months in each treatment arm. ORR was 18 and 19% in the pembrolizumab treated arms and 9% in the docetaxel arm, with median DOR not reached with median follow-up greater than 13 months for pembrolizumab and 6 months for docetaxel (Herbst, 2016). Keytruda® (pembrolizumab) was approved by the FDA in October 2015 for the treatment of patients with metastatic squamous or non-squamous NSCLC with progression on or after platinum-based chemotherapy. Subsequently, a Phase 3 trial of pembrolizumab versus standard chemotherapy in patients with untreated, advanced NSCLC characterized by ≥ 50% tumor PD-L1 expression demonstrated an advantage for pembrolizumab. Improvement was reported across multiple efficacy endpoints including survival, along with a favorable safety profile (Reck, 2016), leading to US approval of pembrolizumab in the first-line treatment setting in this patient population. More recently, the combination of pembrolizumab with a platinum-based doublet chemotherapy regimen demonstrated an OS advantage as compared to chemotherapy plus placebo in the first-line, advanced disease treatment setting (Gandhi, 2018).

Atezolizumab is a humanized mAb against PD-L1 and blocks the interaction between PD-L1 and its receptor PD-1. A Phase 3 trial enrolled 1225 patients with advanced or metastatic NSCLC who had previously received platinum-based chemotherapy. Patients were randomized to receive atezolizumab 1200 mg or docetaxel 75 mg/m² Q3W. The primary analysis was conducted in the first 850 patients enrolled. Median OS was 13.8 months in the atezolizumab arm versus 9.6 months in the docetaxel arm (HR 0.73, p=0·0003). Overall results in secondary efficacy endpoints included median PFS 2.8 months versus 4.0 months, ORR 14% versus 13%, and DOR 16.3 versus 6.2 months (HR 0.34, p<0.0001) in the atezolizumab versus docetaxel treatment arms, respectively (Rittmeyer, 2017). Atezolizumab was approved in the US in April 2017 for patients with NSCLC who have disease progression on or after platinum-based chemotherapy.

Despite the advances with CIT, most patients with advanced NSCLC have incurable disease; additional, effective treatment options are needed, particularly after failure of a platinum-based chemotherapy regimen and resistance to CIT.

Combining an immunotherapeutic PD-1/PD-L1 checkpoint inhibitor with an agent that has both immune modulatory and antitumor properties and targets the molecular and cellular mechanisms of resistance to CIT may improve outcomes by overcoming resistance to CIT.

1.2. Overall Rationale for the Proposed Combination Regimen

Immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway have demonstrated efficacy across a range of cancer types, including non-small cell lung cancer (Brahmer, 2015), (Borghaei, 2015), (Garon, 2015), (Herbst, 2016), (Reck, 2016), (Gandhi, 2018), (Rittmeyer, 2017). While this therapy leads to durable clinical responses in a subset of patients, strategies to improve its clinical efficacy and overcome innate or acquired resistance to checkpoint inhibitor monotherapy are needed. Combination therapy with agents that target the molecular and cellular mechanisms of resistance to CIT is a rational approach to improving outcomes in these patients.

Resistance mechanisms have been described based on fundamental knowledge of the immune system as well as emerging clinical data. Expression of PD-L1 appears to correlate with response in multiple clinical studies (Herbst, 2014), (Tumeh, 2014). In the TME, PD-L1 can be upregulated in tumor cells via oncogenic signaling or in response to immune stimulatory factors such as IFN-γ. Therefore, the absence of PD-L1 expression may reflect a tumor cell population and microenvironment with a suppressed immune response. A potentially related state termed immunological ignorance is characterized by a near complete absence of immune markers in the tumor. Tumors harboring a non-functional immune response or an excluded immune cell infiltrate represent additional cellular patterns found associated with resistance to checkpoint inhibition (Herbst, 2014). Several immune cell types normally function to suppress immune responses, are often found in abundance in cancer, and may underlie resistance mechanisms to checkpoint blockade (Vanneman, 2012). T Regulatory 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 TME and increase the effectiveness of PD-1/PD-L1 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 enhance or restore anti-tumor immunity when combined with nivolumab, a CIT.

1.3. Sitravatinib

Sitravatinib is a spectrum-selective RTK inhibitor that inhibits several closely related RTKs including the TAM family (Tyro3/Axl/MERTK), VEGFR2, KIT, and MET. Receptor tyrosine kinases 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

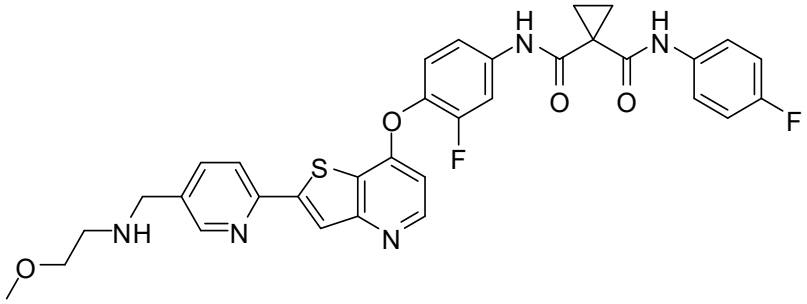
sitravatinib increases the proliferation and fraction of systemic/spleen CD4+ and CD8+ T lymphocytes and reduces the number of systemic MDSCs. Additional studies to investigate the effects of sitravatinib in the TME are ongoing or planned.

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

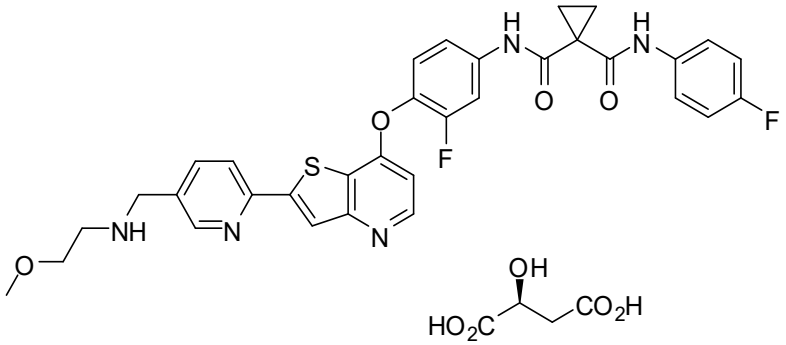
1.3.1. Sitravatinib Drug Substance

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

Sitravatinib (MGCD516) Free Base



Sitravatinib (MGCD516) L-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. Non-Clinical Data

Sitravatinib demonstrated potent, concentration-dependent inhibition of the kinase activity of MET, Axl, MERTK, VEGFR family, PDGFR family, KIT, FLT3, Trk family, RET, DDR2, and selected Eph family members in biochemical assays and inhibited phosphorylation and kinase

dependent function in cell-based assays. Sitravatinib also inhibited oncogenic functions associated with target RTKs including MET-dependent cell viability and migration and endothelial tube formation and angiogenesis. Consistent with this anti-tumor and anti-angiogenic mechanism of action, sitravatinib demonstrated anti-tumor efficacy over a broad spectrum of human tumor xenograft models including robust cytoreductive anti-tumor activity in a subset of models exhibiting genetic alterations in RTK targets including MET, RET, FLT3 and others.

In vitro results from the hERG (human Ether-a-go-go Related Gene) assay demonstrate a half maximal inhibitory concentration (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 (528 and 951 μg/mL), respectively; these values are much higher than the systemic steady state exposure levels observed clinically (C_{trough} of 68 ng/mL).

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. 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 messenger ribonucleic acid (mRNA) levels, or CYP3A4 activity. However, MGCD516 (up to 3 and 10 μM, 1889 and 6297 ng/mL) 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. Sitravatinib is not expected to act as a CYP enzyme inducer at the concentration levels observed clinically.

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. These IC_{50} values are higher than observed MGCD516 concentration levels using the recommended sitravatinib dose of 120 mg QD. It is therefore unlikely that inhibition of the cytochrome P450 enzymes tested will be observed during clinical use of sitravatinib.

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.

For additional non-clinical information, refer to the current Sitravatinib Investigator's Brochure.

1.3.3. Sitravatinib Clinical Experience

1.3.3.1. Sitravatinib Pharmacokinetics

Complete and updated information concerning sitravatinib pharmacokinetics is available in the Investigator's Brochure. After single dose administration of sitravatinib free base capsules, MGCD516 reaches peak concentration in a median time of approximately 3 to 8 hours. Exposure parameters (maximum concentration [C_{max}] and area under the curve [AUC]) were approximately dose proportional with single doses up to 200 mg. Median elimination half-life varies between approximately 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 1.2 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 nivolumab 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 inhibitor nivolumab (MRTX-500, 516-002, and 516-003), and combination studies with the PD-1 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, 516-001 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 segment of the study evaluated sitravatinib dose levels between 10 mg and 200 mg administered QD. Dose limiting toxicities were reported in 4 patients and included Grade 3 palmar-plantar erythrodysesthesia at 80 mg, and intolerable Grade 2 neuropathy, intolerable Grade 2 fatigue, and intolerable Grade 2 mucositis at 200 mg. 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 progression of disease on or after treatment with a checkpoint inhibitor (CIT-experienced) as well as those who have experienced disease progression after treatment with platinum-based doublet chemotherapy (CIT-naïve) are enrolled. The primary objective is to evaluate the clinical activity of the combination study treatments using ORR in accordance with RECIST 1.1. Secondary objectives include evaluation of safety, secondary efficacy endpoints, and PK for the investigational agents. The study began with a lead-in safety evaluation of sitravatinib in combination with nivolumab administered by intravenous infusion, 240 mg Q2W. The starting dose for sitravatinib was 120 mg administered orally, once daily, in 28-day cycles. No protocol defined DLTs were reported in the first 6 evaluable patients treated at the sitravatinib starting dose 120 mg daily in combination with nivolumab administered by intravenous infusion, 240 mg Q2W. Based on the experience of patients enrolled into Studies 516-001 and MRTX-500, 120 mg daily was selected as the 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.

Dose-limiting toxicities (DLTs) with single-agent administration of sitravatinib in Study 516-001 included Grade 3 palmar-plantar erythrodysesthesia (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 every 2 weeks [Q2W]) and sitravatinib (120 mg QD).

Sitravatinib-related adverse events (AEs) reported in ≥20% of 186 patients treated with sitravatinib monotherapy were diarrhea (50%), fatigue (42%), hypertension (39%), nausea (29%), decreased appetite (27%), vomiting (24%), and PPE syndrome (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%).

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, palmar-plantar erythrodysesthesia (PPE) syndrome, 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 AEs in Section 5.4.1.

1.3.3.3. Sitravatinib Clinical Efficacy

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

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.

Patients enrolled into the prior clinical benefit (PCB) stratum of MRTX-500 are the most similar, and relevant, to the patients eligible for Study 516-005. Patients in the PCB stratum have experienced clinical benefit (RECIST confirmed CR or PR or stable disease for at least 12 weeks) on their prior CIT. Updated data as of 04 September 2019 included 79 patients enrolled into the PCB stratum of MRTX-500. 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 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 1.2 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), (CPMP, 1998).

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.

1.3.3.5. Sitravatinib Dosing with Food

An evaluation of sitravatinib PK in the fed state is being conducted as a sub-study within Study MRTX-500. The potential to administer sitravatinib in the fed or fasted state is being investigated to provide flexibility and convenience for future patients enrolling in sitravatinib clinical trials. The sub-study includes dedicated patient cohorts for each formulation evaluated. Patients eligible for the sub-study will have locally advanced, unresectable or metastatic non-squamous NSCLC and will have experienced progression of disease on or after treatment with a CIT. The definition of the fed state for the purpose of this sub-study is consumption of a high fat meal at the time of sitravatinib dosing.

The sub-study will begin with a 7-day lead-in period comprised of a single dose of the assigned sitravatinib formulation followed by sample collection for PK analysis over a 168-hour period. Upon completion of the lead-in period, patients will begin Cycle 1 Day 1 of study treatment as described in the main part of the MRTX-500 study, using the assigned sitravatinib formulation and dose taken with food, in combination with nivolumab. On Cycle 1 Day 15, a steady-state PK profile of sitravatinib administered with a high-fat meal will be evaluated with sample collection over a 24-hour period.

Results of this MRTX-500 sub-study will recommend whether the requirement to administer sitravatinib capsules in the fasted state can be eliminated, as described in Section 5.1.3.

1.4. Nivolumab

Nivolumab (OPDIVO®) is a human mAb 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 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 approved product label (USPI, SmPC).

1.4.1. Nivolumab Drug Substance

Generic Name: Nivolumab

Other Name: OPDIVO®

Molecular Weight: 146 kDa

1.4.2. Nivolumab Non-Clinical Data

The non-clinical experience is described in the current OPDIVO approved product label (USPI, SmPC).

1.4.3. Nivolumab Clinical Data

The following reports information included in the OPDIVO USPI dated September 2021. Refer to the current OPDIVO approved product label (USPI, SmPC) 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 every 2 or 3 weeks 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 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 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 lactate dehydrogenase (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 greater than 1 to 1.5 times ULN and any AST) or moderate hepatic impairment (TB greater than 1.5 to 3 times ULN and any AST). Nivolumab has not been studied in patients with severe hepatic impairment (TB greater than 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 in Clinical Trials

Refer to the current OPDIVO approved product label. for information concerning adverse reactions occurring in clinical trials.

As of September 2021, 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, vomiting, and urinary tract infection.

1.4.3.4. Nivolumab Immune-Related Adverse Events

Refer to the current OPDIVO approved product label (USPI, SmPC), for information concerning irAEs occurring during treatment with nivolumab.

As of September 2021, the OPDIVO USPI includes warnings and precautions for a range of irAEs documented in patients across cancer indications, including, pneumonitis, colitis, hepatitis, endocrinopathies (such as hypophysitis, adrenal insufficiency, hypothyroidism and hyperthyroidism, Type 1 diabetes mellitus), nephritis and renal dysfunction, skin adverse reactions, encephalitis, other rarer irAEs, and infusion reactions.

1.4.3.5. Safety Reported in Non-Small Cell Lung Cancer Trials Clinical Trials

Refer to the current OPDIVO approved product label (USPI, SmPC), for safety information concerning OPDIVO in clinical trials enrolling patients with NSCLC.

The safety of OPDIVO in metastatic NSCLC was evaluated in a randomized open-label, multicenter trial in patients with metastatic squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen (CHECKMATE-017) and a randomized, open-label, multicenter trial in patients with metastatic non-squamous NSCLC and progression on or after one prior platinum doublet-based chemotherapy regimen (CHECKMATE-057).

Patients received 3 mg/kg of OPDIVO administered intravenously over 60 minutes Q2W or docetaxel administered intravenously at 75 mg/m^2 Q3W. The median duration of therapy in OPDIVO-treated patients in CHECKMATE 017 was 3.3 months (range: 1 day to 21.7+ months) and in CHECKMATE-057 was 2.6 months (range: 0 to 24.0+ months). In CHECKMATE-017, 36% of patients received OPDIVO for at least 6 months and 18% of patients received OPDIVO for at least 1 year and in CHECKMATE-057, 30% of patients received OPDIVO for greater than 6 months and 20% of patients received OPDIVO for greater than 1 year.

CHECKMATE-017 and CHECKMATE-057 excluded patients with active autoimmune disease, medical conditions requiring systemic immunosuppression, or with symptomatic interstitial lung disease. For CHECKMATE-017 and CHECKMATE-057, the median age of OPDIVO-treated patients was 61 and 62 years respectively, (range: 37 to 85); 41% and 37%, respectively, were ≥65 years of age, 82% and 52%, respectively, were male, and approximately 90 % were white.

Seven to twelve percent of patients had brain metastases and Eastern Cooperative Oncology Group (ECOG) performance status was 0 (20%-29%) or 1 (71%-79%).

In CHECKMATE-057, in the OPDIVO arm, seven deaths were due to infection including one case of *Pneumocystis jirovecii* pneumonia, four were due to pulmonary embolism, and one death was due to limbic encephalitis. Serious adverse reactions occurred in 46% of patients receiving OPDIVO. OPDIVO was discontinued in 11% of patients and was delayed in 28% of patients for an adverse reaction.

The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were pneumonia, pulmonary embolism, dyspnea, pyrexia, pleural effusion, pneumonitis, and respiratory failure. Across both trials, the most common adverse reactions (reported in at least 20% of patients) were fatigue, musculoskeletal pain, cough, dyspnea, and decreased appetite.

Other clinically important adverse reactions observed in patients treated with OPDIVO and which occurred at a similar incidence in docetaxel-treated patients include: fatigue/asthenia (48% all Grades, 5% Grade 3-4), musculoskeletal pain (33% all Grades), pleural effusion (4.5% all Grades), pulmonary embolism (3.3% all Grades).

1.5. Expectations for Safety of the Combination of Sitravatinib and Nivolumab

1.5.1. Potential for Drug-Drug Interactions

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.

1.5.2. Evaluation of Potential for Increased Toxicity with Combination Use of Sitravatinib and Nivolumab

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 nivolumab 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, irAEs observed using nivolumab monotherapy include pneumonitis, colitis, hepatitis, endocrinopathy, nephritis/renal dysfunction, rash, and encephalitis. While sitravatinib

may have immunostimulatory effects, autoimmune adverse effects have not been reported in clinical trials of single-agent sitravatinib nor are they recognized as class effects for this agent. However, the potential for sitravatinib to exacerbate or promote these AEs when administered in combination with nivolumab should be borne in mind. Adverse event incidence data presented below are as reported in the OPDIVO USPI dated September 2021 and the Sitravatinib Investigator's Brochure dated August 2021. Updates to these data during the conduct of this clinical trial will be found in the current OPDIVO approved product label (USPI, SmPC), and Sitravatinib Investigator's Brochure.

A clinically relevant overlap in toxicity may arise between the immune-related colitis attributed to nivolumab and the non-specific, most often mild to moderate diarrhea observed with sitravatinib. Immune-related colitis has been reported in 2.9% (58/1994) of patients treated with nivolumab, with a median time to onset of 5.3 months (range: 2 days to 20.9 months). Diarrhea 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, occurring in 8% of patients with NSCLC treated at 3 mg/kg Q2W in the CHECKMATE 057 clinical trial (Borghaei, 2015). 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 as a single agent, immune-related hepatitis occurred in 1.8% (35/1994) of patients; the median time to onset was 3.3 months (range: 6 days to 9 months).

Hypothyroidism, including thyroiditis, was reported in 7% (20/287) of NSCLC patients treated with nivolumab. Hypothyroidism has been reported in approximately 17% of subjects treated with sitravatinib monotherapy.

A clinically relevant overlap in toxicity may arise between the immune-related rash attributed to nivolumab and the non-specific, most often mild (Grade 1) rash observed with sitravatinib. Immune-related rash has been reported in 6% (17/287) of NSCLC patients treated with nivolumab. Rash of uncertain etiology has been reported in 11% of patients treated with sitravatinib monotherapy.

1.6. Docetaxel

Docetaxel (TAXOTERE®) is an antineoplastic agent belonging to the taxoid family that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly.

This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells.

Background information in addition to that presented below is available in the current TAXOTERE approved product label (USPI, SmPC).

TAXOTERE or generic equivalent (docetaxel) are acceptable for use in this study.

1.6.1. Docetaxel Drug Substance

Generic Name: Docetaxel

Other Name: TAXOTERE®

1.6.2. Docetaxel Non-Clinical Data

The non-clinical experience is described in the current TAXOTERE approved product label (USPI, SmPC).

1.6.3. Docetaxel Clinical Data

The following reports information included in the TAXOTERE USPI dated May 2021. Refer to the current TAXOTERE approved product label (USPI, SmPC) for updates during the conduct of this clinical trial.

1.6.3.1. Docetaxel Pharmacokinetics

The PK of docetaxel have been evaluated in cancer patients after administration of 20 mg/m^2 to 115 mg/m^2 in phase 1 studies. The AUC was dose proportional following doses of 70 mg/m^2 to 115 mg/m^2 with infusion times of 1 to 2 hours. Docetaxel's PK profile is consistent with a three-compartment pharmacokinetic model, with half-lives for the α, β, and γ phases of 4 min, 36 min, and 11.1 hr, respectively. Mean total body clearance was 21 L/h/m^2. Mean steady state volume of distribution was 113 L. In vitro studies showed that docetaxel is about 94% protein bound, mainly to α1-acid glycoprotein, albumin, and lipoproteins. In three cancer patients, the in vitro binding to plasma proteins was found to be approximately 97%. Dexamethasone does not affect the protein binding of docetaxel.

In vitro drug interaction studies revealed that docetaxel is metabolized by the CYP3A4 isoenzyme, and its metabolism may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4.

A population PK analysis was carried out after TAXOTERE treatment of 535 patients dosed at 100 mg/m^2. Pharmacokinetic parameters estimated by this analysis were very close to those estimated from phase 1 studies. The PK of docetaxel were not influenced by age. The population pharmacokinetics analysis described above also indicated that gender did not influence the pharmacokinetics of docetaxel. In patients with clinical chemistry data suggestive of mild to moderate liver impairment (AST and/or ALT > 1.5 times ULN concomitant with alkaline phosphatase > 2.5 times ULN), total body clearance was lowered by an average of 27%,

resulting in a 38% increase in systemic exposure (AUC). There is, at present, no measurement that would allow recommendation for dose adjustment in such patients. Patients with combined abnormalities of transaminase and alkaline phosphatase should not be treated with TAXOTERE. Patients with severe hepatic impairment have not been studied. Mean total body clearance for Japanese patients dosed at the range of 10 mg/m^2 to 90 mg/m^2 was similar to that of European/American populations dosed at 100 mg/m^2, suggesting no difference in the elimination of docetaxel in these two populations.

1.6.3.2. Docetaxel Adverse Reactions Common in Clinical Trials

Refer to the current TAXOTERE approved product label (USPI, SmPC) for information concerning adverse reactions occurring in clinical trials.

As of May 2021, the most common adverse reactions across all TAXOTERE indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia.

1.7. Study Rationale

Immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway have demonstrated efficacy in patients with NSCLC. While CIT 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 CIT is a rational approach to improving outcomes in patients.

The use of 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 TME may lead to improved efficacy when TKIs are combined with checkpoint inhibitors. The TAM 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). In addition, M2 macrophages express checkpoint ligands such as PD-L1, PD-L2, B7-H1 and B7-H2 that further inhibit T effector cell function (Santarpia, 2015). 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 NK cells and negatively regulate

NK cell activity in the TME as part of a feedback regulatory mechanism resulting in decreased NK cell anti-tumor activity and enhanced tumor progression and metastasis (Paolino, 2014). Given the immunosuppressive function of TAM RTKs in the TME, inhibition of Axl and MERTK may complement PD-1/PD-L1 checkpoint inhibition to unleash the host anti-cancer immune response.

The MET 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 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 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 (ie, 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 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 steps in 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 CIT (anti-PD-1) alone. Since activation of the TAM receptors functions as a mechanism to limit inflammation during the natural course of an immune response, it is likely that differing levels of TAM-dependent immunosuppression exists in most tumors, thus providing a rationale for testing inhibitors of these “innate checkpoints” in combination with adaptive CIT (anti-PD-1) in patients with cancer that has progressed on CIT.

Nivolumab is a human IgG4 mAb 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 efficacy of nivolumab in combination with sitravatinib. Nivolumab will be administered in accordance with approved labeling, by intravenous infusion, 240 mg Q2W or 480 mg Q4W. Sitravatinib will be administered orally at a starting dose of 100 mg QD for the malate capsule formulation, based on the results of Study 516-006 described in Section 1.3.3.4. For patients enrolled in the USA who began treatment with the sitravatinib free base capsule formulation, sitravatinib is administered orally at a starting dose of 120 mg QD in accordance with findings of the prior nivolumab combination study (MRTX-500); patients who began treatment with the sitravatinib free base capsule formulation will remain on the free base capsule formulation throughout the duration of the study. Nonclinical studies indicate that sitravatinib administered to patients at 120 mg daily free base capsule formulation or 100 mg daily malate capsule formulation should achieve the plasma exposure required for inhibition of VEGF and TAM receptors, necessary to achieve antitumor efficacy in the combination setting.

2. STUDY OBJECTIVES

2.1. Objectives

2.1.1. Primary Objective

To compare OS in patients with non-squamous NSCLC who have experienced disease progression on or after platinum-based chemotherapy and CIT, treated with sitravatinib and nivolumab versus docetaxel.

2.1.2. Secondary Objectives

- To evaluate the safety of sitravatinib with nivolumab in the study population.
- To evaluate the relative tolerability of sitravatinib and nivolumab versus docetaxel.
- To evaluate secondary efficacy endpoints in the study population.
- To evaluate the PK of sitravatinib (MGCD516) administered in combination with nivolumab.
- To evaluate health-related quality of life and lung cancer-specific symptoms in the study population.

2.1.3. Exploratory Objective

- To assess correlations between baseline tumor immune biomarkers and gene mutations and treatment-related outcomes.

- To evaluate efficacy endpoints using exploratory disease response criteria.
- To characterize the immunogenicity of nivolumab in combination with sitravatinib.

2.1.4. Primary Endpoint

Overall Survival (OS).

2.1.5. Secondary Endpoints

- Safety characterized by type, incidence, severity, timing, seriousness and relationship to study treatment of adverse events, laboratory abnormalities, and number of patients discontinuing study treatment due to an adverse event.
- Secondary efficacy endpoints:
  - ORR as defined by RECIST 1.1.
  - DOR;
  - CBR;
  - PFS; and
  - 1-Year Survival Rate.
- Blood plasma concentrations of MGCD516.
- PROs:
  - Lung Cancer Symptom Scale (LCSS); and
  - EQ-5D-5L.

2.1.6. Exploratory Endpoints

- Tumor PD-L1 expression.
- Tumor gene alterations.
- Circulating tumor ctDNA.
- Efficacy parameters as evaluated per iRECIST.
- Nivolumab anti-drug antibody (ADA)

3. STUDY DESIGN

Study 516-005 is an open-label, randomized (1:1), multicenter, Phase 3 clinical trial evaluating the efficacy and safety of nivolumab in combination with the investigational agent sitravatinib compared to docetaxel in patients with advanced non-squamous NSCLC who have previously experienced radiographic disease progression on or after treatment with platinum-based

chemotherapy and CIT. The primary objective is to compare OS in the two treatment arms. Secondary objectives include evaluation of safety and tolerability, secondary efficacy endpoints, PK of sitravatinib, and patient reported outcomes. Correlative science endpoints include tumor PD-L1 expression, tumor gene mutations, nivolumab ADA and ctDNA. The Schedule of Assessments to be performed in the study is presented in Table 1.

Patient eligibility for study enrollment based on radiographic disease progression on or after treatment with CIT, either in combination with platinum-based chemotherapy or following platinum-based chemotherapy, will be evaluated by the Investigator. Data entered into the CRF are to include the date of at least one radiographic evaluation prior to the occurrence of disease progression on most recent CIT and the date the radiographic evaluation demonstrating disease progression, as well as specifics about organ systems (e.g., lung, liver, lymph node, bone and/or brain) having tumors that increase in size or are new.

Patient randomization will be stratified based on:

1. prior treatment regimens in the advanced setting (1 versus 2):

   One prior therapy: platinum-based chemotherapy in combination with CIT

   Two prior therapies: platinum-based chemotherapy → disease progression → CIT,
2. ECOG Performance Status at baseline (0 versus 1), and
3. presence of brain metastasis at baseline (presence versus absence).

Patients randomized to the experimental arm will receive treatment with nivolumab in combination with sitravatinib, delivered in 28-day cycles. Nivolumab will be administered as an infusion over approximately 30 minutes (± 5 minutes) at 240 mg every 2 weeks or 480 mg every 4 weeks, at the discretion of the Investigator. Sitravatinib malate capsules will be administered orally at 100 mg QD. Sitravatinib free base capsules will be administered orally at 120 mg QD (for patients who started on free base capsules, USA only). Patients enrolled in the USA who began treatment with the sitravatinib free base capsule formulation will remain on the free base capsule formulation throughout the duration of the study.

Patients randomized to the comparator arm will receive treatment with docetaxel, delivered in 21-day cycles. Docetaxel will be administered by intravenous infusion at 75 mg/m^2 over 1 hour every 3 weeks.

Disease assessments and patient-reported outcomes questionnaires must be performed as scheduled according to the calendar to prevent the introduction of bias based on toxicity into the assessment of efficacy. Disease response and progression per RECIST 1.1 as documented by the Investigator in the CRF will be the basis for patient management and supportive statistical analyses of radiology-based study endpoints.

Central radiology review for disease response and progression will be conducted. Timely and complete disease assessments and transfer of radiographic documentation to the Central Radiology Laboratory is critical to the integrity of this clinical trial.

Patients will receive study treatment as assigned at randomization until disease progression, unacceptable adverse events, investigator decision, 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 1.1 defined disease progression must be provided with and sign an informed consent detailing any available therapies and potential clinical benefit that the patient may be foregoing by continuing study treatment. Patients remaining on study treatment beyond RECIST 1.1. defined progression will continue to undergo disease assessments until study treatment is discontinued. Post-treatment disease assessment will continue until objective disease progression or start of subsequent anti-cancer therapy, whichever is sooner. PRO assessments will continue until start of subsequent anti-cancer therapy. No crossover to the alternative treatment assignment is provided in this study.

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 (ie, Clinical Trial Application [CTA]) and ethics application in the Member State (Section 14.1). 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 (Section 14.2).

The study will employ a group sequential design with one planned interim analysis and one final analysis for OS. The interim analysis will be performed after approximately 242 OS events (65% of total OS events) have occurred, with the possibility of stopping the trial for efficacy or futility. The efficacy boundary is constructed using the O'Brien-Fleming boundary implemented by Lan-DeMets alpha spending function. A non-binding futility boundary based on 2% conditional power (CP) is also constructed at the time of the interim analysis. The study may be declared futile if the estimated HR at interim > 0.92. The exact alpha spent and the futility boundary will be adjusted based on the observed number of events.

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 randomized into 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 to be eligible for enrollment into the study.

1. Histologically or cytologically confirmed non-squamous NSCLC with metastatic (Stage IV) or unresectable, locally advanced (Stage IIIB/IIIC) disease, not amenable to treatment with curative intent including concurrent chemoradiotherapy.

2. Receipt of at least one but not more than two prior treatment regimens in the advanced disease setting to include:
   - Treatment with a CIT (ie, anti-PD-1/PD-L1) and a platinum-based chemotherapy, which may have been in combination or in sequence (ie, platinum-based chemotherapy followed by CIT)
     – Prior treatment may have included maintenance therapy with a chemotherapy agent (eg, pemetrexed) and/or a CIT
   - Most recent treatment regimen must have included a CIT with radiographic disease progression on or after treatment, for example:
     – 1 prior treatment regimen: platinum-based chemotherapy in combination with CIT → radiographic disease progression, or
     – 2 prior treatment regimens: platinum-based chemotherapy → disease progression → CIT → radiographic disease progression

NOTE: Platinum-based adjuvant, neoadjuvant, or definitive chemoradiation therapy given for locally advanced disease followed by recurrent or metastatic disease within 6 months of completing chemotherapy may be considered treatment in the advanced disease setting.

3. Duration of at least 4 months (120 days) from first dose of most recent CIT to date of radiographic disease progression.
4. Availability of source documents for historical disease evaluations to allow Investigator certification of disease progression on or after most recent CIT.
5. Most recent prior therapy (eg, chemotherapy, CIT, or radiation therapy) discontinued at minimum of 2 weeks before the date of randomization; palliative radiation therapy to skeletal metastases and stereotactic radiation for brain metastases allowed if discontinued at least 7 days before the date of randomization.
6. Candidacy to receive treatment with docetaxel as the next line of therapy if randomized to the comparator arm.
7. Recovery from adverse effects of prior therapy to baseline or Grade 1 (excluding alopecia).
8. ≥ 18 years of age.
9. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
10. Life expectancy of at least 3 months.
11. Adequate bone marrow and organ function demonstrated by:
    a. Absolute neutrophil count ≥ 1,500/mm^3 (≥ 1.5 × 10^9/L).
    b. Hemoglobin ≥ 9.0 g/dL not dependent on transfusion support.
    c. Platelet count ≥ 100 × 10^9/L (≥ 100,000 per mm^3).

d. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 1.5 × ULN without liver metastases; < 5.0 x ULN if documented liver metastases; if alkaline phosphatase > 2.5 × ULN then ALT and AST must be ≤ 1.5 × ULN with or without liver metastases.
e. Serum bilirubin ≤ 1.0 x ULN.
f. Calculated creatinine clearance ≥ 40 mL/min, using the Cockcroft-Gault formula.

12. Women of child-bearing potential (WOCBP) or men whose partner is a WOCBP agrees to use contraception while participating in this study, and for a period of 6 months following termination of study treatment.
13. Completed informed consent process, including signing IRB/EC-approved informed consent form.
14. 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. Discontinuation of prior treatment with CIT more than 90 days prior to the date of randomization.
2. Receipt of systemic cancer therapy since discontinuation of CIT, with the exception of maintenance chemotherapy.
3. 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 randomization without the use of anticonvulsants and without the use of corticosteroids (or are on a stable or decreasing dose of ≤10 mg daily prednisone or equivalent).
4. Carcinomatous meningitis.
5. Known history of tumors that test positive for *EGFR*, *ROS1*, *ALK* mutations, or ALK fusions.
6. Prior therapies:
   - Immunotherapies not previously specified, including anti-OX40 and anti–CD137; prior anti-CTLA-4 is permitted.
   - Cancer therapy having the same mechanism of action as sitravatinib (eg, tyrosine kinase inhibitor with a similar target profile or bevacizumab).
7. Known toxicity on prior checkpoint inhibitor treatment:
   a. ≥ Grade 3 immune-related AE related to checkpoint inhibitor.
   b. Grade 2 immune-related AE associated with checkpoint inhibitor unless the AE resolved or was well controlled by withholding the checkpoint inhibitor and/or

treatment with steroids, with the exception of prior colitis, myocarditis, and pneumonitis, which are exclusionary.

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

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

8. Active or prior documented autoimmune disease:
   a. Inflammatory bowel disease (eg, 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 autoimmune disease within the past 2 years. NOTE: Patients with Type 1 diabetes, vitiligo, Graves' disease, residual hypothyroidism due to an autoimmune condition only requiring hormone replacement, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.
9. Active or prior immunocompromising conditions:
   a. Current or prior use of immunosuppressive medication within 28 days before the date of randomization, with the exceptions of topical, ocular, intranasal and inhaled corticosteroids (with minimal systemic absorption) or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid. A brief course (≤ 3 days) of systemic corticosteroids > 10 mg/day of prednisone (or equivalent corticosteroid) for prophylaxis (eg, contrast dye allergy) or for treatment of non-immune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted within the 28 days.
   b. Known acute or chronic human immunodeficiency virus (HIV);
      – Sites in Germany and Switzerland only: HIV infection at screening (positive HIV test).
   c. History of primary immunodeficiency.
   d. History of allogeneic transplant.
10. History of severe hypersensitivity reaction to any monoclonal antibody or polysorbate 80.
11. Criterion #11 removed, but numbering maintained.
12. Use of live vaccines against infectious disease (eg varicella) within 28 days of the date of randomization (note: killed vaccinations (eg influenza) are allowed at any appropriate time before and during the study).
13. Known acute or chronic hepatitis B or hepatitis C. Patients treated for hepatitis C with no detectable viral load are permitted.
    - Sites in Germany and Switzerland (testing required during screening): positive hepatitis B surface antigen [HBsAg] or positive hepatitis C virus [HCV] antibody;

- patients with past or resolved hepatitis B virus (HBV) infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of HBsAg) are eligible only if HBV DNA is negative
- patients treated for hepatitis C with no detectable viral load (HCV RNA negative) are permitted

14. History of hypersensitivity to study treatment excipient.
15. History of stroke or transient ischemic attack within the previous 6 months.
16. Any of the following cardiac abnormalities:
    a. Unstable angina pectoris within the past 6 months.
    b. Symptomatic or uncontrolled atrial fibrillation within the past 6 months.
    c. Congestive heart failure ≥ NYHA Class 3 within the past 6 months.
    d. Prolonged QTc on electrocardiogram > 480 milliseconds.
    e. Left ventricular ejection fraction (LVEF) < 40%.
17. Ongoing need for treatment with concomitant medication known to cause prolonged QTc. Such medication may be discontinued or changed to a different medication prior to enrollment.
18. Uncontrolled arterial hypertension (> 150 mm Hg systolic or > 100 mm Hg diastolic) on multiple observations despite standard of care treatment.
19. Major surgery within 4 weeks of the date of randomization.
20. History of significant hemoptysis or hemorrhage within 4 weeks of the date of randomization.
21. Known or suspected presence of another malignancy that could be mistaken for the malignancy under study during disease assessments.
22. Pregnancy. WOCBP must have a negative serum or urine pregnancy test documented within the screening period prior to the date of randomization.
23. Breast-feeding or planning to breast-feed during the study or within 30 days following the last dose of docetaxel or sitravatinib and within 5 months following the last dose of nivolumab.
24. Any serious illness, uncontrolled inter-current illness, psychiatric illness, active or uncontrolled infection, or other medical condition or history, including laboratory results, which, in the Investigator's opinion, interferes with the patient's capacity to provide informed consent, or would be likely to interfere with the patient's participation in the study, or with the interpretation of the results.

4.3. Life Style Guidelines

Patients, including men whose partner is a WOCBP, who are biologically capable of having children and sexually active must agree to use at least 2 acceptable methods of birth control, one of which must be highly effective 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 birth control methods considered highly effective are the following:

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 sterilization with confirmed absence of sperm in the post-vasectomy ejaculate.
4. Bilateral tubal ligation or bilateral salpingectomy.
5. Sexual abstinence[a]

   [a] In the context of this protocol, sexual abstinence is considered a highly effective method of birth control only if refraining completely from heterosexual intercourse during the entire period of risk (ie, during study treatment, including during temporary breaks from treatment, and for at least 6 months after stopping study treatment).

Acceptable birth control methods **not** considered highly effective include the following:

1. Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
2. Male or female condom with spermicide[a]
3. Cap, diaphragm or sponge with spermicide

   [a] A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

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 (eg, 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. Randomization

Following completion of the study-specific informed consent process, patients will be assigned a patient number, automatically generated, by a centralized Interactive Web Response System (IWRS) via the "screening" function. The patient number must be used on all documentation and correspondence with the Sponsor, Contract Research Organization (CRO) and laboratory vendors. Following review of all screening procedures, patient eligibility will be confirmed by appropriately qualified staff at the investigational site. Patients will be randomized in a 1:1 ratio using IWRS to receive treatment assignment to either sitravatinib and nivolumab or docetaxel. Study treatment should begin within 3 business days of randomization.

5. STUDY TREATMENTS

Investigational Product

An investigational product, also known as an investigational medicinal product in some regions, is defined as a pharmaceutical from of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form. Investigational products must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational products are:

- Sitravatinib (MGCD516)
- Nivolumab (OPDIVO)
- Docetaxel

Non-Investigational Product

Medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis may be considered as non-investigational products. These non-investigational products will be sourced by the investigative sites if available and permitted by local regulations.

In this protocol, non-investigational product(s) is/are:

- Any pre-medications associated with the comparator arm (eg, dexamethasone, or institutional equivalent, given as premedication for docetaxel) and medications used to treat chemotherapy infusion-related reactions.
- Any medications used to treat nivolumab infusion-related reactions (eg, steroids).

5.1. Sitravatinib

5.1.1. Sitravatinib Formulation, Packaging and Storage

This study began patient treatment in the USA with the sitravatinib free base capsule formulation used in previous clinical trials. Transition to use of an alternative formulation, sitravatinib malate capsule formulation, is being implemented with this protocol amendment. Newly randomized patients will be administered the sitravatinib malate capsule formulation. Patients in the USA on study treatment with the free base capsule formulation at the time the sitravatinib malate capsule formulation is introduced will remain on the free base capsule formulation until treatment discontinuation. The formulations are described below.

- (USA only) 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 strength of all sitravatinib capsule formulations are expressed based on MGCD516 free base weight. Dose strengths of sitravatinib 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 US and all countries in which the clinical trial material will be used and will be printed in the languages required in the countries in which the study is conducted.

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. Sitravatinib Preparation, Dispensing, 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 dose cycle. Sufficient supply will be provided for each cycle and extra capsules may be provided to cover an additional 2 days in case of delayed clinic visits or lost capsules.

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 (eg, 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 Administration

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

- The starting dose of sitravatinib using the malate capsule formulation is 100 mg QD.
- The starting dose of sitravatinib using the free base capsule formulation (for patients who started on free base capsule formulation, USA only) is 120 mg QD.

Depending on safety observations, the sitravatinib dose during subsequent cycles of treatment may be reduced in accordance with Table 3 for patients administered the free base capsule formulation and in accordance with Table 4 for patients administered the malate capsule formulation.

The dose selected for the malate capsule formulation is based on delivering sitravatinib exposure comparable to that achieved using the free base capsules at 120 mg QD. Study 516-006 (interim report) demonstrated bioequivalence between the 100 mg sitravatinib malate and 120 mg sitravatinib free base capsule formulations (see Section 1.3.3.4).

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) until notified otherwise by the Sponsor. This requirement may be eliminated based on the outcome of the study described in Section 1.3.3.5. 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 (approximately 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.
- Missed doses should be taken within 12 hours of the scheduled time and the next dose should be taken at its scheduled time.

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

5.1.4. Sitravatinib Dose Modification or Discontinuation

This protocol section provides guidance for dose modification of sitravatinib (ie, interruption, dose reduction or discontinuation) for AEs attributed to sitravatinib. For AEs attributed to nivolumab, see the current OPDIVO approved product label (USPI, SmPC).

Available dose modification levels for each of the sitravatinib formulations are outlined in Table 3 and Table 4. Dose modifications for the sitravatinib free base capsule formulation (Table 3) follow guidelines from Study MRTX-500. Dose modifications guidelines for the sitravatinib malate capsule formulation (Table 4) follow comparable dose reduction proportions used for the sitravatinib free base capsule formulation. Guidelines for sitravatinib dose modifications to be implemented to manage AEs are described in Sections 5.4.1 and 5.4.3. Once the dose has been reduced, re-escalation is generally not recommended but may be considered on a case-by-case basis. If the administration of sitravatinib is interrupted for reasons other than toxicity, then treatment with the study drug may be resumed at the same dose.

The starting dose for sitravatinib using the free base capsule formulation is 120 mg administered once daily (for patients who started on free base capsules formulation, USA only).

Table 3: Sitravatinib Sequential Dose Reductions for Individual Patients on Free Base Capsule Formulation

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

Dose reduction below 60 mg QD to 40 mg QD for the free base capsule formulation may be undertaken after discussion with the Sponsor.

The starting dose for sitravatinib using the malate capsule formulation is 100 mg administered once daily.

Table 4: Sitravatinib Sequential Dose Reductions for Individual Patients on Malate Capsule Formulation

100 mg once daily
70 mg once daily
50 mg once daily

Dose reduction below 50 mg QD to 35 mg QD for the malate capsule formulation may be undertaken after discussion with the Sponsor.

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 from 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 provided by the Sponsor. All administration information, including adverse event management should be in accordance with the current OPDIVO approved product label (USPI, SmPC). The following reports information and guidance included in the OPDIVO USPI dated September 2021. Refer to the current OPDIVO approved product label (USPI, SmPC) provided by the manufacturer for updates during the conduct of this clinical trial.

5.2.1. Nivolumab Formulation and Packaging

OPDIVO is a sterile, preservative-free, non-pyrogenic liquid. OPDIVO injection for intravenous infusion is supplied in single-dose vials. Each mL of OPDIVO solution contains nivolumab 10 mg. Refer to the current OPDIVO approved product label (USPI, SmPC) for further details.

5.2.2. Nivolumab Preparation and Dispensing

Visually inspect drug product solution for particulate matter and discoloration prior to administration. OPDIVO is a clear to opalescent, colorless to pale-yellow solution.

Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.

- Withdraw the required volume of OPDIVO and transfer into an intravenous container.
- Dilute OPDIVO with either 0.9% Sodium Chloride Injection, United States Pharmacopeia (USP) or equivalent or 5% Dextrose Injection, USP or equivalent to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL. The total volume of infusion must not exceed 160 mL.
- For patients with body weights less than 40 kg, the total volume of infusion must not exceed 4 mL/kg of body weight.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials of OPDIVO.

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

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

Do not freeze OPDIVO solutions.

5.2.3. Nivolumab Administration

Nivolumab (OPDIVO) will be administered in this study as an infusion over approximately 30 minutes (± 5 minutes) at 240 mg Q2W or 480 mg Q4W, at the discretion of the Investigator and in accordance with the current OPDIVO approved product label (USPI, SmPC). Sitravatinib dosing should precede nivolumab infusion. Nivolumab infusion can be administered any time after the oral dose of sitravatinib is administered, except on C1D1 where the 30 min post sitravatinib dose PK sample has to be collected before nivolumab infusion.

Administer the OPDIVO infusion through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer). Flush the intravenous line at end of infusion.

5.2.4. Nivolumab Dose Modification or Discontinuation

Required dose modifications (ie, interruption or discontinuation) for nivolumab should be performed per the current OPDIVO approved product label (USPI, SmPC), in addition to potential dose modifications for sitravatinib in accordance to protocol Section 5.4.1.

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

5.3. Docetaxel Study Drug

Docetaxel will be obtained from commercial sources or provided by the Sponsor depending on local country requirements and managed in accordance with the current TAXOTERE approved product label.

TAXOTERE or generic equivalent (docetaxel) are acceptable for use in this study.

The following reports information and guidance included in the TAXOTERE USPI dated May 2021. Refer to the current TAXOTERE approved product label (USPI, SmPC) provided by the manufacturer for updates during the conduct of this clinical trial.

5.3.1. Docetaxel Formulation and Packaging

TAXOTERE (docetaxel) Injection Concentrate, Intravenous Infusion (IV), is a sterile, non-pyrogenic, non-aqueous solution. TAXOTERE is supplied in single use vials, 20 mg/mL and 80 mg/4mL, 50/50 (volume/volume) ratio polysorbate 80/dehydrated alcohol. Refer to the current TAXOTERE approved product label (USPI, SmPC) for further detail.

5.3.2. Docetaxel Preparation and Dispensing

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.

TAXOTERE Injection Concentrate requires no prior dilution with a diluent and is ready to add to the infusion solution. Use only a 21-gauge needle to withdraw TAXOTERE from the vial because larger bore needles (eg, 18 and 19 gauge) may result in stopper coring and rubber particulates. Add drug concentrate into a 250 mL infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 mg/mL to 0.74 mg/mL. If a dose greater than 200 mg of TAXOTERE is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL TAXOTERE is not exceeded. Thoroughly mix the infusion by gentle manual rotation and inspect visually for particulate matter or discoloration prior to administration whenever the solution and container permit.

5.3.3. Docetaxel Administration

- TAXOTERE should be administered in a facility equipped to manage possible complication (eg, anaphylaxis).
- Patients should be premedicated with oral corticosteroids such as dexamethasone 16 mg per day (eg, 8 mg twice daily) for 3 days starting 1 day prior to TAXOTERE administration, unless contraindicated, in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

- For treatment of NSCLC after failure of prior platinum-based chemotherapy, the TAXOTERE recommended dose is 75 mg/m^2 administered intravenously over 1 hour every 3 weeks.

Before each cycle of docetaxel,

- LFTs should be reviewed, and docetaxel should not be given if bilirubin > ULN, or if AST and/or ALT > 1.5 × ULN concomitant with alkaline phosphatase > 2.5 × ULN.
- Blood counts should be reviewed, and docetaxel should not be given if neutrophil counts are < 1500 cells/mm^3.

During this study, institutional or regional standard practice for administration of pre-medications and docetaxel may be followed with the exception of the initial (Cycle 1) dose which should remain 75 mg/m^2.

5.3.4. Docetaxel Dose Modification

The following is guidance provided in the TAXOTERE USPI dated May 2021. Refer to the current TAXOTERE approved product label (USPI, SmPC); a generic equivalent product may be used in the study. Patients who are dosed initially at 75 mg/m^2 and who experience either febrile neutropenia, neutrophils < 500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions, or other Grade 3/4 non-hematological toxicities during TAXOTERE treatment should have treatment withheld until resolution of the toxicity and then resumed at 55 mg/m^2. Patients who develop ≥ Grade 3 peripheral neuropathy should have TAXOTERE treatment discontinued entirely.

During this study, local standard practice for docetaxel administration, with the exception of the initial (Cycle 1) dose which should remain 75 mg/m^2, may be used. Patients requiring more than two dose reductions of docetaxel due to adverse events should discontinue treatment with docetaxel.

5.4. Management of Adverse Events

5.4.1. Sitravatinib-Related Adverse Events

5.4.1.1. General Management of Non-Hematological Toxicities

A complete review of adverse events should be conducted at each clinic visit. Symptomatic Grade 2 sitravatinib-related non-hematological adverse events occurring any time on study, particularly early in treatment (eg, 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 3 (free base capsule formulation) and Table 4 (malate capsule formulation), rather than continued dosing until interruption becomes necessary.

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), treatment may be resumed at the same dose; otherwise, treatment may be resumed at one or more levels below the dose level where toxicity was observed as outlined in Table 5. Treatment with sitravatinib may continue without dose modification (eg, interruption or reduction) in cases of asymptomatic amylase and/or lipase increases in the absence of other clinical evidence of pancreatitis (eg, symptoms, electrolyte abnormalities, radiographic changes) at the investigator's discretion. Recurrence of a toxicity may be managed similarly. If treatment is interrupted for ≥ 28 days, permanent discontinuation of sitravatinib should be considered.

Table 5: 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 or patient discretion[2] Early dose reduction to the next lower dose level is recommended over treatment interruption.	
Grade 3 or 4	Hold until ≤ Grade 1 or return to baseline[2]	Resume at dose one or more levels below that inducing the toxicity. Exceptions presented in footnotes[2,3]

[1] Management of selected adverse events for sitravatinib are presented in Section 5.4.1.3.
[2] The current OPDIVO approved product label (USPI, SmPC) must be consulted to determine appropriate dose modifications for nivolumab.
[3] Patients may resume at the same dose in the following cases:
a. Grade 3 or 4 electrolyte abnormality that is not clinically complicated and resolves spontaneously or with conventional medical treatment within 72 hours;
b. Grade 3 amylase or lipase elevation that is not associated with symptoms or other clinical (eg, electrolyte abnormalities, radiographic changes) manifestations of pancreatitis.

5.4.1.2. 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 until resolution of toxicity to ≤ Grade 2. 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.

5.4.1.3. Management of Selected Adverse Event

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

5.4.1.3.1. Hypertension

Hypertension, including Grade 4 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 6). On the other hand, in cases of Grade 3 hypertension with clinically significant increases in blood pressure (Table 6), 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 6).

Table 6: Sitravatinib Dose Modification for Increased Blood Pressure

Toxicity	Interruption	Reduction
Grade 1 or 2 hypertension	May be implemented based on Investigator and patient discretion	
Grade 3 hypertension without clinically significant increases in BP as defined below	Investigator discretion. Consider anti- hypertensives per Section 5.4.1.3.1	
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

5.4.1.3.2. Palmar-Plantar Erythrodysesthesia

Palmar plantar erythrodysesthesia (PPE) has been reported as a DLT 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.

5.4.1.3.3. Diarrhea

Diarrhea should be evaluated to determine whether it may be immune-mediated colitis due to nivolumab (see Section 5.4.3.1), 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 due to sitravatinib develops. Any patients developing dehydration or clinically significant electrolyte abnormalities due to sitravatinib should interrupt sitravatinib treatment, but treatment may be restarted once diarrhea is controlled.

5.4.1.3.4. 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.

5.4.1.3.5. Thrombotic Events

Though thrombotic events (eg, 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.

5.4.1.3.6. Thyroid Dysfunction Other than Immune-Related

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

5.4.1.3.7. Decreased Left Ventricular Ejection Fraction

Decreased LVEF has been reported with sitravatinib. In addition, decreases of LVEF to < 50% on-study were observed in patients undergoing scheduled echocardiograms (ECHO) or multigated acquisition (MUGA) scans. 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).

5.4.1.3.8. 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.

5.4.2. Nivolumab Adverse Event Management Guidelines

Refer to the local current OPDIVO approved product label (USPI, SmPC) for guidance concerning management of AEs, including irAEs, during treatment with nivolumab.

5.4.3. Management of Immune-Related Adverse Events

Single agent sitravatinib has not been associated with irAEs. However, the potential exists for irAEs associated with nivolumab treatment or for sitravatinib to contribute to irAEs associated with nivolumab treatment. In the event of a Grade 2 irAE during study treatment, administration of sitravatinib and nivolumab should be interrupted until the event stabilizes to Grade ≤ 1 (consistent with guidance provided in the current OPDIVO approved product label [USPI, SmPC]). 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 irAEs should be performed in accordance with the current OPDIVO approved product label (USPI, SmPC). However, recurrent Grade 3, or any Grade 4, irAEs should generally be managed with permanent discontinuation of nivolumab, and temporary or permanent interruption of sitravatinib. Sitravatinib may be resumed at the same or lower dose at the discretion of the Investigator once the event stabilizes to Grade ≤ 1.

5.4.3.1. 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-related colitis. The presence of abdominal pain, mucus or blood in the stool or peritoneal signs should raise the index of suspicion for immune-related 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-

related colitis, all study medications should be withheld and treatment with immuno-suppressive therapy initiated as detailed in the current OPDIVO approved product label (USPI, SmPC).

5.4.3.2. 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-related 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-related, treatment management decisions should be made using Investigator discretion in consideration of clinical factors. Recommended treatment modifications for sitravatinib are provided in Table 7. 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-related hepatitis, all study medications should be withheld and treatment with immuno-suppressive therapy initiated as detailed in the current OPDIVO approved product label (USPI, SmPC).

Table 7: Sitravatinib Dose Modification for Increased Hepatic Transaminase

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 approved product label (USPI, SmPC), and Section 5.4.3, in case the event is deemed to be an irAE, must be consulted to determine appropriate dose modifications for nivolumab.

5.4.4. Management of Hy's Law Cases

In the event a patient develops concurrent increase in AST and/or ALT ≥ 3 × ULN, bilirubin ≥ 2 × ULN but without concurrent increases in alkaline phosphatase (ie, alkaline phosphatase < 2 × ULN), that is not attributable to other causes (eg, liver metastases, biliary obstruction, viral hepatitis, concomitant medication, etc), sitravatinib and nivolumab should be permanently discontinued and steroids administered. Hy's Law cases should be reported as SAEs (Section 8.2.1).

5.4.5. Docetaxel Adverse Event Management Guidelines

Refer to local current TAXOTERE approved product label (USPI, SmPC) for guidance concerning management of AEs during treatment with docetaxel. In addition to local product information and the administration guidelines described in Section 5.3, please specifically note:

Severe hypersensitivity reactions require immediate discontinuation of the docetaxel infusion and aggressive therapy. Patients with a history of severe hypersensitivity reactions should not be re-challenged with docetaxel.

5.5. Medication Error

Medication errors may involve patient exposure to a wrong study drug, at a wrong dosing frequency, or at a wrong dose level (eg, 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 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 or nivolumab. The Investigator will use clinical judgment to treat any overdose.

5.6. Concomitant Therapies

5.6.1. Concomitant Medication(s)

Prior medications, including chronically administered medication, used within the 28-day period preceding Day 1 of the trial, will be reviewed and recorded. Anti-cancer treatment for NSCLC will not be recorded as a prior medication but will be listed separately.

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 2 and for docetaxel in Appendix 3.

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.

Medications with QTc Prolonging Activity with Sitravatinib: 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 2) is to be avoided during sitravatinib treatment. Use of medications with conditional risk of Torsades de Pointes should be used with caution during sitravatinib treatment (examples listed in Appendix 2).

P-gp and BCRP substrates 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 2) should be used with caution during sitravatinib treatment.

P-gp Inhibitors and Inducers with Sitravatinib: Sitravatinib is a substrate of P-gp in vitro. Inhibitors of P-gp (eg, clarithromycin, itraconazole, propafenone, quinidine, ranolazine, ritonavir, verapamil) may increase sitravatinib exposure while inducers of P-gp (eg, rifampin) may decrease sitravatinib exposure. Caution should therefore be used when administering sitravatinib to patients taking medications that inhibit or induce P-gp.

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 2) should be used with caution during sitravatinib treatment.

Strong and Moderate CYP3A4 Inhibitors with Docetaxel: Docetaxel is a CYP3A4 substrate. In vivo studies showed that the exposure of docetaxel increased 2.2-fold when it was co-administered with ketoconazole, a potent inhibitor of CYP3A4 (TAXOTERE USPI). Concomitant use of docetaxel and medications that are strong or moderate inhibitors of CYP3A4 may increase exposure to docetaxel and should be avoided (examples listed in Appendix 3). These medications should be used with caution if they cannot be avoided; close monitoring for toxicity and docetaxel dose reduction should be considered.

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.

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.

*Bisphosphonates (eg, zoledronic acid) and RANK-L inhibitors (eg, denosumab) should be initiated prior to first dose of study therapy.

Growth Factors: Therapeutic colony-stimulating factors should be used in accordance with American Society of Clinical Oncology (ASCO) guidelines.

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

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

5.6.2. 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 (eg, bone lesions at risk for spontaneous micro-fractures or painful lesions). However, these treatments may be used in cases where it is medically necessary. If radiotherapy is required, the Sponsor will provide guidance on duration of sitravatinib interruption.

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.

5.6.3. Other Anticancer or Experimental Therapy

Use of approved or investigational anticancer treatment will not be permitted during the study treatment period, including ramucirumab, chemotherapy, biological response modifiers, hormone therapy* 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 (eg, 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 were not randomized into 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 procedure descriptions in Section 7.

6.3. End of Treatment Assessment

All patients will be followed for non-irAEs for at least 28 days after the last dose of study treatment and followed for irAEs for at least 100 days after the last dose of nivolumab or until subsequent immunotherapy is administered, whichever is earlier. See the Schedule of Assessments (Table 1) for evaluations to be performed at the End of Treatment visit. Assessments completed in the previous 4 weeks do not need to be repeated with the exception of assessment of AEs, hematology and chemistry.

6.4. Initial Follow-up

Initial follow up after discontinuation of study treatment will include the following as outlined in Table 1:

- patients discontinuing treatment for reasons other than objective disease progression (eg, due to an adverse event or delivery of maximal number of cycles per local standard-of-care) will be followed by radiographic evaluation at the intervals established for disease assessment until objective disease progression or start of subsequent anti-cancer therapy, whichever is sooner;
- patients randomized to sitravatinib/nivolumab will undergo blood sampling for ADA assessment at least 80 days after last dose of nivolumab or immediately before the start of subsequent therapy, whichever occurs earlier; and
- all patients will undergo PRO assessments until start of subsequent anti-cancer therapy
- survival status and start of subsequent therapy will be collected.

6.5. Long-Term Follow-up

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

6.6. 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 AEs.

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. Documentation of Disease Progression On or After Prior Chemotherapy and Checkpoint Inhibitor Therapy

Patient eligibility for study enrollment based on radiographic disease progression on or after treatment with CIT, either in combination with platinum-based chemotherapy or following platinum-based chemotherapy, will be evaluated by the Investigator. Data entered into the CRF are to include the date of at least one radiographic evaluation prior to the occurrence of disease progression on most recent CIT treatment and the date of the radiographic evaluation demonstrating disease progression, as well as specifics about organ systems (eg, lung, liver, lymph node, bone and/or brain) having tumors that increase in size or are new.

Radiology reports coinciding with evaluations interpreted by the Investigator as indicating radiographic disease progression on the most recent CIT containing regimen will be appended to the CRF in countries where this is permitted by applicable laws and regulations.

7.2. Efficacy

7.2.1. Overall Survival

Overall survival is the primary efficacy endpoint for this study. Survival status and information concerning subsequent therapies will be collected during initial and long-term follow-up as outlined in the Schedule of Assessments (Table 1). Long term follow-up may be performed by telephone contact or email. In the event a patient discontinues treatment due to loss to follow-up or withdraws consent for use data from medical records, surveillance of public sources of death information (eg, published obituaries) should be undertaken and reported date of death recorded in the CRF.

7.2.2. Radiographic Disease Assessment

All patients enrolled in the study are to undergo disease evaluations as outlined in the Schedule of Assessments (Table 1). On-study disease assessments must be performed as scheduled according to the calendar to prevent the introduction of bias based on toxicity into the assessment of efficacy. Patients discontinuing treatment prior to objective disease progression will be followed by radiographic evaluation until disease progression is documented or until the start of subsequent anti-cancer therapy, whichever is sooner. Patients continuing study treatment beyond RECIST 1.1 defined progression will continue radiographic disease evaluations until discontinuation of study treatment.

The Investigator's assessment of disease response and progression per RECIST 1.1 will be the basis for patient management and supportive statistical analyses of radiology-based study endpoints. Central radiology review for disease response and progression will be conducted. Early central radiology review of screening/baseline assessments for each patient will inform Investigators of the minimum evaluation methods required during on-study assessments to support review by the Central Radiology Laboratory. Timely and complete disease assessments and transfer of radiographic documentation to the Central Radiology Laboratory is critical to the integrity of this clinical trial.

Disease response will be assessed in accordance with RECIST 1.1 (Eisenhauer, 2009). Appendix 4 provides guidance in using the response criteria. In addition, the Central Radiology Laboratory will evaluate disease response and progression in accordance with the exploratory method iRECIST (Seymour, 2017).

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 if local standard for clinical trials), CT with contrast or MRI of the brain with and without gadolinium and, evaluation of any superficial lesions. For patients having effusions or ascites, cytological proof of malignancy should be obtained prior to selection of the effusion as a non-target lesion. New effusions that have not been evaluated using cytology or were found to be non-malignant should not be considered to be cancer lesions. The allowable windows for screening/baseline assessments is 28 days prior to randomization.

Disease assessments performed on-study will include CT of the chest, CT or MRI of the abdomen and assessment of all known and suspected sites of disease and any additional sites, if any, specified for each patient by the Central Radiology Laboratory. Assessments will be performed at 8-week intervals, based on a calendar beginning from randomization, until approximately 1-year and then every 16 weeks; bone scans may be performed half as often as other radiology evaluations (ie, every 16 weeks) and should be performed during assessment for confirmation of disease response. The allowable windows for on-study assessments is ± 10 days. Assessments will be performed until objective disease progression is documented by the Investigator, or subsequent anti-cancer therapy is begun.

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

Patients experiencing tumor response (Partial Response [PR] or Complete Response [CR]) should undergo confirmatory assessment no earlier than 4 weeks after initial documentation; it is acceptable to perform confirmatory assessments at the next appointed evaluation per protocol (ie, 8 weeks after the observation of tumor response). In patients for whom bone lesions were identified at the baseline, bone scan is required as an element of the confirmation of PR or CR.

Patients experiencing early radiographic progression accompanied by deteriorating health status should be evaluated for the possibility of hyperprogression (Kurman, 2018). Patients experiencing rapid clinical and radiographic progression of disease should be discontinued from study treatment.

Materials to be forwarded for independent central radiology review will include all imaging studies performed at screening/baseline and on-study, preferably in digital format, using an electronic transfer through a portal to the review vendor or transfer on compact disc or optical disc. All digital media must be in DICOM format. Films may be forwarded for review if necessary; all films must be originals (second original films acceptable) rather than copies of films. Further information on materials to be forwarded for independent review is provided in the Independent Radiology Study Manual.

The Sponsor will inform investigators when collection of materials for central radiology review is no longer required in this study.

7.3. Safety Assessments

7.3.1. Medical History

Medical history, including clinically significant past and present medical conditions, will be recorded. Lung cancer history will be recorded separately. Signs and symptoms of the patient's cancer diagnosis and/or comorbidities present on Day 1 of study treatment and throughout treatment will be recorded in the CRF as AEs. The actual date of onset should be recorded in all cases. Thus, for signs and symptoms present on Day 1, the date of onset may pre-date the start of study treatment.

7.3.2. 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 when 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 on Day 1 of study treatment and throughout study treatment will be collected on the AE CRFs.

7.3.3. Laboratory Safety Assessments

Laboratory safety assessments for which data will be collected in this study will include hematology, thyroid tests, urinalysis and chemistry parameters presented in Table 8.

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

Table 8: Laboratory Safety Parameters

Hematology Panel	**Blood Chemistry Panel**
Hemoglobin	Aspartate aminotransferase
Platelet count	Alanine aminotransferase
White blood cell count	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
Urinalysis (dip stick)	Sodium
Blood	Potassium
Protein	Chloride
	Bicarbonate or carbon dioxide (CO2)
Thyroid Function Test	Blood urea nitrogen (BUN) or urea
Thyroid-stimulating hormone	Creatinine
	Albumin
	Total Calcium
	Magnesium
	Uric acid

Pregnancy Testing: For patients of childbearing potential, a serum or urine pregnancy test will be performed by the local laboratory at screening. Pregnancy testing will also be performed at the beginning of every treatment cycle and the same frequency, approximately monthly, will be

maintained for at least 1 month after the last dose of sitravatinib, 5 months after the last dose of nivolumab and for 1 month after the last dose of docetaxel. 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.

Sites in Germany and Switzerland only: Patients must be tested for human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) infection (all tests performed by local laboratory) at screening. Testing for HIV infection is by local standards. Hepatitis B serology to include the following: hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb/anti-HBs), and hepatitis B core antibody (HBcAb/anti-HBc); HBV DNA performed only if HBcAb positive and HBsAg negative. Hepatitis C serology: HCV antibody (anti-HCV); HCV RNA performed only if anti-HCV is positive.

7.3.4. Electrocardiograms

Single and triplicate ECGs are to be performed as outlined in the Schedule of Assessments (Table 1 and Table 2). It is preferable that the machine used has a capacity to calculate the standard intervals automatically. Assessments reported by automated read as prolongation of QTc should be over-read by a cardiologist to ensure accuracy of interpretation.

7.3.5. Echocardiogram or Multigated Acquisition Scan

Echocardiogram (preferred) or MUGA will be performed at screening (MUGA option is not available for sites in Germany), and thereafter as in the Schedule of Assessments (Table 1). Additional assessments of LVEF may be performed as clinically indicated at the Investigator's discretion if there are signs or symptoms of cardiotoxicity.

7.4. Laboratory Studies

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

7.4.1. Pharmacokinetic Evaluation

In patients randomized to the sitravatinib/nivolumab treatment arm 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. 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 and irrespective of dose of nivolumab. Full details on sample collection, processing, storage and shipment will be provided in the Study Laboratory Manual.

7.4.2. Nivolumab Anti-Drug Antibody Evaluation

In patients randomized to the sitravatinib/nivolumab treatment arm, the development of ADA to nivolumab will be evaluated using blood samples collected prior to, during and following study treatment as specified in Table 1. All serum samples will be stored frozen and shipped on dry ice according to instructions provided. Analysis of samples will be performed using specific validated bioanalytical methods and irrespective of dose of sitravatinib. Full details on sample collection, processing, storage and shipment will be provided in the Study Laboratory Manual.

7.4.3. Molecular Marker Evaluation

Molecular markers prior to treatment to be investigated include PD-L1 expression and tumor gene alterations in tumor tissue and tumor gene alterations in ctDNA. Full details on sample collection, processing, storage and shipment will be provided in the Study Laboratory Manual.

7.4.3.1. Circulating Tumor DNA

Optional blood samples for ctDNA analysis will be collected at baseline/screening as outlined in Table 1. Blood samples will be collected into two 10 mL Streck brand Cell-Free DNA Blood Collection tubes allowing shipping and stability at ambient temperatures. Tumor gene alterations in ctDNA samples will be determined using NGS performed by a central laboratory. Collection of ctDNA blood samples is not mandatory for study participation.

7.4.3.2. Markers in Tumor Tissue

Freshly biopsied tumor tissue collections at pre-treatment for analysis of PD-L1 expression 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. 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 (ie, > 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. Archival samples may be submitted if more recent tumor specimens or fresh biopsies cannot be obtained. Submission of pre-study tumor samples is not mandatory for study participation.

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 CRF include the type of assay employed, percent tumor and/or immune cell staining (if available) and, categorization of high- versus low-PD-L1 expression.

Tumor gene alterations in freshly biopsied tumor samples will be determined using NGS performed by a central laboratory. For patients in whom tumor tissue has previously been tested using NGS, presence of tumor gene mutations and estimation of total tumor mutation burden

(TMB) will be collected in the CRF. In addition, a copy of the prior report will be appended to the CRF in countries where this is permitted by applicable laws and regulations.

7.5. Patient Reported Outcomes

Patient reported outcomes (PROs) of health-related quality of life and lung cancer-specific symptoms will be evaluated using two tools: the European Quality of Life Five Dimensions Questionnaire (EQ-5D-5L) and the Lung Cancer Symptom Scale (LCSS).

The EQ-5D-5L questionnaire includes two components – the EQ-5D-5L descriptive assessment of five dimensions (including mobility, self-care, usual function status, pain and/or discomfort, and anxiety and/or depression) using 5 levels, and the EQ VAS for the patient's self-rated health using a 20 cm vertical visual analogue scale. The data from this instrument will be used in economic models and analyses.

The LCSS is a lung cancer specific measure of quality of life and includes 9 questions, including patient-reported ratings of six symptoms (appetite loss, fatigue, cough, dyspnea, hemoptysis, pain) and three summary items (symptom distress, activity level, overall quality of life) using 100-mm visual analogue scales. This instrument will be used in the assessment of health-related quality of life.

PRO assessments will be collected at C1D1 and then coincide with disease evaluations as outlined in Table 1. EQ-5D-5L questionnaires should always be completed before LCSS. Assessments should continue until start of other anti-cancer therapy.

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 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 AEs 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 (ie, 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 (eg, cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product.

Cases meeting Hy's Law should be reported as SAEs. Study drug should be permanently discontinued for a Hy's Law case (see Section 5.4.4).

8.2.2. Severity Assessment

AEs occurring during this study will be graded in accordance with the NCI 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 (eg, 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; ie, 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 (eg, 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, eg, 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 AE that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternative 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 AE.

8.3.2. Exposure During Pregnancy

Exposure during pregnancy (ie, 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 (eg, 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 within 6 months of conception or during the pregnancy of his partner.

If EIU 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 (eg, 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 (ie, 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 (ie, 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.

*The reporting period for serious and non-serious irAEs will continue until at least 100 days after the last administration of nivolumab or until subsequent immunotherapy is administered, whichever is earlier.

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.

The control of the overall type 1 error between the primary endpoint and key preidentified secondary efficacy endpoints will be performed using a gatekeeper strategy. The order of testing will be detailed in the SAP.

9.1. Hypotheses and Sample Size

9.1.1. Primary Efficacy Hypothesis

Overall survival (OS) is the primary efficacy endpoint of this study. The study hypotheses are:

- H_0: Hazard Ratio (HR) for OS with sitravatinib/nivolumab versus OS with docetaxel = 1.0, versus
- H_{1a}: HR for OS with sitravatinib/nivolumab versus OS with docetaxel = 0.73

9.1.1.1. Sample Size Determination

The following assumptions were used in the sample size determination:

- Median OS in the control group (docetaxel) is 9.5 months.

Median OS in the experimental group (sitravatinib in combination with nivolumab) is 13.0 months (HR of 0.73). Approximately 372 total OS events will be required to detect the assumed HR at a 2-sided alpha 0.05 and a power of 85%. Assuming an enrollment duration of approximately 25 months and an additional 13 months of follow-up, a sample size of approximately 532 patients is planned to achieve the required number of events. An interim analysis and final analysis are planned for this study.

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. Intent-to-Treat Population

The Intent-to-Treat (ITT) population is defined as all patients who are randomized into this study. The ITT population will be used to describe demographics and in the analyses for the PRO and efficacy endpoints.

9.3.2. Safety Population

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

9.3.3. 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.

9.3.4. Molecular Marker Evaluable Population

The molecular marker evaluable population will consist of all patients who receive at least one dose of either sitravatinib or nivolumab for whom PD-L1 expression or tumor gene alteration results are available.

9.4. Efficacy Endpoint Definitions and Analyses

9.4.1. Overall Survival

Overall survival is defined as the time from date of randomization to death due to any cause. Censoring for the survival endpoint will be assigned on the date of the last on-study follow-up that the patient is reported to be alive.

The Kaplan-Meier method and the unstratified log-rank test will be used to estimate the median OS and to compare the times to death between the two treatment arms.

Moreover, 1-year Survival Rate and the 95% CI of the 1-year survival rate will also be reported.

A Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the hazard ratio). The hazard ratio and its 95% confidence interval from the stratified Cox model with a single treatment covariate will be reported.

The stratified log-rank test will be used to compare OS between the two treatment arms as sensitivity analysis. The stratification factors used for randomization (see Section 3) will be applied to both the stratified log rank test and the stratified Cox model. Patients enrolled under Protocol version 1.0 (with a randomization stratification factor of the duration of previous CIT) will not be included in the analysis due to the different stratification factors after protocol amendment.

Additional sensitivity analyses to test and account for possible non-proportional hazards effect will be described in the SAP.

9.4.2. 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 CR or PR.

Descriptive statistics (frequency and percentage) for ORR will be presented. The 95% CI of the response rate will be calculated using Clopper-Pearson method. A Chi-square test test will be used to compare response rates between the two treatment arms.

A Cochran Mantel Haenszel (CMH) test will be used, controlling for the stratification variables to compare response rates between the two treatment arms as sensitivity analysis. Patients enrolled under Protocol version 1.0 (with a randomization stratification factor of the duration of previous CIT) will not be included in the analysis due to the different stratification factors after protocol amendment.

9.4.3. Clinical Benefit Rate

Clinical Benefit Rate is defined as the percent of patients documented to have a confirmed Complete Response (CR), confirmed Partial Response (PR), or Stable Disease (SD) documented on at least 1 on-study assessment and including at least 8 weeks on study.

An approach similar to that described for ORR in Section 9.4.2 will be used to compare CBR for the two treatment arms.

9.4.4. Duration of Response

Duration of Response 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 in the ITT population with a confirmed 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. Patients who start a new anti-cancer therapy prior to documented PD or death will be censored at the date of the last tumor assessment prior to the start of the new therapy. Patients who discontinue from study will be censored on the date of last evaluable tumor assessment.

Descriptive statistics will be provided for the DOR in responding patients (ie, median duration of response and 95% CIs) by treatment arm, including the associated Kaplan-Meier curves. A stratified log-rank test will be used to compare the duration of response between the two treatment arms.

9.4.5. Progression Free Survival

Progression-free survival is defined as the time from randomization 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. Patients lacking an evaluation of disease after first study treatment will have their PFS time censored on the date of randomization 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 and the stratified log-rank test will be used to obtain the estimate of median PFS time and to compare time to progression between the two treatment arms.

Additional sensitivity analyses (eg, Cox proportional hazard model or different censoring rules) will be performed and described in the SAP.

9.4.6. Subgroup Analyses

Treatment effect on OS will be evaluated in subgroup analyses of the following baseline characteristics where there are sufficient subjects:

- Age (< 65 years, ≥ 65 years)
- Gender (Female, Male)
- Prior treatment regimens in the advanced setting (1 vs 2)
- ECOG Performance Status (0, 1)
- Brain metastases (yes, no)
- Geographic regions: USA, Non-USA
- Smoking status (never, former/current)
- Receipt of maintenance chemotherapy (yes, no)
- Time elapsed since last chemotherapy (cut-off to be determined based on the distribution of the observed data)
- Time from last treatment with prior checkpoint inhibitor (≤ 30 days, > 30 days)
- Most recent tumor PD-L1 expression test result (high, low)
- Most recent TMB test result (high TMB, low TMB).

Subgroup analyses will be further described in the SAP but will utilize Cox proportional hazard models with treatment and baseline characteristic-by-treatment interaction to present HR and 95% confidence intervals within each subgroup of interest.

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 (defined as those occurring from the date of the first dose until 28 days after the last dose of study treatment for non-irAEs and those occurring from the date of the first dose until 100 days after the last dose of nivolumab for irAEs) will be summarized by maximum intensity and relationship to study therapy. Separate summaries will be provided for TEAEs, TESAEs, treatment-related AEs,

AESI, treatment-related SAEs, and other significant AEs (eg, 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, urinalysis, thyroid function tests and chemistry), vital signs, ECHO or MUGA scans 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.

Electrocardiogram assessments will be evaluated for change of QTc from baseline to the highest on-study value. 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 or MUGA scans 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 randomized into the study:

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

A summary of patient 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 duration of treatment, total study drug administered, dose intensity, compliance and reasons for the deviations from planned therapy for each agent separately and for the combination.

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. 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 sitravatinib concentrations will be reported by dose level, formulation, Day and Cycle. The exposure levels as well as the PK parameters of sitravatinib reported in earlier studies will be compared to the current study PK exposure and parameters to evaluate the potential effect of the study population, and concomitant administration of nivolumab on sitravatinib PK. Details of this analysis will be provided in the PKAP. Possible relationships between PK parameters, PD variables, safety, and efficacy may be examined.

9.6.2. Patient Reported Outcomes Analysis

For the EQ-5D-5L, the change from baseline in health state utility values and the visual analogue scale will be compared between treatment arms at each visit using a mixed effect model repeated measurement (MMRM) analysis, which adjusts for the same factors as the primary analysis and also the baseline health state utility value/visual analogue scale as appropriate. Adjusted mean differences between treatments and 95% CIs from these analyses will be presented. Descriptive statistics will be reported for health state domain (eg, proportion in each domain) and the visual analogue scale by visit, as well as the change in the visual analogue scale value and the derived utility index value from baseline.

The LCSS three summary items (symptom distress, activity level, overall quality of life) will be analyzed using a MMRM analysis as described above. Descriptive statistics will also be reported for all scores and change-from-baseline scores.

Further detail of analyses to be performed using the PRO endpoints will be provided in the SAP.

9.7. Interim Analysis

An interim analysis based on OS is planned when approximately 65% of the events (~242 events) are observed. The efficacy boundary is constructed using the O'Brien-Fleming boundary as implemented by Lan-DeMets alpha spending method. The alpha spend at interim and final analysis is 0.0109 and 0.0381. A non-binding futility analysis is also planned at the

time of the interim analysis. The futility boundary is constructed based on 2% conditional power (CP) and the study may be declared futile if the estimated HR at interim> 0.92. The exact alpha spent and the futility boundary will be adjusted based on the observed number of events.

The IDMC will review the safety and efficacy data and may make a recommendation to:

- stop the study for safety or futility,
- continue the study as planned, or
- stop the study for efficacy and may recommend submitting interim results for full marketing approval.

If the study continues as planned, the final analysis will include approximately 372 OS events and is expected to occur approximately 38 months after the start of enrollment.

9.8. Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will oversee the conduct of the study as outlined in the IDMC Charter. The IDMC will have access to open-label trial data and will perform the following functions:

- Review the conduct of the study and accruing safety data at 6-month intervals and on an ad hoc basis as safety questions arise.
- Review the interim analysis and recommend the appropriate course of action as outlined in Section 9.7.

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 (eg, 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/Research Ethics Board (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

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 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 and Privacy Protection

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.

Ethnic factors could influence the effects (safety and efficacy) of medicines and the risk/benefit assessment in different populations. Race and Ethnicity data are collected in CDISC SDTM (SDTM Implementation Guide v3.2), in accordance with ICH guidance (ICH E5) adopted by the EMA and FDA, to support population pharmacokinetic (PK) analysis, which is a well-established, quantitative method that can quantify and explain the variability in drug concentrations among patients. Variability can be attributed to intrinsic factors (eg, body weight, age, gender, race/ethnicity), or to extrinsic factors (eg, concomitant medications). In some cases, intrinsic or extrinsic factors lead to clinically relevant changes in drug concentrations that require a change in the dose or dosing regimen. Results from population PK analyses will be incorporated into drug product labeling to provide guidance on the dose or dosing regimen including any potential dose adjustment in some subpopulations (eg, race or ethnic group). Therefore, collecting race/ethnicity data in the study is essential to understand whether race/ethnicity could influence the PK, safety and/or efficacy.

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 (ie, 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 will be documented in writing by the Sponsor, as an Administrative Letter or amended protocol. 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 (eg, 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

In accordance with Regulation EU No 536/2014, the End of Trial in a Member State of the European Union is defined as the last visit of the last patient included in a member state, or at a later point in time defined in the protocol.

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, eg, 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. 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[1]

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
Domperidone (Only on Non US Market)	Motilium, Motillium, Motinorm Costi, Nomit	Antiemetic	Nausea, vomiting

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
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
Hydroxychloroquine	Plaquenil, Quineprox	Antimalarial, Anti-inflammatory	Malaria, SLE, rheumatoid arthritis
Ibogaine (Only on Non US Market)		Psychedelic	Narcotic addiction, unproven

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
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)

[1] 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[1]

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

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
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
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

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
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
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

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
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

[1] 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 3. EXAMPLES OF STRONG AND MODERATE CYP3A4 INHIBITORS

Strong CYP3A4 Inhibitors	Boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, diltiazem, elvitegravir/ritonavir, grapefruit juice, idelalisib, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, paritaprevir/ritonavir/ombitasvir plus dasabuvir, posaconazole, ritonavir, saquinavir/ritonavir, telaprevir, tipranavir/ritonavir, troleandomycin, voriconazole.
Moderate CYP3A4 Inhibitors	Aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil.

APPENDIX 4. ABBREVIATED PRESENTATION OF RECIST VERSION 1.1 GUIDELINES

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 randomization. If the baseline assessment is inadequate, subsequent statuses generally should be not evaluable.

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 (eg, '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 not evaluable.

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.
- Not evaluable:
  - 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.
- Not evaluable: 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.

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. 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), (EMA, 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 Protocol 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.

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 for patients in the combination arm. Visit windows of ± 3 days are allowed for Day 8 clinic visits for patients in the docetaxel arm.
Clinic Visits	Clinic visits may be conducted remotely by telephone/video conference; any missed assessments or procedures (eg, tumor assessment, laboratory assessments, vital signs, study drug administration, etc) should be documented as Protocol Deviations.
Clinic Visits	Clinic visits may be conducted at the patient's residence by qualified home health care professionals; any missed assessments or procedures (eg, 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.