Official Title of Study:

A Randomized Phase 3 Study of MRTX849 versus Docetaxel in Patients with Previously Treated Non-Small Cell Lung Cancer with KRAS G12C Mutation

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PROTOCOL TITLE:	A Randomized Phase 3 Study of MRTX849 versus Docetaxel in Patients with Previously Treated Non-Small Cell Lung Cancer with *KRAS* G12C Mutation
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STUDY SUMMARY

Title: A Randomized Phase 3 Study of MRTX849 versus Docetaxel in Patients with Previously Treated Non-Small Cell Lung Cancer with *KRAS* G12C Mutation

Rationale: RAS proteins are part of the family of small GTPases and are activated in response to growth factor stimulation and various other extracellular stimuli to regulate intracellular signaling pathways responsible for growth, migration, survival and differentiation of cells. The activation of RAS proteins at the cell membrane by growth factors results in the binding of key effector molecules, formation of signaling complexes, and the initiation of a cascade of intracellular signaling pathways within the cell including the RAF and PI3 kinase pathways. RAS proteins normally alternate between GTP- and GDP-bound conformations, where the GTP-bound conformation represents the "On" and GDP-bound the "Off" state. Dependence of RAS and other GTPases on guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs) to switch them on and off allows both processes to be highly regulated and responsive to multiple signal inputs. In contrast, oncogenic mutants of RAS generally function by preventing hydrolysis of GTP, thereby generating constitutively active GTP-bound RAS molecules with severe consequences for the cell including uncontrolled cellular growth and malignant transformation.

KRAS is the most frequently mutated gene of the RAS family, and *KRAS* mutations occur in approximately 30% of lung adenocarcinomas, 50% of colorectal cancers, and 90% of pancreatic ductal adenocarcinomas. Mutation of the glycine at residue 12 produces a steric block that prevents GAP proteins from accessing KRAS, thereby inhibiting GTP hydrolysis resulting in a highly activated GTP-bound form of RAS. Mutation of that amino acid residue to cysteine, noted as *KRAS* G12C (also known as *KRAS* p.G12C), comprises approximately 14% of lung adenocarcinoma and defines a unique segment of lung cancer without a current targeted therapy option. Large genomics studies characterizing lung cancers have indicated that *KRAS* mutations, including G12C, are mutually exclusive with other known oncogenic driver mutations in non-small cell lung cancer (NSCLC) including *EGFR*, *ALK*, *ROS1*, *RET*, and *BRAF* indicating that *KRAS* mutations define a unique segment of lung cancer without a current targeted therapy option. Functional genomics studies have demonstrated that NSCLC cancer cells exhibiting *KRAS* mutations are highly dependent on KRAS function for cell growth and survival.

	MRTX849 (also known as adagrasib) is a potent and orally available small molecule inhibitor of KRAS G12C. MRTX849 demonstrated potent inhibition of KRAS-dependent signal transduction and cancer cell viability with selectivity for KRAS G12C of over 1000-fold compared to KRAS wild-type. MRTX849 demonstrated broad-spectrum antitumor activity across several *KRAS* G12C-positive patient- or cell-derived tumor models implanted in mice, including complete tumor responses in a subset of models. Collectively, these results support the evaluation of MRTX849 in patients with malignancies having *KRAS* G12C mutations. Initial clinical trial observations with MRTX849 include demonstration of confirmed objective responses in NSCLC and colorectal cancer. This Phase 3 study compares the efficacy of MRTX849 versus docetaxel in patients with unresectable, locally advanced or metastatic NSCLC with *KRAS* G12C mutation who have previously received treatment with a platinum-based chemotherapy regimen and an immune checkpoint inhibitor.
Target Population:	Patients with unresectable, locally advanced or metastatic NSCLC with *KRAS* G12C mutation and disease progression on or after treatment with a platinum-based regimen and an immune checkpoint inhibitor.
Number in Trial:	Approximately 450 patients
Primary Objective:	To compare the efficacy of MRTX849 versus docetaxel in patients with NSCLC with *KRAS* G12C mutation and who have received prior treatment with a platinum-based regimen and immune checkpoint inhibitor therapy.
Secondary Objectives:	• To evaluate secondary efficacy endpoints in the study population. • To evaluate the safety and tolerability in the study population. • To evaluate the pharmacokinetics (PK) of MRTX849 administered in the study population. • To evaluate health-related quality of life (HRQOL) and lung cancer-specific symptoms in the study population.
Exploratory Objective	• To explore correlations between gene alterations (baseline and upon treatment resistance) with efficacy. • To evaluate the Progression-Free Survival in the next-line of therapy (PFS2) in the study population. • To evaluate efficacy outcome in the central nervous system (CNS) • To explore intracranial activity in patients with brain metastases using exploratory efficacy endpoints

Primary Endpoint:	• Progression-Free Survival (PFS)
Secondary Endpoints:	• Secondary efficacy endpoints: – Overall Survival (OS), – Objective Response Rate (ORR), – Duration of Response (DOR), and – 1-Year Survival Rate. • Safety characterized by type, incidence, severity, timing, seriousness and relationship to study treatment of adverse events (AEs), laboratory abnormalities, and number of patients discontinuing study treatment due to an adverse event. • Population PK parameters of MRTX849. • Patient Reported Outcome (PRO) scores using the following: – Lung Cancer Symptom Scale (LCSS), and – European Quality of Life Five Dimensions Questionnaire (EQ-5D-5L).
Exploratory Endpoints	• Gene alterations in tumor tissue and circulating tumor deoxyribonucleic acid (ctDNA). • Progression-Free Survival-2 (PFS2). • Time to CNS Progression. • Intracranial activity using CNS RECIST 1.1 endpoints in patients with brain metastases, including intracranial objective response rate (icORR), intracranial duration of response (icDOR), intracranial progression-free survival (icPFS) and intracranial time to progression (icTTP).
Study Design:	Study 849-012 is an open-label, randomized Phase 3 clinical trial comparing the efficacy of MRTX849 (adagrasib) versus docetaxel in patients with NSCLC with *KRAS* G12C mutation and who have received prior therapy with a platinum-based regimen and an immune checkpoint inhibitor. Secondary objectives include evaluation of safety and tolerability, secondary efficacy endpoints, PROs, and MRTX849 PK in the study population. The presence of *KRAS* G12C mutation in tumor tissue for the purpose of patient eligibility must be established using Sponsor pre-approved methods and laboratories. Presence of tumor *KRAS* G12C mutation may be established using Sponsor-approved local tests or the Sponsor-provided central laboratory test. For all enrolled patients *KRAS* mutation status and correlative tumor gene alterations will be

retrospectively tested using the tumor samples submitted no later than 30 days after the first dose of study treatment.

Patient eligibility for study enrollment based on objective disease progression on or after a platinum-based regimen and an immune checkpoint inhibitor will be evaluated by the Investigator.

Data entered into the case report form (CRF) are to include prior regimens, best overall response, if progression occurred on or after treatment and date of progression.

Eligible patients will be randomized in a 2:1 ratio to receive MRTX849 or docetaxel, respectively. Randomization will be stratified by:

1. Region (non-Asia-Pacific versus Asia-Pacific)
2. Sequential versus concurrent (administration of last prior platinum-based chemotherapy and anti-PD-1/PD-L1 antibody)

The requirements for tumor *KRAS* G12C for determining eligibility are presented in Table 1 and Figure 1. The Schedule of Assessments is presented in Table 2.

Study treatment will be administered in 3-week cycles. Patients randomized to the investigational arm will receive MRTX849 administered orally (PO) at a starting dose of 600 mg twice daily (BID). Patients randomized to the comparator arm will receive treatment with docetaxel. 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 local standards.

Disease response and progression will be evaluated in accordance with Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Blinded independent central review (BICR) for disease response and progression will be performed for the purpose of statistical analyses of these study endpoints. Disease assessments must be performed as scheduled according to the calendar to prevent the introduction of bias in the assessment of efficacy based on toxicity. 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 AEs, Investigator decision, patient refusal or death. Patients experiencing clinical benefit in the judgment of the Investigator may continue study treatment beyond Investigator assessed disease progression as defined by RECIST 1.1. Patients

considering continuation of study treatment beyond RECIST 1.1-defined disease progression must be provided with and sign an informed consent form detailing any available therapies and potential clinical benefit that the patient may be foregoing by continuing study treatment and will continue to undergo disease assessments until study treatment is discontinued. Imaging should continue to be submitted for BICR review until BICR confirmed disease progression. In the event a patient discontinues study treatment for a reason other than objective disease progression, disease assessments post-treatment should continue until objective disease progression is documented by the Investigator and BICR or start of subsequent anticancer therapy, whichever is sooner.

Patients randomized to the docetaxel arm will be offered the opportunity to crossover to the MRTX849 study treatment arm upon development of RECIST 1.1-defined disease progression per BICR provided that patient crossover eligibility criteria are met. Patients must sign a crossover informed consent form and meet all eligibility criteria for further treatment as described in Section 4.3 and Section 4.4 and will use the dosing regimen described in Section 5.3. The required assessments for patients who crossover are listed in Appendix 6.

Statistical Considerations:

Study 849-012 will utilize the fixed-sequence testing procedure on the endpoints with an overall 0.05 (2-sided) level of significance.

For the PFS endpoint, the study has 90% power to detect a HR of 0.645 (under an assumed median PFS for docetaxel arm of approximately 4 months compared to 6.2 months for the MRTX849 arm) at a 2-sided level of significance of 0.05 based on 246 PFS events.

For the secondary endpoint OS, the study has 80% power to detect a HR of 0.72 (under an assumed median OS for docetaxel arm of approximately 10 months compared to 13.9 months in the MRTX849 arm) at a 2-sided level of significance of 0.05 based on 334 death events. Assuming an enrollment duration of approximately 37 months at an average rate of 12 patients per month (approximately 450 patients), and an additional 15 months of follow-up will be required to reach the number of required death events.

There will be one analysis for the PFS endpoint and an interim analysis of OS (~50% of the expected death events), and one final analysis for the OS endpoint. The enrollment into the study is anticipated to be completed when the PFS analysis occurs. A group sequential design will be used with the O'Brien-Fleming boundary as implemented by the Lan-DeMets alpha spending method. A nonbinding futility boundary using the Rho family spending function with parameter of 3.0 is also constructed for OS. If the OS endpoint is statistically significant at

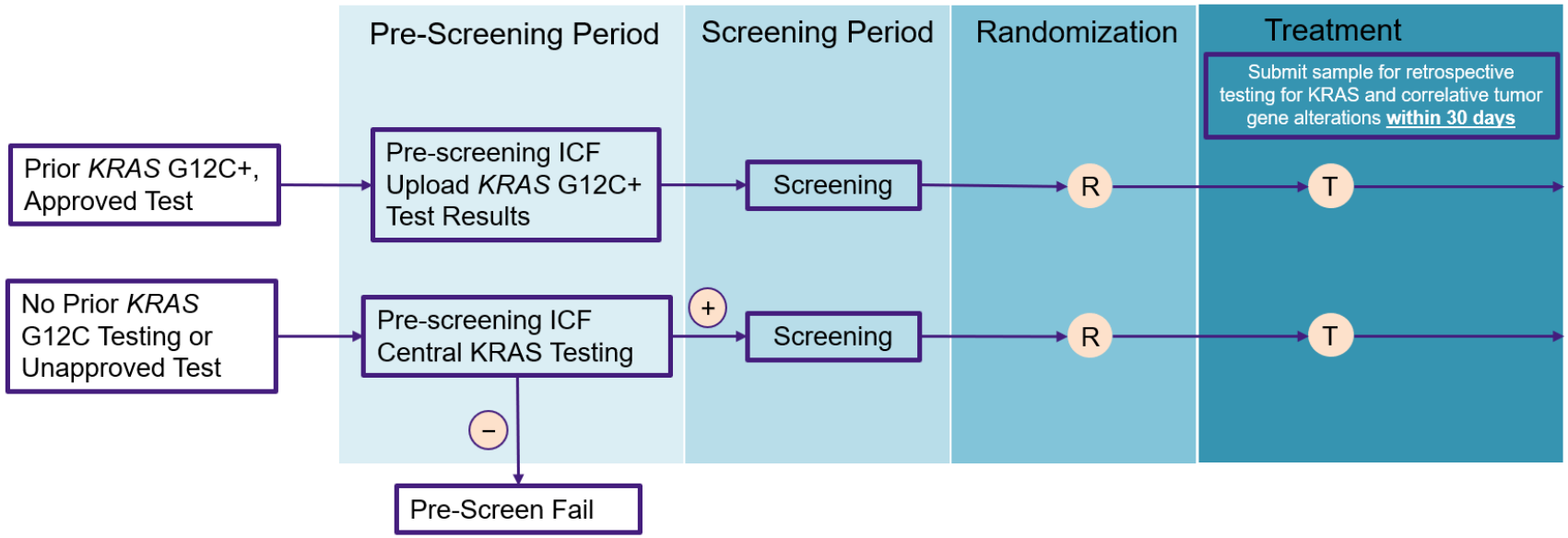
interim, the formal OS final analysis will not be conducted per group sequential design, and a survival update following the PFS analysis may be conducted as warranted.

Table 1: Pre-Screening Assessments

Patient eligibility for enrollment based on the presence of *KRAS* G12C mutation in the tumor may be established using Sponsor-approved local tests or a Sponsor-provided central laboratory test.

	Guidance
Evaluation of overall health status for potential clinical trial participation	Study eligibility requires adequate performance status and organ function. Patients undertaking pre-screening with the goal of considering participation in this study should have health status consistent with meeting eligibility criteria.
Informed Consent	Prior to sending results of a local Sponsor-approved tumor genotyping test to the Sponsor for review or sending tumor tissue to the Sponsor-approved central laboratory for genotyping, informed consent must be obtained using the IRB/EC-approved pre-screening ICF. After local or central laboratory documentation of *KRAS* G12C mutation, the main study consent should be obtained, followed by the required study-specific screening procedures.
Tumor Tissue Testing	Testing for *KRAS* G12C mutation is required for all patients. • For patients with previous test results using a Sponsor-approved method demonstrating *KRAS* G12C mutation, the existing result may be used for pre-screening and enrollment. • For patients without prior testing, the Sponsor-provided central laboratory test should be used during the pre-screening period. • For all enrolled patients, retrospective *KRAS* G12C mutation status and evaluation of correlative tumor gene alterations will be performed using tumor sample submitted to the central laboratory during pre-screening or within 30 days after first dose of study treatment. For central laboratory genotyping, tumor samples from the most recent biopsy or excision are preferred; however, if no recently obtained materials are available, samples from any time during patient's prior disease course are accepted. Tumor biopsies having significant risk should not be performed for the purpose of determining genetic eligibility. Note: Patients enrolled at sites in Germany will not undergo tumor lesion biopsy for the purpose of the study after the Screening period.

Figure 1: Timing of Pre-Screening Assessments



– = negative test; + = positive test; ICF = informed consent form; R = randomization; T = treatment.

Table 2: Schedule of Assessments

The Schedule of Assessments provides an overview of clinic visits and protocol procedures. Additional, unplanned assessments should be performed as clinically indicated, including for the purpose of fully evaluating AEs.

	Screening Within 28 Days	**Cycles 1-4**		**Cycles 5 + Day 1 (± 2 days)**[19]	**End of Treatment Visit**[1] **28-35 Days After Last Dose**	**Long Term Follow-up Every 2 Months (± 14 days)**
		Day 1 C1 (- 2) C2-C4 (± 2)	**Day 15 (± 2 days)**			
Informed Consent[2]	X					
Tumor Genotyping[3]	X		At disease progression (optional)			
Randomization	X					
Medical History & Prior Therapy	X					
ctDNA[4]	X		At disease progression (optional)			
Demographics & ECOG	X					
Physical Exam[5] - Full (F), Abbrev (A)	F	A	A	A	F	
Vital Signs[6]	X	X	X	X	X	
Hematology[7]	X	X	X	X	X	
Chemistry[7]	X	X		X	X	
TSH[7]	X	C3		C5	X	
HIV, HBV, HCV Serology (in specified countries)[8]	X					
Pregnancy or FSH Test[9]	X	As clinically indicated except where required routinely[9]			X	
Single 12-Lead ECG[10]	X	As clinically indicated			X	

	Screening Within 28 Days	**Cycles 1-4**		**Cycles 5 + Day 1 (± 2 days)**[19]	**End of Treatment Visit**[1] **28-35 Days After Last Dose**	**Long Term Follow-up Every 2 Months (± 14 days)**
		Day 1 C1 (- 2) C2-C4 (± 2)	**Day 15 (± 2 days)**			
ECHO or MUGA (preferred except in Germany)[11]	Within 45 days			C5 & C9 (- 7 to + 2 day window)		
Disease Evaluation[12]	X	Every 6 weeks (± 10 days) until Week 49, then every 12 weeks				
PK Sampling[13] & Triplicate ECGs[14]		C1 & C2 – Predose & Peak; C3 – Predose		C5 & C7 Predose		
MRTX849 Dispensing (D) & Reconciliation (R)		D, R (C2-4)		D, R	R	
Docetaxel Admin. & Premeds[15]		X		X		
PRO Questionnaires[16]		X	X	X	X	
AEs[17] & Concomitant Medications	SAEs only	Throughout				
Survival & Anticancer Therapies[18]						X

Abbreviations: A = abbreviated, symptom-directed evaluation, Ab = antibody; AE =adverse event; BICR = blinded independent central review; C = cycle; ctDNA = circulating tumor deoxyribonucleic acid; CTFG = Clinical Trials Facilitation Group; D = dispense; ECG = electrocardiogram; ECHO = echocardiogram; F = full physical examination; FSH = follicle stimulating hormone; HBcAb = hepatitis B core antibody; HBV = hepatitis B; HCV = hepatitis C virus antibody; HGRAC = Human Genetic Resource Administration of China; HIV = human immunodeficiency virus; ICF = informed consent form; LCSS = Lung Cancer Symptom Scale; LFT = liver function test; MUGA = multigated acquisition scan; PI = Principal Investigator; PK = pharmacokinetic; PRO = patient reported outcome; R = reconcile; RNA =ribonucleic acid; SAE = serious adverse event; TSH = thyroid-stimulating hormone.

[1] End of Treatment: Visit occurs 28-35 days after last dose of study treatment. Repeat of assessments completed in the previous 4 weeks is not required with the exception of assessment of AEs, hematology, chemistry and pregnancy test as applicable.

[2] Informed Consent: May be performed more than 28 days prior start of study treatment and must be completed prior to initiation of any study-specific assessments.

[3] Tumor Genotyping for *KRAS* G12C and Other Mutations: Genotyping of tumor tissue for eligibility may occur at any time prior to the study screening period in patients considered for enrollment. If no prior genomic testing for *KRAS* mutation has been performed using a Sponsor-approved laboratory, testing to determine eligibility will be provided by the Sponsor. Informed consent using the pre-screening ICF is required prior to sending results of a local test to the Sponsor for review or submission of samples for study-specific testing. For all patients randomized into the study, adequate tumor tissue samples for retrospective testing of *KRAS* G12C mutation status and correlative gene alterations must be provided to the central laboratory during pre-screening or within 30 days after first dose of study treatment. Tumor tissue samples for eligibility should be from the most recent biopsy or excision. Tumor biopsies having significant risk should not be performed for the purpose of determining patient eligibility. Optional tumor tissue may also be obtained at the time of progression for those patients with an objective tumor response or prolonged stable disease (> 4 months) on study. Note: Patients enrolled at sites in Germany will not undergo tumor lesion biopsy for the purpose of the study after the Screening period.

[4] Blood samples for ctDNA: Baseline sample collection may be performed during the screening period through the first dose day. Optional on-study blood samples for ctDNA may be obtained at the time of progression for those patients with an objective tumor response or prolonged stable disease (>4 months) on study. In China, the samples for ctDNA testing will be collected after the Human Genetic Resource Administration of China (HGRAC) approval.

[5] Physical Examinations: A full physical examination (F) required at Screening and End of Treatment only. All other evaluations will be abbreviated, symptom-directed evaluations (A). Allowed time windows permit evaluation within two calendar days (Friday assessments permitted for Monday dosing) in advance of busy days, eg, PK profile collection.

[6] Vital Signs: Weight, temperature, blood pressure, pulse rate, and respiratory rate to be assessed prior to dosing as indicated. Vital signs are to be performed in the semi-recumbent position. Height will be recorded at screening only.

[7] Safety Laboratory Assessments: Hematology, chemistry, and thyroid function will be performed using local laboratories. Parameters to be assessed are presented in Table 15. Repeat baseline assessment not required if assessment performed within 7 days before the first dose. Allowed time windows permit evaluation within two calendar days (Friday assessments permitted for Monday dosing) in advance of busy days, eg, PK profile collection. Additional assessments of any laboratory parameters may be performed according to standard of care or as clinically indicated.

[8] HIV, HBV, HCV Serology for sites in Germany, Czech Republic, and Portugal: Patients must be tested for HIV Ab, hepatitis B core antibody (HBcAb), and hepatitis C virus (HCV Ab) infection (by local laboratory) at screening. Patients with a positive HBcAb test should also be tested with HBsAg test, and those patients with a positive HBsAg test should also be tested for HBV DNA. Patients with a positive HCV Ab test should undergo a nucleic acid test for HCV RNA (also known as viral load).

[9] Pregnancy and Follicle Stimulating Hormone Test: If the patient is a woman of childbearing potential, negative urine or serum pregnancy test performed by the local laboratory at Screening and End of Treatment will be required (in the United Kingdom and Germany, screening test required ≤ 7 days and ≤ 72 hours, respectively, before first dose of study treatment). In addition, in regions where required by regulation (eg, European Union), monthly pregnancy testing will be performed until the end of systemic exposure to study treatments (testing may be performed at the beginning of each 3-week treatment cycle for convenience). At study sites in Austria, Belgium, France, Italy, Portugal, South Korea, and Spain and as required at other sites, pregnancy testing will be performed at the beginning of every treatment cycle and the same frequency (approximately monthly) for at least 1 month after the last dose of MRTX849 or docetaxel. Additional pregnancy testing is to be performed whenever pregnancy is suspected during the study. Verification of postmenopausal status at screening should be documented by follicle stimulating hormone (FSH) testing in countries operating in compliance with Clinical Trials Facilitation Group (CTFG) guidelines.

[10] Single 12-lead ECGs to be performed unless otherwise stated. In addition, ECGs are to be performed as clinically indicated. ECGs are to be performed in the semi-recumbent position. Assessments will include an evaluation of heart rate, PR, QRS, RR, QT, and QTc intervals.

[11]MUGA or ECHO: MUGA is preferred (except in Germany where it is not an option); the same modality should be used throughout a patient's participation when possible. May be performed within 45 days (different from 28-day window for other assessments).

[12]Disease Evaluations: To be performed at screening (28-day window allowed) and every 6 weeks from the date of randomization (± 10-day window for all other assessments except screening) until week 49 (~12 months) and then every 12 weeks. In Czech Republic, bone lesion assessment must be performed at 12-week intervals and no more than 4 times per year. Assessment locations to be included are listed in Table 13 and recommended imaging modalities are listed in Table 14. In the event of treatment discontinuation for reasons other than objective disease progression, disease assessments post-treatment should continue until objective disease progression is documented by the Investigator and BICR or start of subsequent anticancer therapy, whichever is sooner. More detailed guidance on assessments to be performed and exceptional circumstances is provided in Section 7.3.

[13]Pharmacokinetic Sampling: PK sampling will be collected from patients in the MRTX849 arm only. Predose samples should be collected up to 30 minutes prior to dosing in clinic. Peak samples should be collected 4 to 6 hours after dosing unless logistically infeasible. In addition to the scheduled samples, an unscheduled predose PK blood sample (along with a triplicate ECG, see below) should be collected as soon as possible after an SAE, immediately prior to treatment interruption or dose reduction for a treatment-related nonserious AE, and at a clinic visit at least one week following a dose reduction of MRTX849. If MRTX849 has been held or discontinued for ≥ 3 days, unscheduled PK collections are not required.

[14]Triplicate ECGs: Triplicate ECGs will be collected from patients in the MRTX849 arm only. To be performed after the patient has rested in the supine position for at least 5 minutes. All ECGs will be obtained prior to and as close as possible to PK sample collection. Three individual ECG tracings should be obtained as closely as possible in succession, between 1 and 2 minutes apart. The full set of triplicates should be completed in approximately 4 minutes or less.

[15]Docetaxel Administration and Premedication: Patients randomized into the docetaxel arm should receive premedication with dexamethasone (or institutional equivalent) and in accordance with labeling instructions and institutional guidelines. Initiation of glucocorticoid premedication should only occur after randomization but may be initiated a few days prior to docetaxel administration. Prior to each subsequent dose of docetaxel, blood counts and laboratory values (including LFTs) should be checked to ensure dosing consistent with package labeling. Patients randomized to the docetaxel arm will have the option to receive MRTX849 study treatment upon development of RECIST 1.1-defined disease progression per BICR, provided that all crossover eligibility criteria are met and the crossover informed consent form is signed. If patient has completed docetaxel treatment, in accordance with local standards, and is awaiting crossover eligibility, imaging should continue on schedule (including BICR submission) and end of docetaxel treatment information should be collected in the docetaxel End of Treatment Form. End of Treatment visit and Long-term Follow-up should only be completed once final study treatment is given (ie, after crossover treatment). Patients who complete docetaxel treatment in accordance with local standards are not required to complete on study visits every 3 weeks while awaiting crossover.

[16]PRO Questionnaires: Generally, to be performed prior to other assessments during clinic visits. Exceptions include assessments that are scheduled in other departments prior to the clinic visit, and vital signs if they are performed during patient check-in. EQ-5D-5L questionnaires should always be completed before LCSS.

[17]Adverse Events: SAEs should be reported from the time of the prescreening informed consent until resolution. During the pre-screening period (ie, after pre-screening informed consent and before the main study informed consent), reporting of SAEs is limited to events associated with study required assessments (eg, biopsies for tumor genotype testing). Beginning at the time of signing the main study informed consent to begin clinical eligibility screening, reporting of all SAEs is required. Other AEs occurring from the first day of study treatment until the End of Treatment visit should be recorded.

[18]Long-term Follow-up: Survival status and subsequent anticancer therapies will be collected as described in Section 6.4 every 2 months (± 14 days) from the End of Treatment visit until death or lost to follow-up.

[19] Patients on MRTX849 for at least 12 months whom the PI believes are clinically stable on current dose regimen, may reduce frequency of clinic visits from every cycle to every other cycle (ie, Day 1 visits required every 6 weeks vs. 3 weeks).

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LIST OF ABBREVIATIONS

Abbreviation	Definition
Ab	Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AT	Accelerated Titration
AUC	Area Under the Curve
BCRP	Breast Cancer Resistance Protein
BE	Bioequivalence
BICR	Blinded Independent Central Review
BID	Twice daily
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CI	Confidence Interval
CIT	Checkpoint Inhibitor Therapy
CK	Creatine Kinase
CL_{int}	Intrinsic Clearance
CNS	Central Nervous System
CR	Complete Response
CRC	Colorectal Cancer
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography Scan
CTA	Clinical Trial Application
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumor Deoxyribonucleic Acid
CTFG	Clinical Trials Facilitation Group
CV	Coefficient of Variation
CYP	Cytochrome P450
DDI	Drug-Drug Interaction

Abbreviation	Definition
DHEA	Dehydroepiandrosterone
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
DOR	Duration of Response
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EQ-5D-5L	European Quality of Life Five Dimensions Questionnaire
ER	Extraction Ratio
ERK1/2	Extracellular Signal-regulated Kinases 1/2
EIU	Exposure In-Utero
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
^{18}F-NaF	Fluorine 18–Sodium Fluoride
FSH	Follicle Stimulating Hormone
GAP	GTPase-Activating Proteins
GCP	Good Clinical Practice
GEF	Guanine Nucleotide Exchange Factor
GSH	Glutathione
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B
HBC	Hepatitis C
HCV Ab	Hepatitis C Virus Antibody
HDPE	High-Density Polyethylene
hERG	human Ether-a-go-go Related Gene
HIV	Human Immunodeficiency Virus
HNSTD	Highest Non Severely Toxic Dose
hr	Hour
HR	Hazard Ratio

Abbreviation	Definition
IB	Investigator's Brochure
IC_{50}	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation
icDOR	Intracranial Duration of Response
icORR	Intracranial Objective Response Rate
icPFS	Intracranial Progression-Free Survival
icTTP	Intracranial Time to Progression
IDMC	Independent Data Monitoring Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intrauterine Device
IV	Intravenous
IWRS	Interactive Web Response System
kg	Kilogram
K_i	Inhibition Constant
LCSS	Lung Cancer Symptom Scale
LLN	Lower Limit of Normal
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
MM	Medical Monitor
MMRM	Mixed Effect Model Repeat Measurement
MRI	Magnetic Resonance Imaging
msec	Millisecond
mTPI	Modified Toxicity Probability Interval
MUGA	Multigated Acquisition Scan
NCI	National Cancer Institute
NE	Not Evaluable
NGS	Next Generation Sequencing
NOAEL	No-Observed-Adverse-Event-Level

Abbreviation	Definition
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PBPK	Physiologically-based Pharmacokinetics
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
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
PO	Oral
PPI	Proton Pump Inhibitor
PR	Partial Response
PVC	Polyvinyl Chloride
PTR	Peak-To-Trough Concentration Ratio
QD	Once Daily
QTc	Corrected QT Interval
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
shRNA	Short Hairpin Ribonucleic Acid
SMT	Safety Management Team
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Terminal Elimination Half-life
TEAE	Treatment-Emergent Adverse Event

Abbreviation	Definition
TI	Therapeutic Index
t_{max}	Time to Maximum Plasma Concentration
TMB	Tumor Mutation Burden
TPS	Tumor Proportion Score
TSH	Thyroid-Stimulating Hormone
UI	Utility Index
ULN	Upper Limit of Normal
US	United States
VAS	Visual Analogue Scale
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization
WOCBP	Women of Child Bearing Potential
µg	Microgram
µM	Micromolar

1. INTRODUCTION AND RATIONALE

1.1. Therapeutic Strategy Targeting KRAS

RAS proteins are part of the family of small GTPases that are activated in response to growth factor stimulation and various other extracellular stimuli to regulate intracellular signaling pathways responsible for growth, migration, survival and differentiation of cells. The activation of RAS proteins at the cell membrane by growth factors results in the binding of key effector molecules, formation of signaling complexes, and the initiation of a cascade of intracellular signaling pathways within the cell including the RAF and PI3 kinase pathways (Simanshu, 2017). Since defects in RAS may result in uncontrolled cellular signaling and malignant transformation, the activation of RAS proteins is tightly controlled in normal cells. To initiate intracellular signaling, RAS proteins must be activated or turned "on" by extracellular stimuli. RAS proteins normally alternate between GTP- and GDP-bound conformations, where the GTP-bound conformation represents the "On" and GDP-bound the "Off" state. Dependence of RAS and other GTPases on guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs) to switch them on and off allows both processes to be highly regulated and responsive to multiple signal inputs. In contrast, oncogenic mutants of RAS generally function by preventing hydrolysis of GTP, thereby generating constitutively active GTP-bound RAS molecules with severe consequences for the cell including uncontrolled cellular growth and malignant transformation.

The *RAS* family of genes is comprised of 3 members; *KRAS*, *NRAS*, and *HRAS* and constitute the most frequently mutated family of oncogenes in human cancer. *RAS* mutant cancers account for nearly 25% of all human cancers and one million deaths per year worldwide. The majority of *RAS* family mutations are missense mutations that result in amino acid changes at residues (codons) 12, 13, and 61; the frequency of mutation at each of these residues, and the isoform mutated, varies across different cancer types (Ostrem, 2016). Among the *RAS* family members, missense mutations most frequently occur in *KRAS* (85%), and far less frequently in *NRAS* (12%) and *HRAS* (3%) (Simanshu, 2017). *KRAS* is the most frequently mutated gene of the RAS family, with mutations occurring in approximately 30% of lung adenocarcinomas, 50% of colorectal cancers, and 90% of pancreatic ductal adenocarcinomas. The vast majority of *KRAS* missense mutations affect residue 12. The mutation of the glycine at residue 12 to an amino acid residue other than proline produces a steric block that prevents GAP proteins from accessing KRAS, thereby inhibiting GTP hydrolysis and resulting in a highly activated GTP-bound form of RAS (Ostrem, 2016).

In NSCLC, *KRAS* G12C is the most common mutation comprising nearly half of all *KRAS* mutations (Simanshu, 2017), followed by G12V and G12D (Campbell, 2016), (Matikas, 2017). Large genomics studies characterizing lung cancers have indicated that *KRAS* mutations, including G12C, are mutually exclusive with other known oncogenic driver mutations in NSCLC including *EGFR*, *ALK*, *ROS1*, *RET*, and *BRAF*, where the development of therapeutic strategies directly targeting oncogenic genomic alterations has resulted in substantial benefits for patients with a variety of cancers. These observations suggest that *KRAS* mutations similarly define a unique segment of lung cancer for which a targeted therapy option is currently unavailable

(Campbell, 2016). Importantly, large scale functional genomics studies utilizing short hairpin ribonucleic acid (shRNA) knockdown technology to block the function of thousands of gene products across hundreds of cancer cell lines have demonstrated that cancer cells exhibiting *KRAS* mutations are highly dependent on KRAS function for cell growth and survival (McDonald, 2017). Together, these findings illustrate a critical role for *KRAS* mutations as a causative factor in a significant number of human tumors and highlight a compelling opportunity for therapeutic agents targeting KRAS to make an impact in treating these cancers.

Despite over 30 years of KRAS drug discovery research, development of therapies targeting KRAS has been elusive. Small molecules that bind tightly to KRAS proteins have been difficult to find, mostly because KRAS proteins lack a deep pocket to which small molecules could bind with high affinity. However, recent studies indicate that targeting the KRAS G12C mutant variant may be feasible through irreversible targeting of the mutated cysteine with covalent small molecule inhibitors that block the catalytic activity and signal transduction downstream of mutant KRAS (Ostrem, 2013), (Lito, 2016). This work led to the development of MRTX849, a potent and orally available small molecule inhibitor of KRAS G12C. MRTX849 binds covalently to the mutant cysteine residue, shows high selectivity, and has demonstrated broad-spectrum activity in xenograft models harboring the *KRAS* G12C mutation. Objective tumor responses in patients with NSCLC and CRC have also been observed in the Phase 1 setting.

1.2. 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.

1.2.1. First-line Treatment of NSCLC

Most patients with advanced NSCLC are treated with chemotherapy and immune checkpoint inhibitor therapy (CIT). Platinum-based chemotherapy doublets, with or without bevacizumab in selected patients, have until recently been the standard of care for most patients with advanced NSCLC in the first-line treatment setting (Schiller, 2002), (Sandler, 2006), (Scagliotti, 2008). The recent development of pembrolizumab for the treatment of NSCLC has led to its rapid incorporation of this agent as a key component of first-line treatment. Initially pembrolizumab was compared against standard chemotherapy in patients with untreated, advanced NSCLC characterized by ≥ 50% tumor PD-L1 tumor proportion score (TPS) expression, and an improvement in survival was observed along with a favorable safety profile (Reck, 2016), leading to US FDA approval of pembrolizumab in the first-line treatment setting for this patient population. Subsequently, efficacy of pembrolizumab was also demonstrated as monotherapy in untreated patients with nonsquamous NSCLC with a PD-L1 TPS of ≥ 1% (Mok, 2019), and in combination with a platinum agent and pemetrexed in patients with metastatic nonsquamous

NSCLC regardless of PD-L1 TPS (Gandhi, 2018). These trials led to broad use of pembrolizumab combined with platinum-based chemotherapy as a standard option for first-line treatment of nonsquamous NSCLC, and pembrolizumab monotherapy as an option for some patients with untreated, advanced NSCLC, particularly those with disease characterized by PD-L1 TPS of ≥ 50%.

1.2.2. Second-Line Treatment of NSCLC

For patients with advanced NSCLC previously treated with platinum-based chemotherapy, approved treatment options include docetaxel alone or in combination with ramucirumab, and pemetrexed. Median OS reported in randomized clinical trials using these regimens as experimental or comparator therapies has varied between approximately 5.7 and 10.5 months while median PFS has ranged between 2.3 to 4.5 months and ORR has ranged from 5.5 to 23% (Shepherd, 2000), (Hanna, 2004), (Krzakowski, 2010), (Scagliotti, 2009), (Tomasini, 2016), (Garon, 2014). More recently, immune CITs have been approved by the US FDA for second-line treatment of advanced NSCLC. Based on improved outcomes with nivolumab, pembrolizumab, and atezolizumab in the second-line setting compared to docetaxel (Borghaei, 2015), (Brahmer, 2015), (Garon, 2015), (Herbst, 2016), (Rittmeyer, 2017), these agents have been approved by the FDA for treatment of patients with advanced NSCLC with progression on or after platinum-based chemotherapy. However, the incorporation of pembrolizumab into first-line treatment of advanced NSCLC has limited the use of immune CITs in the second-line treatment setting for many patients, where options include a clinical trial or a docetaxel-based regimen.

Thus, despite the significant advances of chemotherapy and immunotherapy for NSCLC, including those for patients with *KRAS* G12C tumor mutation, patients ultimately develop progressive disease, and the outcome of patients with advanced NSCLC after treatment with platinum-based chemotherapy and an immune CIT remains poor.

1.3. MRTX849

MRTX849 (also known as adagrasib) is a small molecule that elicits antitumor activity through selective, high affinity, covalent binding to and inhibition of the KRAS G12C mutant variant.

Background information in addition to that presented below is available in the MRTX849 Investigator's Brochure.

1.3.1. MRTX849 Drug Substance

The chemical formulation of MRTX849 is as follows:

MRTX849 Free Base

Chemical Formula: $C_{32}H_{35}ClFN_7O_2$

Molecular Weight: 604.1 g/mol

1.3.2. Nonclinical Pharmacology of MRTX849

Pharmacology studies have been conducted to characterize the pharmacologic targets, activity, mechanism of action, PD, and antitumor efficacy of MRTX849 both in vitro and in vivo (Hallin, 2020).

1.3.2.1. In Vitro Activity of MRTX849

Biochemical and cellular assays demonstrate that MRTX849 inactivates mutant KRAS by covalent binding to the cysteine 12 of KRAS G12C. MRTX849 proved to be highly selective for KRAS G12C over other surface-exposed cysteines in NCI-H358 cells.

In studies of KRAS-dependent signal transduction pathways in cells with the *KRAS* G12C mutation, MRTX849 inhibited phosphorylated ERK1/2 with an IC_{50} value of 17 nM. In cell-based assays, MRTX849 inhibited viability in 17 *KRAS* G12C mutant cell lines in a 3D assay format (IC_{50} values from 0.2 to 1042 nM). In contrast, IC_{50} values were greater than 3000 nM in 3 non-G12C-mutant *KRAS* models evaluated indicating that MRTX849 elicits antitumor activity mediated through selective binding to and inhibition of the *KRAS* G12C mutant variant.

To evaluate the effect of two MRTX849 human metabolites, M11 and M68, on KRAS-dependent downstream signal transduction, phosphorylation of ERK1/2 was evaluated over a range of concentrations. Metabolite M68 was not active and M11 was greater than 80-fold less active compared to MRTX849. These data suggests that both M11 and M68 do not contribute significantly to the pharmacological activity of MRTX849.

1.3.2.2. In Vivo Activity of MRTX849

MRTX849 effectively modified KRAS G12C protein and inhibited KRAS-dependent signal transduction in patient- and cell line-derived human tumor xenograft models harboring *KRAS* G12C mutations. A dose-dependent increase in MRTX849 plasma concentration, KRAS protein modification, and KRAS-dependent signal transduction through pERK and pS6 was observed following oral administration of 10, 30, and 100 mg/kg doses of MRTX849. Consistent with these observations, MRTX849 demonstrated dose-dependent antitumor efficacy in *KRAS* G12C-mutant xenograft models, with tumor growth inhibition observed at doses as low as 3 mg/kg and maximal tumor regression observed at 100 mg/kg. MRTX849 administered at 100 mg/kg demonstrated broad cytoreductive antitumor efficacy in 18 out of 23 patient- and cell line-derived *KRAS* G12C-mutant human tumor xenograft models but did not significantly inhibit tumor growth in 3 non-G12C-mutant *KRAS* models.

1.3.2.3. Secondary Pharmacodynamics of MRTX849

The selectivity of MRTX849 was profiled against a broad panel of 44 receptors, ion channels and enzymes. The initial screen at 10 µM resulted in 50% inhibition against 18 targets. The follow-up assay to determine K_i for these receptors identified 4 receptors with K_i values less than 1 µM. The receptors included alpha 1A adrenergic antagonist, muscarinic M2 antagonist, serotonin 5HT1A agonist, and serotonin 5HT1B antagonist, with K_i of 0.15 µM, 0.30 µM,

0.17 μM, and 0.14 μM, respectively. These K_i values are approximately 2- to 4-fold higher than the observed geometric mean steady-state unbound C_{max} of 0.08 μM associated with the MRTX849 600 mg twice daily (BID) in patients (Study 849-001, n = 17).

1.3.2.4. Safety Pharmacology of MRTX849

A series of in vitro and in vivo safety pharmacology studies demonstrate that MRTX849 poses minimal risk for adverse effects on major physiological systems. Based on in vitro human ether-a-go-go related gene (hERG) binding, an in vitro Guinea pig Langendorff study, and ECG parameters collected in the repeat-dose dog toxicology study, MRTX849 does not pose a risk for QT prolongation. In addition, there were no changes in heart rate or blood pressure in dogs treated at doses up to 25 mg/kg/day. CNS effects were monitored during the conduct of the rat and dog 28-day repeat-dose toxicology studies. There were no remarkable clinical signs suggestive of CNS effects, nor were there microscopic changes in neuronal tissues.

1.3.3. Nonclinical Pharmacokinetics and Metabolism of MRTX849

In vitro studies were conducted to assess MRTX849 absorption and protein binding. Assays using Caco-2 cells demonstrate that MRTX849 has high permeability. Studies indicated reversible protein binding for MRTX849 ranging from 97 to 99% across species.

In vivo studies were conducted to assess MRTX849 pharmacokinetics and metabolism. MRTX849 exhibited good oral bioavailability and extensive tissue distribution. No major differences in pharmacokinetic properties related to sex were observed. In general, oral plasma exposure increased dose-proportionately within the projected efficacious dose range with less-than-proportional increases observed at relatively higher dose levels, possibly due to saturation of absorption. MRTX849 demonstrated moderate hepatic extraction ratios across species in vitro with oxidative metabolism identified as the predominant elimination route with additional contribution from GSH-mediated clearance. In vivo, MRTX849 parent was the predominant species identified in plasma circulation or excreted in urine and bile following oral administration. MRTX849 metabolites identified in vitro and in vivo include 2 major oxidative metabolites identified at the pyrrolidine ring as well as electrophile GSH and cysteine conjugates of both parent and oxidative metabolites. No individual metabolites comprised greater than 20% of all MRTX849-related material. The *N*-desmethyl metabolite exhibited comparable potency to MRTX849 and has the potential to contribute to antitumor activity. Reaction phenotyping studies indicated that CYPs 3A4 and 2C8 mediate the majority of oxidative metabolism. Overall, metabolite profiles were consistent in vitro and in vivo and across all species evaluated indicating that a similar overall metabolism pattern was present in nonclinical efficacy and toxicology species compared to humans.

The contribution of CYP2C8 to MRTX849 metabolism at steady state when CYP3A4 is inhibited by MRTX849 (ie, auto-inhibition) was evaluated using human hepatocyte assays. Substrate depletion experiments were conducted in the presence of CYP3cide to inhibit all CYP3A4 mediated metabolism. With the addition of gemfibrozil glucuronide, MRTX849 intrinsic clearance was inhibited by a further 46%. Therefore, CYP2C8 accounts for 46% of non-CYP3A4 mediated hepatic metabolism of MRTX849 at steady state.

Reversible or time-dependent inhibition of CYPs by MRTX849 was evaluated in human liver microsomes. MRTX849 did not inhibit CYP1A2, CYP2C8, and CYP2C19 (IC_{50} > 50 μM) and was found to be a weak to moderate reversible inhibitor of CYP2B6-, CYP2C9-, CYP2D6-, and CYP3A4-mediated substrate metabolism. The *Ki* values for inhibition exceeded 10 μM for all but CYP2B6, CYP2C9, and CYP3A4 which displayed *Ki* values of 4.0, 3.2, and 8.2 μM, respectively. MRTX849 was not a time-dependent inhibitor of CYP2C8, CYP2C9, or CYP2D6 at concentrations up to 50 μM. MRTX849 was a time-dependent inhibitor of CYP3A4-mediated midazolam hydroxylation and the *Kinact* and *Ki* values were determined to be 0.035 min^{-1} and 1.85 μM, respectively. These results indicate that MRTX849 is a moderately potent competitive inhibitor of CYP2B6, CYP2C9, and CYP3A4, as well as a time-dependent inhibitor of CYP3A4 in vivo. MRTX849 inhibition of *KRAS* G12C was > 100-fold greater compared with *Ki* values for competitive or time-dependent inhibition of each evaluated CYP enzyme, indicating that the inhibition potential is predicted to be dependent on dose and plasma exposure of MRTX849 achieved in human studies.

Nonclinical studies were also conducted to investigate whether MRTX849 is a substrate as well as an inhibitor of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) in transfected-cell monolayer transport assays. MRTX849 was determined to be a substrate of both P-gp and BCRP. MRTX849 also inhibited P-gp and BCRP-mediated efflux of probe substrate molecules, indicating that it is also a likely inhibitor of P-gp and BCRP in vivo. The IC_{50} value for MRTX849 inhibition of P-gp-mediated quinidine efflux was 0.98 μM and the IC_{50} value for MRTX849 inhibition of BCRP-mediated prazosin efflux was 15.2 μM. Based on the estimate of the intestinal luminal concentration of MRTX849 (I_{gut}) for a 600 mg dose relative to the IC_{50} for P-gp and BCRP inhibition, MRTX849 has a potential to inhibit P-gp and BCRP. MRTX849 is neither a substrate nor inhibitor of the OAT1, OAT3, OAT1B1, OATP1B3, or OCT2 uptake transporters.

Collectively, these in vitro studies indicated that further investigations (ie, clinical drug-drug interaction study and/or modeling) are warranted to evaluate: 1) the clinical effect of MRTX849 on CYPs 2B6, 2C9, 2D6, and 3A4 and drug transporters P-gp, BCRP, and MATE1; and 2) the clinical effect of strong inhibitor or inducer of CYP3A/P-gp and BCRP on the PK of MRTX849. Refer to Section 1.3.5.2 for PK results of these clinical investigations.

1.3.4. Nonclinical Toxicology of MRTX849

The nonclinical safety profile of MRTX849 was well characterized through the conduct of repeat-dose studies of up to 13-weeks in duration and genetic toxicology studies. The primary target organ effects in repeat-dose studies in both rats and dogs were primarily driven by possible phospholipidosis in multiple tissues. In the rat, the target tissues included lung, trachea, heart, skeletal muscle, bone marrow, spleen, pancreas and female sex organs. In the dog target tissues included bone marrow, lung, heart and spleen. The extent of vacuolization and the presence of foamy macrophages were more prominent in the rat as compared to dogs, and these effects occurred at doses above the projected human efficacious concentrations and were reversible. Phospholipidosis is a common finding in toxicology studies conducted with cationic amphiphilic drugs like MRTX849.

In both species, common target organs include the heart, spleen, lung and bone marrow. The changes in the lung appear to be associated with foamy alveolar macrophages, possibly due to phospholipidosis. Similarly, the splenic changes may also be related to scavenging of peripheral foamy inflammatory cells. This effect was not considered adverse in the dog, while in the moribund rats, it was associated with necrosis in the spleen and considered adverse. In the dog, the bone marrow changes of decreased erythropoiesis led to decreases in red blood cell parameters and decreased reticulocyte counts. However, in the rat 28-day study, a minor decrease in erythropoiesis was present within the bone marrow but was not reflective of a decrease in peripheral reticulocyte counts. In the heart, the microscopic findings differed between the rat and dog. In one high dose dog, the microscopic heart finding was characterized as myocardial necrosis in the papillary muscle. This type of cardiac lesion in dogs is commonly associated with exposure to positive inotropic/vasodilating drugs, and dogs appear to be overly sensitive to having this effect (Dogterom, 1992). Although MRTX849 did not appear to exhibit a blood pressure change in dogs as measured by indirect tail-cuff or changes in ECG parameters, MRTX849 was shown to inhibit the alpha-1-adrenergic receptor with a K_i value of 0.15 µM, which could lead to vasodilation. In the rat, the changes in the heart were limited to vacuolation in the 300 mg/kg/day group that was terminated in extremis on Day 23. There were no vacuole changes in the heart of rats treated at the designated no-observed-adverse-event-level (NOAEL) in the rat of 150 mg/kg/day, which results in average exposure that is 2-fold above the projected human efficacious exposures. Similarly, in the dog 28-day study, the NOAEL and HNSTD at 25 mg/kg/day indicated a 2-fold safety margin above the human efficacious exposure. The nonclinical safety findings related to MRTX849 administration represent toxicities that are considered clinically manageable, reversible, and of acceptable risk in the advanced cancer setting.

The genotoxicity of MRTX849 was assessed in vitro for mutagenicity and clastogenicity initially in screening assays followed by definitive studies. These in vitro assays were conducted with and without exogenous Aroclor-induced rat liver S9 and MRTX849 concentrations up to those limited by cytotoxicity or solubility. In vivo, the clastogenic effects of MRTX849 were evaluated in rats by measuring micronuclei present in peripheral blood reticulocytes after oral dosing at 250, 500, and 1000 mg/kg/day for 2 days. MRTX849 was negative in all genotoxicity studies.

1.3.5. MRTX849 Clinical Experience

Study 849-001 is a multi-center, Phase 1/2, multiple expansion cohort trial evaluating the safety, PK, metabolites, PD and clinical activity/efficacy of MRTX849 in patients with advanced solid tumor malignancies with *KRAS* G12C mutation. The study includes evaluation of MRTX849 monotherapy and in combination with selected cancer therapies.

Study 849-001 began with the Accelerated Titration (AT) design in which single patient dose escalation cohorts receiving MRTX849 at 150 mg, 300 mg, 600 mg and 1200 mg administered once daily. Based on emerging results (post dosing emesis possibly affected by pill burden at the 1200 mg dose), dose escalation using the once daily schedule was discontinued and a BID dosing schedule was initiated at 600 mg BID. In addition, the Phase 1 segment of the study transitioned

from the AT design to the mTPI design. MRTX849 administered at 600 mg BID has been selected for Phase 2 evaluation and is the starting dose in the Phase 1 combination sub-studies.

1.3.5.1. MRTX849 Clinical Safety

As of a data cutoff date of 27 November 2020, a total of 231 patients had been enrolled into Study 849-001, including 202 patients administered MRTX849 monotherapy and 29 patients administered MRTX849 in combination with pembrolizumab or cetuximab. Adverse events (AEs) are summarized for the 202 patients who were administered MRTX849 monotherapy. Among patients administered MRTX849 monotherapy, 197 initiated MRTX849 dosing at 600 mg BID. The most frequently reported treatment-related AEs in patients administered MRTX849 monotherapy are shown in Table 3, and treatment-emergent adverse events (TEAEs) are shown in Table 4. Refer to the current version of Investigator's Brochure (IB) for updated information.

Table 3: Treatment-Related Treatment-Emergent Adverse Events Reported in ≥ 5% of Patients Administered MRTX849 Monotherapy (N = 202)

Adverse Event Preferred Term, n (%)	Any Grade n (%)	Grade 1/2 n (%)	Grade 3/4 n (%)	Grade 5 n (%)
Any TEAE	161 (79.7)	108 (53.5)	51 (25.2)	2 (1.0)
Nausea	107 (53.0)	100 (49.5)	7 (3.5)	0
Diarrhoea	94 (46.5)	88 (43.6)	6 (3.0)	0
Vomiting	72 (35.6)	68 (33.7)	4 (2.0)	0
Fatigue	55 (27.2)	46 (22.8)	9 (4.5)	0
Alanine aminotransferase increased	33 (16.3)	26 (12.9)	7 (3.5)	0
Aspartate aminotransferase increased	27 (13.4)	22 (10.9)	5 (2.5)	0
Blood creatinine increased	27 (13.4)	25 (12.4)	2 (1.0)	0
Electrocardiogram QT prolonged	24 (11.9)	20 (9.9)	4 (2.0)	0
Decreased appetite	23 (11.4)	20 (9.9)	3 (1.5)	0
Anaemia	20 (9.9)	19 (9.4)	1 (0.5)	0
Blood alkaline phosphatase increased	16 (7.9)	13 (6.4)	3 (1.5)	0
Dysgeusia	16 (7.9)	16 (7.9)	0	0
Lipase increased	13 (6.4)	6 (3.0)	7 (3.5)	0
Oedema peripheral	13 (6.4)	13 (6.4)	0	0

Abbreviation: TEAE = treatment-emergent adverse event.

Table 4: Treatment-Emergent Adverse Events Reported in ≥ 5% of Patients Administered MRTX849 Monotherapy (N = 202)

Adverse Event Preferred Term, n (%)	Any Grade n (%)	Grade 1/2 n (%)	Grade 3/4 n (%)	Grade 5 n (%)
Any TEAE	186 (92.1)	78 (38.6)	95 (47.0)	13 (6.4)
Nausea	119 (58.9)	110 (54.5)	9 (4.5)	0
Diarrhoea	105 (52.0)	99 (49.0)	6 (3.0)	0
Vomiting	84 (41.6)	79 (39.1)	5 (2.5)	0
Fatigue	76 (37.6)	63 (31.2)	13 (6.4)	0
Anaemia	44 (21.8)	32 (15.8)	12 (5.9)	0
Blood creatinine increased	39 (19.3)	37 (18.3)	2 (1.0)	0
Alanine aminotransferase increased	38 (18.8)	29 (14.4)	9 (4.5)	0
Dyspnoea	36 (17.8)	25 (12.4)	11 (5.4)	0
Aspartate aminotransferase increased	33 (16.3)	27 (13.4)	6 (3.0)	0
Decreased appetite	31 (15.3)	27 (13.4)	4 (2.0)	0
Oedema peripheral	31 (15.3)	28 (13.9)	3 (1.5)	0
Hyponatraemia	26 (12.9)	17 (8.4)	9 (4.5)	0
Electrocardiogram QT prolonged	25 (12.4)	21 (10.4)	4 (2.0)	0
Abdominal pain	23 (11.4)	19 (9.4)	4 (2.0)	0
Blood alkaline phosphatase increased	23 (11.4)	20 (9.9)	3 (1.5)	0
Constipation	21 (10.4)	21 (10.4)	0	0
Hypoalbuminaemia	20 (9.9)	18 (8.9)	2 (1.0)	0
Hypokalaemia	20 (9.9)	17 (8.4)	3 (1.5)	0
Dizziness	18 (8.9)	18 (8.9)	0	0
Dysgeusia	18 (8.9)	18 (8.9)	0	0
Rash	18 (8.9)	17 (8.4)	1 (0.5)	0
Weight decreased	18 (8.9)	17 (8.4)	1 (0.5)	0
Hypomagnesaemia	17 (8.4)	17 (8.4)	0	0
Lipase increased	17 (8.4)	7 (3.5)	10 (5.0)	0
Lymphocyte count decreased	17 (8.4)	6 (3.0)	11 (5.4)	0
Arthralgia	16 (7.9)	16 (7.9)	0	0
Back pain	16 (7.9)	15 (7.4)	1 (0.5)	0
Dehydration	16 (7.9)	14 (6.9)	2 (1.0)	0
Headache	15 (7.4)	15 (7.4)	0	0

Adverse Event Preferred Term, n (%)	Any Grade n (%)	Grade 1/2 n (%)	Grade 3/4 n (%)	Grade 5 n (%)
Pyrexia	14 (6.9)	14 (6.9)	0	0
Hypotension	13 (6.4)	9 (4.5)	4 (2.0)	0
Amylase increased	11 (5.4)	9 (4.5)	2 (1.0)	0
Blood lactate dehydrogenase increased	10 (5.0)	10 (5.0)	0	0
Dyspepsia	10 (5.0)	10 (5.0)	0	0
Lung infection	10 (5.0)	3 (1.5)	7 (3.5)	0
Muscular weakness	10 (5.0)	8 (4.0)	2 (1.0)	0

Abbreviation: TEAE = treatment-emergent adverse event.

Treatment-emergent serious adverse events have been reported for 68 of the 202 patients administered MRTX849 monotherapy; events reported in more than 4 (2.0%) of patients include pneumonia (n = 8, [4.0%]); n = 6 (3.0%) patients each for hyponatraemia and lung infection; n = 5 (2.5%) each for acute kidney injury, anaemia, and dyspnoea; and n = 4 (2.0%) each for blood creatinine increased, hypotension, hypoxia, malignant neoplasm progression, nausea, pyrexia, and vomiting.

1.3.5.2. MRTX849 Clinical Pharmacokinetics

The pharmacokinetics of MRTX849 in NSCLC patients was characterized in Study 849-001 Phase 1/1b. MRTX849 exhibits the following single-dose PK characteristics following a single 600 mg oral dose administration of MRTX849 capsules under fasting conditions:

- Median t_{max} was 4.17 hours, indicating that MRTX849 is steadily absorbed following oral administration.
- The between-patient variability for C_{max}, and AUC_{∞} was relatively high as the geometric CV% ranged from 95% to 142%.
- Geometric mean CL/F and V_z/F was 16.0 L/h and 527 L, respectively.
- Arithmetic mean $t_{1/2}$ was 23.0 h.

MRTX849 exhibits the following multiple-dose PK characteristics following administration of MRTX849 600 mg BID (capsules) under fasting conditions:

- Median t_{max} values on C1D1 and C1D8 were 6.03 and 2.96 hours, respectively. The shorter t_{max} on C1D8 could be due to the relatively flat concentration-time profile and low geometric mean peak-to-trough concentration ratio (PTR) of 1.07 on C1D8.
- Between-patient variability (geometric mean CV%) for MRTX849 exposure measures (C_{max} and AUC_{τ}) reduced from C1D1 (approximately 76 to 95%) to C1D8 (approximately 37 to 44%).

- Steady state appeared to have been reached by C1D8. The geometric mean C_{min} on C1D8 was 2693 ng/mL.
- Multiple dosing of 600 mg BID resulted in approximately 5- to 6-fold accumulation (Rac) and a low PTR of 1.07 at steady state. Additionally, steady-state concentrations exceeded the target efficacious average concentration derived from the least sensitive preclinical xenograft model.
- Multiple dosing of 150 and 300 mg QD resulted in less drug accumulation (approximately 3- to 4-fold) and a higher PTR (approximately 3) in individual patients compared to the 600 mg BID regimen. Additionally, concentrations at C1D8 were all substantially below the target efficacious average concentration derived from the least sensitive preclinical xenograft model.

The relative bioavailability of the MRTX849 capsule and tablet formulations was evaluated in healthy subjects. Results showed comparable rate and extent of absorption of MRTX849 following a single oral dose of 600 mg (3 × 200-mg) MRTX849 capsules or tablets under fasting conditions. Median t_{max} ranged from 6.07 to 7.50 hours for the capsules and 6.05 to 7.00 hours for the tablets. Between-subject variability (CV%) for exposure measures (C_{max}, AUC_{last}, and AUC_{∞}) ranged up to approximately 59% for the capsules and up to approximately 63% for the tablets. Results from statistical analyses demonstrated that AUC_{∞} and AUC_{last} met the regulatory bioequivalence (BE) criteria but C_{max} did not meet the regulatory BE criteria. An equivalent AUC between the 2 formulations is expected to maintain the same efficacy profile for MRTX849 as data from the nonclinical human xenograft models showed that AUC was the most closely correlated PK parameter with the extent of anti-tumor activity as opposed to C_{max} for MRTX849. Therefore, the tablet and capsule formulations are considered functionally bioequivalent. A slightly lower C_{max} (~15%) in the MRTX849 tablet formulation compared to C_{max} in the capsule formulation is not considered to be clinically meaningful based on the following considerations:

- A lower C_{max} is not expected to impact the efficacy profile of MRTX849. On the other hand, a lower C_{max} may improve the safety/tolerability profile of MRTX849.
- Daily fluctuations in MRTX849plasma concentrations at steady state are low for the 600-mg BID regimen in patients, with a mean peak-to-trough ratio at steady state of 1.07. Therefore, a minor change in C_{max} observed after a single dose of MRTX849 is anticipated to exhibit no meaningful effect on its flat PK profile at steady state.

In conclusion, there is no clinically meaningful difference in MRTX849 exposure between the capsule and tablet formulation.

The effect of a high-fat meal on the PK of MRTX849 tablets was also evaluated in healthy subjects. A high-fat, high-calorie meal increased C_{max} and AUC_{∞} of the tablet formulation by approximately 20% and 38%, respectively. However, the increased exposure is not clinically relevant based on the following considerations:

- The efficacy and safety profiles of MRTX849 in patients have been characterized for the 600 mg BID regimen in the Phase 1/2 Study 849-001 using only the capsule formulation under fasting conditions.

- Accounting for the relative bioavailability of the tablet formulation compared to the capsule formulation (under fasting conditions), the tablet formulation under fed conditions is expected to result in a similar C_{max} and 22% higher AUC compared to the capsule formulation under fasted conditions for which MRTX849 safety and efficacy profiles were established. Furthermore, between-subject variability in MRTX849 tablet exposure was approximately 2-fold lower under fed conditions (~24% to 30%) compared to fasted conditions (~45% to 57%), indicating that food did not increase PK variability of the tablet formulation.

Results from a clinical drug-drug interaction (DDI) study and physiologically-based PK (PBPK) modeling showed the following:

- MRTX849 as a potential perpetrator of DDI: Coadministration of oral midazolam (a sensitive CYP3A4 substrate) with multiple doses of MRTX849 (400 mg BID) increased midazolam AUC by approximately 21-fold in healthy subjects. Administration of multiple doses of MRTX849 at 600 mg BID in patients is predicted to increase oral midazolam AUC by 31-fold. Coadministration of warfarin (a sensitive CYP2C9 substrate) with multiple doses of MRTX849 at 600 mg BID in patients is predicted to increase warfarin AUC by 2.93-fold, indicating that MRTX849 is a moderate inhibitor of CYP2C9. Administration of MRTX849 at 600 mg BID in patients is predicted to increase dextromethorphan AUC by 2.37-fold, indicating that MRTX849 is a moderate inhibitor of CYP2D6. Administration of multiple doses of MRTX849 at 600 mg BID in patients is predicted to increase oral bupropion (a sensitive CYP2B6 substrate) AUC by 1.14-fold, indicating that MRTX849 is a weak inhibitor of CYP2B6. Administration of MRTX849 at 600 mg BID in patients is predicted to increase digoxin (a P-gp substrate) AUC by 1.48-fold, indicating that MRTX849 is a weak inhibitor of P-gp. Administration of MRTX849 at 400 mg BID increased rosuvastatin AUC by 1.35-fold in healthy subjects, indicating that MRTX849 is a weak inhibitor of BCRP. Administration of MRTX849 at 600 mg BID in patients is predicted to have no effect of the exposure of metformin, a MATE substrate.
- MRTX849 as a potential victim of DDI: Coadministration of multiple doses of itraconazole 200 mg QD (a strong CYP3A4 and P-gp inhibitor) with a single 200 mg dose of MRTX849 increased MRTX849 C_{max} and AUC by approximately 2.4-fold and 4-fold, respectively in healthy subjects (Study 849-006). However, coadministration of multiple doses of itraconazole 200 mg QD with multiple doses of MRTX849 (600 mg BID) in patients is predicted to have a negligible effect on MRTX849 steady-state exposure. The lack of itraconazole effect on MRTX849 steady-state exposure is due to the extent of auto-inhibition by MRTX849 at 600 mg BID steady state, thus the majority of CYP3A4-mediated intrinsic clearance (CL_{int}) is already inhibited by MRTX849. Based on these data, no dose adjustment of MRTX849 is needed when MRTX849 is coadministered with CYP3A/P-gp inhibitors. Coadministration of multiple doses of rifampin 600 mg QD (a strong CYP3A4 and P-gp inducer) with a single 600 mg dose of MRTX849 decreased

MRTX849 C_{max} by 88% and AUC by 95% in healthy subjects. Coadministration of multiple doses of rifampin (600 mg QD) with multiple doses of MRTX849 (600 mg BID) in patients is predicted to decrease MRTX849 C_{max} by 61% and AUC by 66%. MRTX849 is a substrate of BCRP. The effect of inhibitors of BCRP (eg, curcumin, cyclosporin, and eltrombopag) on MRTX849 has not been evaluated.

- Coadministration of repeat doses of pantoprazole (a proton pump inhibitor, PPI) with a single dose of MRTX849 decreased MRTX849 C_{max} and AUC by approximately 38% and 32%, respectively, in healthy subjects.

Based on these results, guidance on use of concomitant medications is provided in Section 5.9.1 and Appendix 2.

1.3.5.3. MRTX849 Clinical Activity

Initial clinical trial observations of MRTX849 in patients with NSCLC who were previously treated with a platinum agent and a checkpoint inhibitor have shown clinical activity. The Phase 2 segment of Study 849-001 is evaluating the clinical activity of MRTX849 in cohorts of patients having tumors with *KRAS* G12C mutation. As of 30 August 2020, clinical activity data has been reported for patients with NSCLC administered MRTX849 at the Phase 2 dose of 600 mg BID in Phase 1/1b or Phase 2 cohorts.

Among patients with NSCLC with *KRAS* G12C mutation with measurable disease and at least 1 on-study disease assessment, 23/51 patients (45%) experienced a Partial Response in accordance with RECIST 1.1 based on investigator assessment (Jänne, 2020). Unconfirmed responses were initially documented among 5/23 responders, all of which were confirmed during continued study treatment. The disease control rate (PR plus stable disease) was 96.1% (49/51 of patients). Refer to the current version of IB for updated information.

1.4. Docetaxel

Docetaxel is an antineoplastic agent belonging to the taxoid family. Docetaxel disrupts 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, leading to the production of microtubule bundles without normal function and that inhibit mitosis.

Background information in addition to that presented in this protocol is available in locally approved product label.

1.4.1. Docetaxel Drug Substance

Generic Name: Docetaxel

Other Name: TAXOTERE®

Molecular Weight: 861.9 kDa

1.4.2. Docetaxel Nonclinical Data

Docetaxel nonclinical experience is described in locally approved product label.

1.4.3. Docetaxel Clinical Data

The following reports information included in the TAXOTERE® US Prescribing Information (USPI TAXOTERE [docetaxel]) dated May 2020. Refer to the current locally approved product label for updates during the conduct of this clinical trial.

1.4.3.1. Docetaxel Pharmacokinetics

Absorption: The pharmacokinetics 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 area under the curve (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 pharmacokinetic 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.

Distribution: The initial rapid decline represents distribution to the peripheral compartments and the late (terminal) phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Mean steady-state volume of distribution was 113 L. In vitro studies showed that docetaxel is about 94% protein bound, mainly to α_1-acid glycoprotein, albumin, and lipoproteins. In 3 cancer patients, the in vitro binding to plasma proteins was found to be approximately 97%. Dexamethasone does not affect the protein binding of docetaxel.

Metabolism: 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.

Elimination: A study of ^{14}C-docetaxel was conducted in 3 cancer patients. Docetaxel was eliminated in both the urine and feces following oxidative metabolism of the *tert*-butyl ester group, but fecal excretion was the main elimination route. Within 7 days, urinary and fecal excretion accounted for approximately 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity recovered in feces is excreted during the first 48 hours as 1 major and 3 minor metabolites with very small amounts (less than 8%) of unchanged drug.

Population pharmacokinetic analyses have indicated that the pharmacokinetics of docetaxel were not influenced by age or gender and no significant differences were observed between Japanese and European/American populations.

1.4.3.2. Docetaxel Adverse Reactions Common in Clinical Trials

As of May 2020, the most common adverse reactions across all docetaxel 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. Incidence varies depending on the indication.

In patients receiving docetaxel as monotherapy for unresectable, locally advanced or metastatic NSCLC previously treated with platinum-based chemotherapy, the most common treatment-emergent adverse reactions regardless of relationship (≥ 20%) were neutropenia, leukopenia, anemia, infection, fluid retention, neurosensory, skin reactions, nausea, vomiting, diarrhea, alopecia, asthenia, stomatitis, and pulmonary reactions.

1.5. Study Rationale

Elucidation of the underlying genetic aberrations occurring in lung adenocarcinoma by the Cancer Genome Atlas Research Network has demonstrated that recurrent aberrations leading to activation of the RTK/RAS/RAF pathway occur in 76% cases of lung adenocarcinoma, including activating *KRAS* mutations in 32.2% of cases (TCGA, 2014), thereby implicating this pathway in the underlying carcinogenesis. Additionally, *KRAS* mutations occur in up to approximately 2% of NSCLC patients with squamous histology (AACR Project GENIE Consortium, 2017), (TCGA, 2012) and are expected to play the same role in KRAS activation, notwithstanding the potential for histologic misclassification based on morphology (Rekhtman, 2012). The importance of RAS pathway is further supported by nonclinical data indicating the dependency of *KRAS*-mutant tumors on KRAS signaling (McDonald, 2017), and the clinical activity of several targeted agents approved for use in NSCLC, including those targeting EGFR, ALK1, BRAF, ROS1, and TRK family members. These observations suggest that *KRAS* mutations similarly define a unique segment of lung cancer for which a targeted therapy option is currently unavailable (Campbell, 2016).

Notably, *KRAS* mutations have been associated with a worse prognosis (Slebos, 1990), (Mascaux, 2005), and despite the significant advances of chemotherapy and immunotherapy for NSCLC (see Section 1.2), including those for patients with *KRAS* G12C tumor mutation, patients ultimately develop progressive disease; thus, additional treatment options are warranted. The proposed population for this study, those treated in the second and higher lines of therapy, have an unmet medical need, and agents targeted against mutant KRAS hold the promise of significant clinical activity similar to that observed with other targeted agents in NSCLC.

Subsequent to the initiation of this trial (Study 849-012), sotorasib, a direct inhibitor of KRAS G12C, received accelerated approval from the U.S. FDA (USPI LUMAKRAS [sotorasib]) for the treatment of adult patients with *KRAS* G12C-mutated locally advanced or metastatic NSCLC who have received at least one prior systemic therapy. This approval provides clinical validation for direct KRAS G12C inhibition in patients with *KRAS* G12C mutant NSCLC in the second line and later treatment setting. Based on this shift in standard therapy and the clinical activity observed with the direct KRAS G12C inhibitor MRTX849 in this patient population (Section 1.3.5.3), the study design has been modified to allow patients randomized to the docetaxel arm who develop RECIST 1.1-defined progressive disease per blinded independent central review (BICR) while on study to crossover and receive MRTX849 study treatment, if the inclusion and exclusion requirements as outlined in Section 4.3 and Section 4.4 are met.

1.5.1. Choice of Control Arm Treatment

After failure of front-line chemotherapy and checkpoint inhibition, docetaxel with or without ramucirumab remains the most common standard of care outside of a clinical trial. Although docetaxel has demonstrated efficacy, careful patient selection and monitoring are important due to the possibility of toxic deaths, hepatotoxicity, neutropenia, hypersensitivity reactions, and fluid retention. Additionally, ramucirumab, a recombinant monoclonal antibody that targets VEGF receptor, improves survival when used in combination with docetaxel, although AEs of special concern with the combination include risk for severe hemorrhage, Grade 3 to 4 gastrointestinal bleeding, gastrointestinal perforation or fistula, impaired wound healing, and poorly controlled hypertension. Importantly, however, docetaxel monotherapy is recommended as a standard option for NSCLC patients after failure of chemotherapy and an inhibitor of PD-(L)1 (NCCN, 2020) and an appropriate comparator treatment for the intended study population, namely patients with unresectable, locally advanced or metastatic NSCLC with *KRAS* G12C mutation with disease progression on or after treatment with platinum-based chemotherapy and anti-PD-1/PD-L1 therapy.

1.5.2. Choice of Dosing Regimen

The starting dosing regimen of MRTX849 was selected based on the Phase 1 data demonstrating exposures predicted to sufficiently inhibit KRAS G12C with a manageable safety profile and preliminary evidence of clinical activity as described in Section 1.3.5.3.

1.5.3. Benefit/Risk Assessment

Patients with NSCLC harboring a *KRAS* G12C mutation and who have received prior treatment with a platinum regimen and CIT have a serious and life-threatening disease with an estimated median survival of 5.7 to 10.5 months. Treatment-related, Grade 3/4 adverse events reported with MRTX849 include fatigue, ALT increased, lipase increased, nausea, diarrhea, AST increased, QT prolongation, vomiting, blood alkaline phosphatase increased, decreased appetite, blood creatinine increased, and anemia, and the entry criteria and safety assessments have been included in the study to mitigate risks. Clinical activity has been reported for this patient population with a response rate of 45% among 51 patients treated with MRTX849 600 mg BID in the Phase 1/1b or Phase 2 setting, which exceeds the reported response rate of 23% reported with docetaxel plus ramucirumab. Taking risks into consideration with the preliminary clinical activity of MRTX849 in this population, as well as the adverse event risk mitigation procedures, the overall benefit/risk balance of this study is acceptable.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

To compare the efficacy of MRTX849 versus docetaxel in patients with NSCLC with *KRAS* G12C mutation and who have received prior treatment with a platinum-based regimen and immune CIT.

2.1.2. Secondary Objectives

- To evaluate secondary efficacy endpoints in the study population.
- To evaluate the safety and tolerability in the study population.
- To evaluate the pharmacokinetics (PK) of MRTX849 administered in the study population.
- To evaluate health-related quality of life (HRQOL) and lung cancer-specific symptoms in the study population.

2.1.3. Exploratory Objectives

- To explore correlations between gene alterations (baseline and upon treatment resistance) with efficacy.
- To evaluate the Progression-Free Survival in the next-line of therapy (PFS2) in the study population
- To evaluate efficacy outcome in the CNS
- To explore intracranial activity in patients with brain metastases using exploratory efficacy endpoints

2.2. Endpoints

2.2.1. Primary Endpoint

- Progression-Free Survival (PFS)

2.2.2. Secondary Endpoints

- Secondary efficacy endpoints:
  - Overall Survival (OS),
  - Objective Response Rate (ORR),
  - Duration of Response (DOR), and
  - 1-Year Survival Rate

- Safety characterized by type, incidence, severity, timing, seriousness and relationship to study treatment of AEs, laboratory abnormalities, and number of patients discontinuing study treatment due to an adverse event.
- Population PK parameters of MRTX849.
- Patient Reported Outcome (PRO) scores using the following:
  - Lung Cancer Symptom Scale (LCSS).
  - European Quality of Life Five Dimensions Questionnaire (EQ-5D-5L).

2.2.3. Exploratory Endpoints

- Gene alterations in tumor tissue and ctDNA.
- Progression-Free Survival-2 (PFS2).
- Time to CNS Progression.
- Intracranial activity using CNS RECIST 1.1 endpoints in patients with brain metastases, including intracranial objective response rate (icORR), intracranial duration of response (icDOR), intracranial progression free survival (icPFS) and intracranial time to progression (icTTP).

3. STUDY DESIGN

Study 849-012 is an open-label, randomized Phase 3 clinical trial comparing the efficacy of MRTX849 versus docetaxel in patients with NSCLC with *KRAS* G12C mutation and who have received prior therapy with a platinum-based regimen and an immune checkpoint inhibitor. Secondary objectives include evaluation of safety and tolerability, secondary efficacy endpoints, PROs, and MRTX849 PK in the study population.

The presence of *KRAS* G12C mutation in tumor tissue for the purpose of patient eligibility must be established using Sponsor pre-approved methods and laboratories. Presence of tumor *KRAS* G12C mutation may be established using Sponsor-approved local tests or the Sponsor-provided central laboratory test. For all enrolled patients *KRAS* G12C mutation status and correlative tumor gene alterations will be retrospectively tested using tumor samples submitted no later than 30 days after the first dose of study treatment.

Patient eligibility for study enrollment based on objective disease progression on or after a platinum-based regimen and an immune checkpoint inhibitor will be evaluated by the Investigator.

Data entered into the case report form (CRF) are to include prior regimens, best overall response, if progression occurred on or after treatment and date of progression.

Eligible patients will be randomized in a 2:1 ratio to receive MRTX849 (adagrasib) or docetaxel respectively. Randomization will be stratified by:

1. Region (non-Asia-Pacific versus Asia-Pacific)
2. Sequential versus concurrent (administration of last prior platinum-based chemotherapy and anti-PD-1/PD-L1 antibody)

The requirements for tumor *KRAS* G12C for determining eligibility are presented in Table 1 and Figure 1. The Schedule of Assessments is presented in Table 2.

Study treatment will be administered in 3-week cycles. Patients randomized to the investigational arm will receive MRTX849 administered orally (PO) at a starting dose of 600 mg BID. Patients randomized to the comparator arm will receive treatment with docetaxel. 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 local standards.

Disease response and progression will be evaluated in accordance with RECIST 1.1 (Eisenhauer, 2009). Blinded independent central review for disease response and progression will be performed for the purpose of statistical analyses of these study endpoints. Disease assessments must be performed as scheduled according to the calendar to prevent the introduction of bias in the assessment of efficacy based on toxicity. 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 AEs, 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 following criteria are met: absence of clinical symptoms or signs indicating clinically significant disease progression; no significant decline in performance status; absence of rapid disease progression or threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention; and no significant, unacceptable or irreversible toxicities related to study treatment. 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 and will continue to undergo disease assessments until study treatment is discontinued. Imaging should continue to be submitted for BICR review until BICR confirmed disease progression.

In the event a patient discontinues study treatment for a reason other than objective disease progression, disease assessments post-treatment should continue until objective disease progression is documented by the Investigator and BICR or start of subsequent anticancer therapy, whichever is sooner.

Patients randomized to the docetaxel arm will be offered the opportunity to receive MRTX849 treatment upon development of RECIST 1.1-defined disease progression per BICR. Patients must sign a crossover informed consent form and must meet all eligibility criteria for further

treatment as described in Section 4.3 and Section 4.4 and will use the dosing regimen described in Section 5.3. The required assessments for patients who crossover included in Appendix 6.

4. SUBJECT SELECTION AND ENROLLMENT

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

4.1. Inclusion Criteria

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

1. Histologically or cytologically confirmed diagnosis of NSCLC with *KRAS* G12C mutation.
2. Receipt of prior treatment with a platinum (cisplatin or carboplatin)-containing regimen and an immune checkpoint inhibitor (ie, anti-PD-1/PD-L1 inhibitor) concurrently or sequentially for advanced or metastatic disease with the outcome of objective disease progression on or after treatment. Source documents for historical disease evaluations to allow Investigator certification of disease progression on or after prior treatment must be available.
3. Candidacy to receive treatment with docetaxel in accordance with the local product label. Patients with known hypersensitivity to docetaxel or polysorbate 80 are excluded from this study.
4. Unresectable, locally advanced or metastatic disease.
5. Presence of evaluable or measurable disease per RECIST version 1.1.
6. Expected availability of representative tumor specimen (primary or metastatic, archival or newly obtained) for central laboratory testing of *KRAS* G12C mutation status and correlative gene alterations (minimum of 7 slides, preferably 15 slides).
7. Age ≥ 18 years (Legal age of consent for participation in an adult clinical trial differs in each country. In countries where the legal age of consent is higher than 18 years, participants must meet the legal age requirements of that country).
8. Life expectancy of at least 3 months.
9. Recovery from the adverse effects of prior therapy to baseline or Grade 1 (excluding alopecia).
10. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
11. Laboratory values within the screening period:
    a. Absolute neutrophil count ≥ 1,500/mm^3 (≥ 1.5 × 10^9/L)

b. Platelet count ≥ 100,000/mm^3 (≥ 100 × 10^9/L)
c. Hemoglobin ≥ 9 g/dL, in the absence of transfusions for at least 2 weeks
d. Total bilirubin ≤ 1.0 × upper limit of normal (ULN)
e. Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 1.5 × ULN; if associated with liver metastases, ≤ 5 × ULN. If alkaline phosphatase > 2.5 × ULN, then ALT and AST must be ≤ 1.5 × ULN with or without liver metastases.
f. Creatinine clearance ≥ 50 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 (ICF).
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. Prior treatment with an agent targeting KRAS G12C (eg, AMG 510, sotorasib).
2. Active brain metastases. Patients are eligible if brain metastases are treated and patients are neurologically stable for at least 2 weeks prior to randomization. If patients require the use of corticosteroids, patients must be on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) prior to randomization.
3. Carcinomatous meningitis.
4. Major surgery within 4 weeks prior to randomization.
5. History of intestinal disease or major gastric surgery likely to alter absorption of study treatment or inability to swallow oral medications.
6. Any of the following cardiac abnormalities:
   a. Unstable angina pectoris or myocardial infarction within 6 months prior to randomization.
   b. Symptomatic or uncontrolled atrial fibrillation within 6 months prior to randomization.
   c. Congestive heart failure ≥ NYHA Class 3 within 6 months prior to randomization.
   d. Prolonged QTc interval > 480 milliseconds or family or medical history of congenital Long QT Syndrome.
7. History of stroke or transient ischemic attack within 6 months prior to randomization.
8. Ongoing need for a medication with any of the following characteristics that cannot be switched to alternative treatment prior to study entry (see Appendix 2): known risk of QT prolongation or Torsades de Pointes; sensitive CYP3A4 substrate listed in Appendix 2;

substrate of P-gp with narrow therapeutic index; strong inducer of CYP3A4; inhibitor of BCRP; and proton pump inhibitors.

9. Known human immunodeficiency virus (HIV) infection or acute or chronic hepatitis B (HBV) or C (HCV) infection. Note that the following are permitted:
   - Patients with prior HBV infections who are:
     – Considered to have past or resolved HBV infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of hepatitis B surface antigen [HBsAg]); or
     – Considered to be in an inactive HBV carrier state (defined as HBsAg-positive, with normal ALT, and HBV DNA <2,000 IU/mL or <10,000 copies/mL).

   Note: For patients in an inactive HBV carrier state or with a resolved HBV infection, the risk of HBV reactivation should be considered and the need for anti-HBV prophylaxis prior to randomization should be carefully assessed in accordance with local guidelines.
   - Patients treated for HCV with no detectable viral load.
   - Patients treated for HIV with no detectable viral load on current regimen for at least 1 month prior to randomization.

   Note: Refer to Appendix 3 for medications to be avoided during treatment with docetaxel, in particular anti-HIV strong CYP3A4 inhibitors, and Exclusion Criterion 8 regarding drug-drug interactions of concomitant anti-HIV agents and in particular sensitive CYP3A4 substrates.
10. Known or suspected presence of another malignancy that could be mistaken for the malignancy under study during disease assessments.
11. Pregnancy. WOCBP must have a negative serum or urine pregnancy test documented prior to randomization.
12. Breastfeeding or planning to breast-feed during the study or within 6 months after the last dose of study treatment.
13. 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, would be likely to interfere with the patient's capacity to provide informed consent, with the patient's participation in the study, or with the interpretation of the results.
14. Hypersensitivity to any component of the MRTX849 drug product.
15. Administration of a live/attenuated vaccine within 30 days before the first dose of study treatment.
16. Patients who have received prior treatment with docetaxel.

4.3. Crossover Inclusion Criteria

Patients randomized to docetaxel arm must meet all of the following criteria to be eligible for crossover into MRTX849 study treatment arm:

1. Evidence of RECIST 1.1 defined disease progression on docetaxel per BICR.
2. ECOG performance status 0 - 2.
3. Laboratory values that meet criteria per Inclusion Criterion 11 at least 7 days after the last dose of docetaxel
    a. Exception: Allow hemoglobin ≥ 8 g/dL and transfusion of red blood cells
4. Recovery from all docetaxel-related adverse effects to Grade 1 or baseline, with the exceptions of peripheral neuropathy and alopecia for which Grade 2 is acceptable.

4.4. Crossover Exclusion Criteria

Patients randomized to docetaxel arm presenting with any of the following will be excluded from crossover into MRTX849 study treatment arm:

1. Receipt of any other systemic anti-cancer therapy after last administration of docetaxel on the study.
2. Any severe acute or chronic medical or psychiatric condition, or laboratory abnormality that may increase the risk associated with continued study participation or study drug administration, or may interfere with the interpretation of study results, and in the judgment of the investigator would make the patient inappropriate for crossover to MRTX849 treatment.

4.5. Life Style Guidelines

4.5.1. Dietary Restrictions

Patients should be instructed to avoid the following substances due to the possibility of interactions of these substances with the pharmacokinetics of MRTX849 and/or docetaxel:

1. Grapefruit and grapefruit juice (avoid with docetaxel only)
2. St. John's wort and other herbal preparations (see Section 5.9.1) (avoid for both MRTX849 and docetaxel)

4.5.2. Reproductive Health

The informed consent process must include discussion of the risks associated with pregnancy and adequate contraception methods. Patients (including men whose partner is a WOCBP) who are biologically capable of having children and sexually active must agree to use at least one acceptable, highly effective method of contraception for the duration of the treatment period and for at least 6 months after the last dose of study treatment. In addition, in some regions participating in this study (eg, the European Union), patients are required to use 2 acceptable

methods of contraception, one of which must be highly effective, in accordance with local regulations. The Investigator will counsel the patient on selection of contraception method and instruct the patient in its consistent and correct use. Examples of methods of birth control considered to be highly effective include:

4.5.2.1. Women

1. Oral, inserted, injected or implanted hormonal methods of contraception, associated with inhibition of ovulation provided it has been used for an adequate period of time to ensure effectiveness.
2. Correctly placed copper containing intrauterine device (IUD).
3. Bilateral tubal ligation or bilateral salpingectomy.
4. Sexual abstinence. Sexual abstinence is acceptable only as true abstinence, defined in the context of this protocol as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. The entire period of risk is defined as study treatment, including during temporary breaks from treatment, and at least 6 months after stopping study treatment.
5. Vasectomy with confirmed absence of sperm for male partners of women patients who are of childbearing potential.

4.5.2.2. Men

1. Sexual abstinence. 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).
2. All men on study, including men who have had vasectomy, with partners of childbearing potential must use condoms for the duration of the treatment period and for at least 6 months after the last dose of study drug.

Highly effective or effective contraceptive methods may also be considered for female partners who are WOCBP.

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 is considered acceptable as one method of contraception in regions where patients are required to use 2 acceptable methods of contraception, however they are not considered highly effective. A combination of male

condom with either cap, diaphragm or sponge with spermicide (double barrier methods) is also considered one acceptable, but not highly effective, birth control methods.

3. Cap, diaphragm or sponge with spermicide.

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 and in countries operating in compliance with Clinical Trials Facilitation Group (CTFG) guidelines, the reproductive status of the woman should be confirmed by follicle stimulating hormone level assessment.

In accordance with docetaxel product labeling in some regions in which this study will be conducted, men randomized to receive docetaxel should consider sperm preservation before starting study treatment.

4.6. Pre-screening, Screening and Randomization into Study

4.6.1. Study Number Assignment

At the time of the pre-screening informed consent process, patients will be assigned an automatically generated patient number. The patient number must be used on all documentation and correspondence with the Sponsor, Contract Research Organization (CRO) and laboratory vendors throughout the patient's experience in this study.

4.6.2. Tumor Tissue KRAS Mutation Testing

Patient eligibility for enrollment based on the presence of *KRAS* G12C mutation in the tumor may be established using Sponsor-approved local tests or a Sponsor-provided central test (see Table 1 and Section 7.1 for details). For all enrolled patients the *KRAS* mutation status and correlative tumor gene alterations will be retrospectively tested using tumor samples submitted no later than 30 days after the first dose of study treatment.

If the Sponsor-provided central laboratory is used to perform tumor genotyping to establish eligibility for the study, an up to 10 to 14-day turn-around time should be expected from the time of receipt of adequate samples at the central lab to test results returned to the study site. Questions concerning adequacy of samples will cause delay beyond this timeframe.

For central laboratory genotyping, tumor samples from the most recent biopsy or excision are preferred; however, if no recently obtained materials are available, samples from any time during patient's prior disease course are accepted. When possible, the same tissue source used to establish study eligibility should be submitted to the central laboratory in order to minimize the potential for discordance between the local test and central laboratory test results. Tumor biopsies having significant risk should not be performed for the purpose of determining genetic

eligibility. Note: Patients enrolled at sites in Germany will not undergo tumor lesion biopsy for the purpose of the study after the Screening period.

After local or central laboratory documentation of the *KRAS* G12C mutation, the main study consent should be obtained, followed by the required screening procedures.

4.6.3. Randomization

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 2:1 ratio using a centralized Interactive Web Response System (IWRS) to receive treatment assignment to either MRTX849 or docetaxel. Study treatment should begin within 3 business days of randomization.

5. STUDY TREATMENTS

5.1. Investigational and Non-Investigational Medicinal Products

Investigational medicinal products are pharmaceutical forms of an active substance or placebo being tested (ie, test substance) or used as a reference (ie, reference substance) in a clinical trial. In this clinical trial, the investigational medicinal products are:

- MRTX849 – test substance, and
- docetaxel – reference substance.

Non-investigational medicinal products include medications used for preventative or therapeutic reasons. In this clinical trial, non-investigational medicinal products include pre-medications associated with docetaxel (eg, dexamethasone, or institutional equivalent) and medications used to treat docetaxel-related infusion reactions.

5.2. MRTX849 Study Drug

5.2.1. MRTX849 Formulation

MRTX849 clinical trial material is provided by the study Sponsor.

Two formulations of MRTX849 may be used in this study. See the Pharmacy Manual for further information including capsule and tablet unit strength and details on packaging description.

MRTX849 Capsule Formulation and Packaging

The MRTX849 capsule formulation contains active pharmaceutical ingredient (API).

MRTX849 (capsule) clinical trial material is packaged in high-density polyethylene (HDPE), white opaque, round bottles. A tamper-proof heat induction seal and a child-resistant closure are used.

MRTX849 Tablet Formulation and Packaging

The MRTX849 tablet formulation is available as immediate release, white to off-white, film-coated tablets. Excipients in the tablet formulation include microcrystalline cellulose, mannitol, crospovidone, colloidal silicon dioxide, and magnesium stearate. The film coat is Opadry II White (57U18539) which consists of hypromellose, titanium dioxide, polydextrose, talc, maltodextrin, and medium chain triglycerides (vegetable).

MRTX849 tablets are packaged in HDPE white, opaque, square bottles with child resistant closures with heat induction seals.

Labeling

MRTX849 medication labels comply with the legal requirements of the US and/or other countries where clinical drug supply is used and will be printed in the languages required in the countries in which the study is conducted.

Storage

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. MRTX849 clinical trial material should be stored under the conditions stated on the container labels and the Pharmacy Study Manual.

Refer to the Pharmacy Study Manual for details on available dose strengths, packaging and suggested storage conditions.

5.2.2. MRTX849 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, including clinical trial material provided for this study.

Study site personnel will dispense MRTX849 clinical trial material on Day 1 of each dose cycle, unless otherwise specified by the study site's Standard Operating Procedures. Sufficient supply should be provided to patients for each cycle and extra may be provided to cover an additional 2 days in case of delayed clinic visits or lost clinical trial material. The provided clinical trial material bottles may be labeled for specific patient use and given to the patient if the unit count is the needed number.

Patients will be asked to record their daily dosing on Sponsor-provided diary cards and report any missed doses or lost doses. Written dosing instructions for MRTX849 are provided (eg., fasting instructions, take with water, etc.) on the back of each Sponsor-provided diary card. Patients should be told to bring study clinical trial material bottle(s) (empty or not) and completed dosing diaries (as applicable) with them to each clinic visit for a compliance check and capsule/tablet count. Study site personnel will retain the bottle(s) until a monitor has completed reconciliation and retain dosing diaries (as applicable) with site study files.

All MRTX849 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.

At the end of the study, all unused MRTX849 clinical trial material 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.

5.3. MRTX849 Patient Treatment

5.3.1. MRTX849 Oral Administration

The following guidelines should be followed for oral administration of MRTX849:

- On the days of PK sampling, the first doses of the day should be taken in the clinic and administration time recorded.
- Twice daily dosing should be at 12-hour intervals to the extent possible.
- MRTX849 tablets may be taken with or without food.
- Study drug product should be taken with at least 240 mL (8 ounces) of water.
- Study drug product should be swallowed whole and not chewed.
- If vomiting occurs, doses should not be replaced.
- If a dose is inadvertently missed, the dose should be skipped if > 4 hours has elapsed since the expected dosing time. Dosing may resume at the next appointed time.

5.3.2. MRTX849 Study Treatment

5.3.2.1. Treatment Regimen

Study treatment will be expressed in 3-week cycles.

The planned regimen for MRTX849 is 600 mg BID, administered orally on a continuous basis until disease progression.

5.4. Guidelines for MRTX849 Dose Modification and Adverse Event Management

Provided below are guidelines for the management of MRTX849 treatment-related AEs and recommended dose modifications. Severity of AEs as described in dose modification tables is as defined by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE, Version 5.0].

5.4.1. Dose Reduction Steps for MRTX849 in Response to Treatment-Related Adverse Events

In the event of treatment-related AEs requiring dose reduction (Section 5.4.2), available MRTX849 dose reduction steps are presented in Table 5. Further dose reductions may be undertaken after discussion with the Sponsor.

Table 5: MRTX849 Dose Reduction Steps in Response to Treatment-Related Adverse Events

Dose Level	MRTX849
Starting Dose Level	600 mg BID
-1	400 mg BID
-2	600 mg QD

The following are general guidelines for the interruption, resumption or re-challenge of treatment with MRTX849:

- following MRTX849 dose reduction and control of the AE, re-challenge at a higher MRTX849 dose may be permitted after discussion with the Sponsor;
- if resumption of dosing for MRTX849 is delayed for ≥ 14 days due to an AE that is at least suspected to be attributable to study treatment, then resumption at a reduced dose should be considered;
- if treatment with MRTX849 is withheld for ≥ 22 consecutive days, then permanent discontinuation from treatment should be considered; and
- if a treatment-related AE recurs despite dose reduction of MRTX849 to the lowest dose anticipated in Section 5.4.1, then permanent discontinuation from study treatment should be considered, unless after discussion with the Sponsor it is in the best interest of the patient to continue.

Treatment interruptions and modification guidelines are provided in the tables below. Documentation of discussions with the Sponsor concerning study treatment decisions should be retained with patient records as source documents.

5.4.2. Guidelines for the Management of Study Treatment-Related Adverse Events

Provided below are guidelines for dose modification and management of potential study treatment-related AEs. In the event that dose reduction of MRTX849 is needed, available dose reduction steps are presented in Section 5.4.1.

5.4.2.1. Hematological Toxicities

Hematological toxicities that are considered to be causally related to MRTX849 should initially be managed with interruption of MRTX849 as outlined in Table 6. Following resolution of toxicity to the specified degree, dose reduction of MRTX849 should be implemented.

Table 6: Hematological Toxicities – MRTX849 Dose Modifications

Hematological Toxicity	Treatment Interruption	Dose Modification
Grade 1/2 AEs	Implement at Investigator and Patient Discretion	
Specific Grade 3/4 AEs		
• Grade 4 Anemia • Grade 4 Neutropenia ≥ 8 days • Grade 3/4 Febrile Neutropenia • Grade 3 Thrombocytopenia with Clinically Significant Bleeding • Grade 4 Thrombocytopenia	Hold until ≤ Grade 1 or return to baseline	Decrease one dose level
Other Grade 3/4 AEs	Hold until ≤ Grade 1 or return to baseline	May resume at the same dose level

Abbreviation: AE = adverse event

5.4.2.2. Gastrointestinal Toxicities

Patients should be advised of the possibility of developing nausea, vomiting, and diarrhea. When possible, patients should have anti-emetics available to self-administer soon after onset. Patients assessed as having greater potential to develop nausea may be treated prophylactically. Alternatives to ondansetron should be used (due to the possibility of QT prolongation due to ondansetron; see Section 5.9.1 for additional guidance related to ondansetron). Due to the observation of creatinine increases with MRTX849, fluid status should be evaluated in patients who develop vomiting or diarrhea, and oral and/or intravenous hydration should be considered if clinically warranted. In addition, more frequent electrolyte monitoring that includes potassium and magnesium should be considered along with supplementation for levels below the lower limit of normal in order to mitigate the risk for QT prolongation.

Gastrointestinal toxicities that are considered to be causally related to MRTX849 should initially be managed with treatment interruption as outlined in Table 7. Following resolution of toxicity to the specified degree, dose reduction of MRTX849 should be implemented.

Table 7: Gastrointestinal Toxicities – MRTX849 Dose Modifications

Gastrointestinal Toxicity	Treatment Interruption	Dose Modification
Grade 1/2 AEs	Implement at Investigator and Patient Discretion	
Specific Grade 3/4 AEs		
• Grade 3 Nausea > 72 hours, despite therapy • Grade 3/4 Vomiting > 24 hours despite therapy (or > 72 hours while optimizing therapy) • Grade 3 Diarrhea > 48 hours, despite therapy	Hold until ≤ Grade 1 or return to baseline	Decrease one dose level
• Grade 4 Diarrhea, despite therapy	Discontinue study treatment	
• Asymptomatic Grade 3 Amylase or Lipase Elevation > 8 days	Hold until ≤ Grade 1 or return to baseline	May resume at the same dose level
• Symptomatic Grade 3/4 Amylase or Lipase Elevation	Hold until ≤ Grade 1 or return to baseline	May resume one dose level lower
• Grade 3/4 Pancreatitis	Discontinue study treatment	
Other Grade 3 AEs	Hold until ≤ Grade 1 or return to baseline	May resume at the same dose level or one dose level lower
Other Grade 4 AEs	Discontinue study treatment	

Abbreviation: AE = adverse event

5.4.2.3. Hepatic Toxicities

Hepatic toxicities that are considered to be causally related to MRTX849 should initially be managed with treatment interruption as outlined in Table 8. Evaluation for confounding factors (eg, cholestasis, metastasis, or viral infection) should be performed as clinically indicated, and more frequent monitoring of a hepatic panel (including AST, ALT, alkaline phosphatase, and bilirubin) should be considered for those patients with transaminase increases. Following resolution of toxicity to the specified degree, dose reduction of MRTX849 should be implemented.

Table 8: Hepatic Toxicities – MRTX849 Dose Modifications

Hepatic Toxicity	Treatment Interruption	Dose Modification
Grade 1 AEs	Implement at Investigator and Patient Discretion	
Specific Grade 2 AEs		
• Grade 2 Increased Hepatic Transaminase (ALT, AST)	Not Required	Decrease one dose level
Other Grade 2 AEs	Implement at Investigator and Patient Discretion	
Specific Grade 3/4 AEs		
• Grade 3 Increased Hepatic Transaminase (ALT, AST)	Hold until ≤ Grade 1 or return to baseline	Decrease one dose level
• Grade 4 Increased Hepatic Transaminase (ALT, AST) • Hy's Law Case[1]	Discontinue study treatment	
• Grade 3 Increased Bilirubin ≤ 22 days (Without Increases in Transaminases or Alkaline Phosphatase)	Hold until ≤ Grade 1 or return to baseline	Decrease one dose level
• Grade 3 Increased Bilirubin > 22 days (Without Increases in Transaminases or Alkaline Phosphatase)	Discontinue study treatment	
Other Grade 3/4 AEs	Hold until ≤ Grade 1 or return to baseline	May resume at the same dose level or one dose level lower

Abbreviation: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = Upper Limit of Normal.

[1] 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 liver metastases or biliary obstruction (ie, meeting Hy's Law), all study treatment should be permanently discontinued and steroids administered; these cases should be reported as SAEs in accordance with Section 8.2.1.

5.4.2.4. Other Laboratory Investigation-Based Toxicities

Other laboratory investigation-based toxicities that are considered to be causally related to MRTX849 should initially be managed with treatment interruption of MRTX849 as outlined in Table 9. Following resolution of toxicity to the specified degree, dose reduction of MRTX849 should be implemented.

Table 9: Other Laboratory Investigation-Based Toxicities – MRTX849 Dose Modifications

Other Laboratory Investigation-Based Toxicities	Treatment Interruption	Dose Modification
Grade 1/2 AEs	Implement at Investigator and Patient Discretion	
Specific Grade 3/4 AEs		
• Grade 3 or 4 Creatinine Increased ≤ 22 days	Hold until ≤ Grade 1 or return to baseline	May resume at the same dose level or one dose level lower
• Grade 3 or 4 Creatinine Increased > 22 days	Discontinue MRTX849	
Other Grade 3/4 AEs	Hold until ≤ Grade 1 or return to baseline	May resume at the same dose level or one dose level lower

Abbreviation: AE = adverse event.

5.4.2.5. Cardiac Toxicities

Cardiac toxicities that are considered to be causally related to MRTX849 should initially be managed with treatment interruption of MRTX849 as outlined in Table 10. Cardiology consultation should be obtained for cases of QTcF prolongation or LVEF decreases falling into the categories indicated in Table 10. In addition, more frequent monitoring of electrolytes that include potassium and magnesium should be considered for patients with vomiting, diarrhea, or past instances of hypokalemia or hypomagnesemia that could recur, and oral and/or intravenous supplementation should be considered for levels below the lower limit of normal. Additionally, arrythmia should be included in the differential diagnosis of relevant AEs (eg, palpitations, syncope, pre-syncope, or unexplained dyspnea), and unscheduled ECGs should be performed for patients with such events or electrolyte abnormalities as clinically indicated. Patients who discontinue study treatment due to QTcF prolongation per the criteria listed in Table 10 should initiate close and clinically appropriate continuous ECG monitoring in a hospital setting until a cardiologist assessment is made.

Following resolution of toxicity to the specified degree, dose reduction of MRTX849 should be implemented.

Table 10: Cardiac Toxicities – MRTX849 Dose Modifications

Cardiac Toxicity	Treatment Interruption	Dose Modification
QTcF Prolongation[1] > 500 msec and increase > 60 msec on at least 2 ECGs ≤ 22 days	Hold until ≤ Grade 1 or return to baseline (< 15 msec above baseline)	Decrease by one or 2 dose levels
QTcF Prolongation[1] > 500 msec and increase > 60 msec on at least 2 ECGs > 22 days	Discontinue study treatment	
• Decrease in LVEF ≥ 20% from baseline and below LLN • Symptomatic left ventricular systolic dysfunction	Discontinue study treatment	
Other Grade 3/4 AEs	Hold until ≤ Grade 1 or return to baseline	May resume at one dose level lower

Abbreviation: AE = adverse event; ECG = electrocardiogram; LLN = lower limit of normal; LVEF = left ventricular ejection fraction; QTcF = QT interval corrected using Fridericia's formula.
[1] In addition to dose modifications for QTc prolongation, consideration should be given to supplement potassium and magnesium levels if they are below the lower limit of normal. Patients who discontinue study treatment due to QTcF prolongation per the criteria listed above should initiate close and clinically appropriate continuous ECG monitoring in a hospital setting until a cardiologist assessment is made.

5.4.2.6. Pneumonitis

Pneumonitis considered to be causally related to MRTX849 should be initially managed with treatment interruption of MRTX849 as outlined in Table 11. Following resolution of toxicity to the specified degree, dose reduction of MRTX849 should be implemented.

Table 11: Pneumonitis – MRTX849 Dose Modifications

Pneumonitis	Treatment Interruption	Dose Modification
Grade 1	Not Required	Decrease by one dose level
Grade 2	Hold until ≤ Grade 1 or return to baseline For Grade 2 recurrent pneumonitis, discontinue study treatment	If resumed, decrease by one dose level
Grade 3 or 4	Discontinue study treatment	

5.4.2.7. Other Toxicities

Other toxicities that are considered to be causally related to MRTX849 should initially be managed with treatment interruption as outlined in Table 12. Following resolution of toxicity to the specified degree, dose reduction of MRTX849 should be implemented.

Table 12: Other Toxicities – MRTX849 Dose Modifications

Other Toxicity	Treatment Interruption	Dose Modification
Grade 3/4 Fatigue or Asthenia ≤ 8 days	Hold until ≤ Grade 1 or return to baseline	May resume at same dose level or a lower dose level
Grade 1/2 AEs	Implement at Investigator and Patient Discretion	
Grade 3 AEs	Hold until ≤ Grade 1 or return to baseline	Resume one or more dose levels lower
Grade 4 AEs	Hold until ≤ Grade 1 or return to baseline	For AEs that are not life-threatening and that can be managed, treatment may resume at a lower dose level. Otherwise, discontinue study treatment.

Abbreviation: AE = adverse event

5.4.2.8. Hormonal Contraceptives and Thrombotic Events

In female patients using hormonal contraceptives, the potential exists for MRTX849 to inhibit hepatic cytochrome P450 CYP3A4 and increase exposure to hormonal contraceptive levels, with the associated risk of venous thromboembolism (eg, deep vein thrombosis or pulmonary embolism). Precautions should be taken in patients with recent, clinically significant thrombotic events, and all patients using hormonal contraceptives should be closely monitored for emerging signs of thrombotic events. Treatment with MRTX849 should be interrupted in patients with signs or symptoms of thrombosis and permanently discontinued in patients who develop clinically significant thromboembolic complications. If in the judgment of the Investigator resumption of treatment with MRTX849 is in the best interest of the patient, concomitant treatment with hormonal contraceptives should be discontinued.

5.5. 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 locally 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 2020. Refer to the current locally approved product label provided by the manufacturer for updates during the conduct of this clinical trial.

5.5.1. 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, 20 mg/0.5mL and 80 mg/4mL, 50/50 (volume/volume) ratio polysorbate 80/dehydrated alcohol. Refer to the current locally approved product label for further detail.

5.5.2. 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 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. Use of infusion equipment containing polyvinyl chloride (PVC) is not recommended. 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.

5.5.3. 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,

- Liver function tests 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 or platelet counts are < 100,000 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.

5.5.4. Docetaxel Dose Modification

The following is guidance provided in the TAXOTERE® US Prescribing Information (USPI TAXOTERE [docetaxel]); 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 2 dose reductions of docetaxel due to AEs should discontinue treatment with docetaxel.

5.6. Management of Docetaxel Adverse Events

Refer to locally approved product label for guidance concerning management of AEs during treatment with docetaxel. In addition to local product information and the administration guidelines described in Section 5.5, 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.

5.7. 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 serious adverse event (SAE) forms. In all cases of medication error, the Sponsor should be notified immediately.

There is currently no specific treatment in the event of an overdose of MRTX849. The Investigator will use clinical judgment to treat any overdose.

5.8. Crossover

Patients randomized to docetaxel study treatment arm whose disease meets RECIST 1.1 criteria for disease progression according to BICR may crossover to receive treatment with MRTX849. Patients must sign a crossover informed consent form and must meet all eligibility criteria for further treatment as described in Section 4.3 and Section 4.4 and will use the dosing regimen described in Section 5.3. The required assessments for patients who crossover is included in Appendix 6.

If a patient has been deemed to have disease progression according to Investigator assessment by RECIST 1.1, but is not confirmed by BICR, they are not eligible to crossover to MRTX849 study treatment at that time. Should it be in the patient's best interest, docetaxel treatment may be continued or patient may end treatment with docetaxel. If the patient continues to receive docetaxel or ends docetaxel treatment but has not yet started a subsequent anticancer therapy, sites are to continue to submit follow-up imaging for BICR review according to Table 2 for crossover eligibility.

5.9. Concomitant Therapies

5.9.1. Concomitant Medications

Prior medications, including chronically administered medication, used within the 28-day period preceding Day 1 of the trial, will be reviewed and recorded. Prior anticancer treatments 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 comorbidities, disease signs and symptoms and TEAEs 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.

Guidance on concomitant medications to be used with caution or avoided during treatment with MRTX849 or docetaxel is provided in Appendix 2 and Appendix 3, respectively.

Prophylactic Medications: These medications may be used as indicated in the current approved product label. Prophylaxis for nausea or diarrhea may be used at Investigator discretion.

Gastric Acid Reducing Medications: Because MRTX849 solubility is maximal at low pH, concomitant use with gastric acid reducing medications may decrease MRTX849 exposure which may reduce MRTX849 efficacy. PPIs should be avoided. As an alternative to PPIs, preference should be given first to antacids administered more than 2 hours before and more than 2 hours after dosing with MRTX849, and second to H_2 antagonists can be used with staggered administration (ie, administer MRTX849 at least 2 hours before or 2 hours after antacids, administer MRTX849 at least 2 hours before and 10 hours after the dose of H2 antagonists).

Anti-emetics: Prophylactic anti-emetics may be used at the discretion of the Investigator. It is recommended that patients use drugs that do not cause QT prolongation. Note that some anti-emetics have a known risk for Torsade de Pointes (see below Medications with QTc Prolonging Activity and Appendix 2). Ondansetron is included in the list of drugs with a known risk of Torsades de Pointes, and alternatives should be used. If effective alternative anti-emetics are not available, oral administration of ondansetron at doses up to 4 mg every 6 hours, with a maximum total daily dose of 16 mg, is permitted in patients without underlying bradycardia, congestive heart failure (CHF), or congenital Long QT Syndrome provided that an ECG is obtained at the beginning of each cycle, and that potassium and magnesium levels are obtained at the beginning of each cycle and supplemented if below the reference range. Oral dosing of ondansetron at 4 mg every 6 hours has been simulated to result in a mean difference in QTcF of 2.3 msec (Zuo, 2014). Use of intravenous administration of ondansetron is to be avoided.

Anti-diarrheals: Lomotil and octreotide can be used with MRTX849. Loperamide is included in the list of drugs with a known risk of Torsades de Pointes (cases of prolongation of the QT/QTc interval, Torsades de Pointes, other ventricular arrhythmias, cardiac arrest, some resulting in death, have been reported with use of higher than recommended doses per day of loperamide), and alternatives should be used. MRTX849 is expected to increase loperamide exposure by at least 4-fold. Considering the QTc effect of MRTX849 and loperamide and expected increase in loperamide concentration, loperamide should be avoided with MRTX849. If effective alternative anti-diarrheals are not available, oral administration of loperamide at low doses of 0.5 mg – 1 mg per dose, up to 3 mg total daily dose is permitted in patients without underlying bradycardia, CHF, or congenital Long QT Syndrome. An ECG, potassium and magnesium levels should be obtained at the beginning of each cycle and supplemented, if below the reference range.

Strong Inducers of CYP3A4: MRTX849 is a substrate of CYP3A4. Coadministration of MRTX849 or docetaxel with strong CYP3A4 inducers may significantly decrease the exposure to the study treatment, which may decrease the efficacy of the study treatment. Discontinue use of strong inducers of CYP3A4 a minimum of 7 days or 5 times their half-life, whichever is longer, prior to study treatment. Therefore, use of strong inducers of CYP3A4 is to be avoided during the study (list of examples provided in Appendix 2). In accordance with labeling instructions for docetaxel, strong inducers of CYP3A4 should also be generally avoided. Consider using alternative medications that are not strong inducers of CYP3A4.

Strong Inhibitors of CYP3A4: MRTX849 is a substrate of CYP3A4 and also inhibits its own CYP3A4 metabolism. Avoid concomitant use with strong CYP3A4 inhibitors until MRTX849 has reached steady-state (eg, approximately 8 days after continuous MRTX849 dosing). Once MRTX849 is at steady-state there are no restrictions on concomitant use of strong inhibitors of CYP3A4. Docetaxel is metabolized by CYP3A4. Coadministration of docetaxel with strong CYP3A4 inhibitors may significantly increase the exposure docetaxel, which may increase the risk of adverse reactions. In accordance with labeling instructions for docetaxel, inhibitors of CYP3A4 are to be avoided for patients in the docetaxel arm during the study (list provided in Appendix 3).

Strong Inhibitors of CYP2C8: CYP2C8 may play an important role in the metabolism of MRTX849 at steady-state. Concomitant use with strong CYP2C8 inhibitors may increase MRTX849 exposure. Strong inhibitors of CYP2C8 should be used with caution.

Substrates of Cytochrome P450: MRTX849 is a strong inhibitor of CYP3A4. Concomitant use with MRTX849 increases exposure of CYP3A4 substrates, which may increase the risk of adverse reactions related to these substrates. Patients are advised to avoid co-administration of MRTX849 with sensitive CYP3A4 substrates unless otherwise recommended in the Prescribing Information for these substrates. Sensitive CYP3A4 substrates that must always be avoided are listed in Appendix 2.

MRTX849 is a moderate inhibitor of CYP2C9 and CYP2D6. Concomitant use with MRTX849 increases exposure of CYP2C9 and CYP2D6 substrates, which may increase the risk of adverse reactions related to these substrates. Patients are advised to avoid coadministration of MRTX849 with sensitive substrates of CYP2C9 or CYP2D6 where minimal concentration changes may lead

to serious adverse reactions (ie, substrates with a narrow therapeutic index) unless otherwise recommended in the Prescribing Information for these substrates.

For patients in the experimental arm (MRTX849), example substrates of the specified CYP isozymes that should be avoided are provided in Appendix 2.

Inhibitors of BCRP: MRTX849 is a substrate of BCRP. The effect of inhibitors of BCRP (eg, curcumin, cyclosporin, and eltrombopaq) on MRTX849 has not been evaluated. For patients in the experimental arm (MRTX849), inhibitors of BCRP should be avoided (list of examples provided in Appendix 2).

P-gp Substrates: MRTX849 inhibits P-gp. Avoid use with P-gp substrates where minimal concentration changes may lead to serious adverse reactions (ie, substrates with a narrow therapeutic index) unless otherwise recommended in the Prescribing Information for these substrates.

Medications with QTc Prolonging Activity: A positive relationship between MRTX849 concentrations and QTc change was observed in patients. Based on a linear mixed-effect concentration-QTc model, the predicted mean (90% CI) ΔQTcP and ΔQTcF were 18.8 (16.4, 21.1) msec and 17.93 (15.13, 20.73) msec, respectively, at the population geometric mean $C_{max,ss}$ in patients after administration of MRTX849 600 mg BID. Use of medications known to prolong QTc and pose risk of Torsades de Pointes (as listed in Appendix 2) is to be avoided.

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

Transfusions: Packed red blood cell and platelet transfusions may be administered as clinically indicated.

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 and RANKL Inhibitors: The use of bisphosphonates or RANKL inhibitors regardless of indication is allowed, provided patients have been on stable oral doses for at least 2 weeks prior to study entry or stable with at least 2 parenteral injections prior to study entry; this stable dose should be maintained during the treatment period. Patients requiring initiation of bisphosphonates or a RANKL inhibitor during the course of the study should be evaluated to rule out disease progression.

Growth Factors: Therapeutic colony-stimulating factors should be used in accordance with national or international guidelines.

Vaccines: Vaccines made from inactivated micro-organisms, such as the injectable influenza vaccine, or from agents derived from or similar to pathogenic micro-organisms or toxins are

permitted. Vaccines developed using RNA technology, such as some COVID-19 vaccines, are permitted. Vaccines consisting of live, attenuated micro-organisms are not permitted and should not be used within 30 days prior to first dose of study treatment to 90 days after the last dose of study treatment.

5.9.2. Concomitant Surgery or Radiation Therapy

The use of elective surgery to manage cancer lesions during study treatment is discouraged. 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.

In the event that major surgery is needed during study treatment, the patient should, if possible, interrupt dosing with MRTX849 1 week in advance of the surgery and resume dosing 1 week after the surgery. Guidance for interruptions for radiation therapy will be made on a case-by-case basis taking into consideration the size and location of the radiation portal and the radiation dose.

5.9.3. Other Anticancer or Experimental Therapy

Use of approved or investigational anticancer treatment will not be permitted during the study treatment period, including chemotherapy, biological response modifiers, hormone 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. Pre-screening, Clinical Screening, and Crossover Eligibility Screening

Voluntary, written, dated, and signed informed consent must be obtained before any study-specific procedures are performed (see Section 4.6). Patients who complete the informed consent process but do not enroll on the study will be considered as screen failures. Limited information will be recorded in the CRF for these patients.

For details on procedures during the pre-screening period (ie, testing for the presence of *KRAS* G12C mutation in tumor tissue), see the Pre-screening Assessments as shown on Table 1 and Figure 1, and procedure descriptions in Section 7.1.

For details on procedures during the clinical screening period, see the Schedules of Assessments as shown in Table 2, and procedure descriptions in Section 7.

For details on procedures required during the crossover eligibility screening period, see Appendix 6.

6.2. Study Period

For details on procedures during the study period, see Schedules of Assessments as shown in Table 2, and procedure descriptions in Section 7.

6.3. End of Treatment Assessment

All patients will be followed for AEs for at least 28 days after the last dose of Study Treatment. See the Schedules of Assessments (Table 2) for evaluations to be performed at the End of Treatment visit.

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

Survival status and subsequent therapies will be collected during long term follow-up as outlined in the Schedules of Assessments (Table 2) until death or lost to follow-up. Beyond 28 days after last treatment, follow-up may be performed by visit, telephone, or e-mail. Treatments received following participation in the study will be collected in the CRF.

6.5. Patient Discontinuation/Withdrawal

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

For patients randomized to docetaxel study treatment arm whose disease meets RECIST 1.1 criteria for disease progression according to BICR, crossover to MRTX849 may be an option. Refer to Section 5.8 for more information, including crossover inclusion (Section 4.3) and exclusion criteria (Section 4.4).

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 record in the source document 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. Detection of *KRAS* G12C Tumor Mutation

The presence of *KRAS* G12C mutation in tumor tissue for the purpose of patient eligibility must be established using Sponsor pre-approved methods and laboratories. Presence of tumor *KRAS* G12C mutation may be established using Sponsor-approved local tests or the Sponsor-provided central laboratory test. For all enrolled patients, KRAS mutation status (to support a subsequent bridging study) and correlative tumor gene alterations will be tested retrospectively using tumor samples which must be submitted no later than 30 days after the first dose of study treatment.

Sponsor's pre-approval process includes review of analytical performance and validation of tests to ensure locked-down assay cutoffs (ie, criteria to determine whether subjects are biomarker-positive or -negative) before use of the test(s) in the study for patient enrollment.

The information required for Sponsor-approval of a specific local test to detect the presence of *KRAS* G12C mutation is as follows and should be emailed to [redacted]:

- Site number
- Site name
- Name of the test
- Name of the laboratory running the test
- Accreditation(s) of the laboratory running the test
- Analytical validation/performance summary of the test
- Copy of a sample report without any protected health information

Confirmation of Sponsor approval or approval denial will be provided to sites via email by the Sponsor.

In the United Kingdom (UK), the Sponsor will only approve local tests that are CE-marked for the detection of *KRAS* G12C or partially CE-marked for analytical performance to detect *KRAS* G12C.

Informed consent using the study-specific pre-screening ICF is required prior to submission of results from local genotyping or submission of samples for central genotyping. Biopsies having significant risk should not be performed for the purpose of determining patient eligibility, including but not limited to biopsies of the lung/mediastinum or endoscopic procedures extending beyond the esophagus, stomach, or bowel. However, in the event that a patient desires to consider study participation and no tumor specimen is available, procedures having less risk may be considered.

Platforms to be used for pre-screening tumor mutational analyses include Polymerase Chain Reaction (PCR) and Next-Generation Sequencing (NGS). The Sponsor-provided central laboratory test is:

- Qiagen therascreen KRAS RGQ PCR Kit.

Tumor tissue samples adequate for prospective or retrospective *KRAS* G12C mutation testing include a representative paraffin embedded tumor block or a minimum of 7 unstained slides (unless Sponsor approves fewer); however, 15 slides are preferable. Fresh biopsies are preferred, but archival biopsies are acceptable.

Full details on sample collection, processing, storage and shipment will be provided in the Study Laboratory Manual.

7.2. Documentation of Disease Progression On or After Prior Platinum-Based Chemotherapy and Checkpoint Inhibitor Therapy

Patient eligibility for study enrollment based on objective disease progression on or after a platinum-based regimen and an immune checkpoint inhibitor will be evaluated by the Investigator.

Data entered into the case report form (CRF) are to include prior regimens, best overall response, if progression occurred on or after treatment and date of progression.

7.3. Efficacy

All patients enrolled in the study are to undergo disease evaluations as outlined in the Schedule of Assessments (see Table 2).

Tumor assessment locations should include those outlined in Table 13 and using the recommended imaging modalities outlined in Table 14.

Table 13: Tumor Assessment Locations

Location	Screening/ Baseline	On-Study	At Response Confirmation
Brain	Required	Required If no brain metastases are present at baseline, may be obtained at every other imaging assessment (ie, at 12-week intervals)	Required
Chest	Required	Required	Required
Abdomen (including Pelvis)	Required	Required	Required
Bone	Required	Required May be obtained at every other imaging assessment (ie, at 12-week intervals)[1]	Required

[1] In Czech Republic, bone lesion assessment must be performed at 12-week intervals and no more than 4 times per year.

Table 14: Recommended Imaging Modalities

Location	Preferred Option 1	Preferred Option 2	Contraindication for IV Contrast for CT
Brain	MRI with contrast[1]	MRI with contrast[1]	MRI with contrast
Chest	CT with IV contrast	PET/CT (requires CT to be a diagnostic study with IV contrast and a reconstruction interval of 2.5 to 5 mm)	CT without IV contrast
Abdomen (including Pelvis)	CT with oral and IV contrast		MRI with IV contrast[2]
Bone	Bone Scan or PET[3] Scan		Bone Scan or PET[3] Scan

CT = Computed Tomography Scan; PET = Positron Emission Tomography; MRI = Magnetic Resonance Imaging.
[1] If MRI of the brain cannot be obtained, CT with IV contrast is acceptable.
[2] If MRI with contrast is not expected to adequately depict the individual's disease, CT without IV contrast may be used.
[3] A PET scan for bone imaging only may be performed using fluorodeoxyglucose (FDG) or fluorine 18 sodium fluoride (^{18}F-NaF).

For patients having effusions or ascites, cytological proof of malignancy should be obtained prior to selection of the effusion as a non-target lesion. Effusions that have not been evaluated using cytology or were found to be non-malignant should not be considered to be cancer lesions.

The allowable window for screening/baseline assessments is 28 days prior to randomization.

Assessments will be performed at 6-week intervals, based on a calendar beginning from randomization, until approximately 1-year and then every 12 weeks. The allowable windows for on-study assessments is ± 10 days.

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 with contrast) 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 with contrast 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 with contrast 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 IV 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.

Disease response will be assessed in accordance with RECIST 1.1 (Eisenhauer, 2009). Appendix 4 provides guidance in using the response criteria and includes modifications to RECIST 1.1 to address potential temporary treatment effects including tumor necrosis, cavitation, flare response or pseudoprogression. For patients with brain metastases for whom

central radiology review is performed, disease response will be assessed by CNS RECIST 1.1 for intracranial response.

Patients experiencing tumor response (Partial Response [PR] or Complete Response [CR]) should undergo confirmatory assessment at least 4 weeks after initial documentation; it is acceptable to perform confirmatory assessments at the next appointed evaluation per protocol (ie, 6 weeks after the observation of tumor response).

Potential exists for individual patients to experience tumor flare or pseudoprogression or, for individual tumor lesions to cavitate or become otherwise difficult to evaluate for a period of time as the result of beneficial study treatment impact. For this reason, in patients who are otherwise clinically stable, Investigators may delay reaching the conclusion of disease progression until subsequent on-study disease assessments are performed. Confirmatory assessments may be performed at least 4 weeks after the initial documentation; it is acceptable to perform confirmatory assessments at the next appointed evaluation per protocol (ie, 6 weeks after the observation of tumor increase).

BICR for disease response and progression will be performed for the purpose of statistical analyses of these study endpoints.

In the event a patient discontinues study treatment for a reason other than objective disease progression, disease assessments post-treatment should continue until objective disease progression is documented by the Investigator and BICR or start of subsequent anticancer therapy, whichever is sooner. Patients randomized to the docetaxel arm will be offered the opportunity to crossover to the MRTX849 study treatment arm upon development of RECIST 1.1-defined disease progression per BICR provided that patient crossover eligibility criteria are met.

Disease assessments must be performed as scheduled according to the calendar to prevent the introduction of bias in the assessment of efficacy based on toxicity. Timely and complete disease assessments and transfer of radiographic documentation to the Central Radiology Laboratory is critical to the integrity of this clinical trial.

Tumor markers are not required for assessment of efficacy.

7.4. Safety Assessments

7.4.1. Medical History

Medical history, including clinically significant past and present medical conditions, will be recorded at the time of screening. Cancer history will be recorded separately. Signs and symptoms of the patient's cancer diagnosis and/or comorbidities present on Cycle 1 Day 1 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 that are clinically relevant and present on Cycle 1 Day 1, the date of onset may pre-date start of study treatment.

7.4.2. Physical Examination and Vital Signs

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

Vital signs to be assessed include weight, body temperature, blood pressure, pulse rate and respiratory rate. Height will be recorded at screening only. On days where 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 as present and clinically relevant on Cycle 1 Day 1 of study treatment and throughout study treatment will be collected on the AE CRFs.

7.4.3. Laboratory Safety Assessments

Laboratory safety assessments for which data will be collected in this study will include hematology, thyroid tests and chemistry parameters presented in Table 15.

Laboratory tests will be drawn at the time points described in the Schedule of Assessments (Table 2) 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 AEs, or as clinically indicated.

Table 15: Laboratory Safety Parameters

Hematology Panel	**Blood Chemistry Panel**
Hemoglobin	Aspartate aminotransferase (AST)
Platelet count	Alanine aminotransferase (ALT)
White blood cell count (WBC)	Alkaline phosphatase (ALP)
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	Creatinine
Monocyte Count	Blood urea nitrogen (BUN)[1]
	Uric acid
	Total protein
	Albumin
	Glucose (non-fasted preferred)
Thyroid Function	Sodium
Thyroid-stimulating hormone (TSH)	Potassium
	Chloride
	Bicarbonate or CO_2
	Total calcium
	Phosphate
	Magnesium
	Lipase
	Amylase
	Creatine kinase (if elevated, abnormal creatine kinase value should be handled by the Investigator in accordance with their site standard of care practices)

[1] Urea is acceptable if blood urea nitrogen (BUN) is not an option.

7.4.4. Pregnancy and Follicle Stimulating Hormone Testing

For patients who are women of childbearing potential, a urine or serum pregnancy test will be performed by the local laboratory at Screening and at End of Treatment. In addition, in regions where required by regulation (eg, European Union), monthly pregnancy testing will be performed until the end of systemic exposure to study treatments (testing may be performed at the beginning of each 3-week treatment cycle for convenience). Pregnancy tests will also be done whenever pregnancy is suspected during the study.

In countries operating in compliance with CTFG guidelines, a follicle stimulating hormone test should be performed at screening to confirm a postmenopausal state in women considering enrollment into this study.

7.4.5. Hepatitis and Human Immunodeficiency Virus Testing

In Germany, Czech Republic, and Portugal only, patients must be tested for HIV, HBV and HCV infection (all tests performed by local laboratory) at screening. Testing for HIV infection should typically be performed using an HIV Ab test, and if warranted, further testing by local standards (eg, nucleic acid test). Hepatitis B serology to include the following: hepatitis B core antibody (HBcAb/anti-HBc), and if positive hepatitis B surface antigen (HBsAg); HBV DNA should be performed if HBsAg is positive. Hepatitis C serology: HCV antibody (anti-HCV); HCV RNA performed only if anti-HCV is positive.

7.4.6. Electrocardiogram (ECG)

Single and triplicate ECGs are to be performed as outlined in the Schedule of Assessments (see Table 2). It is preferable that the machine used has a capacity to calculate the standard intervals automatically.

7.4.7. MUGA or ECHO

A Multigated Acquisition Scan (MUGA) (preferred except in Germany where it is not an option) or echocardiogram (ECHO) will be performed as outlined in the Schedule of Assessments (see Table 2). Additional assessments of LVEF may be performed as clinically indicated at the Investigator's discretion if there are signs or symptoms of cardiotoxicity. The same assessment method (MUGA or echocardiogram) should be used for all cardiac imaging examinations throughout the study for each patient.

7.5. Laboratory Studies

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

7.5.1. Pharmacokinetic Evaluation

7.5.1.1. PK for MRTX849

The PK blood samples will be collected at specified time points as outlined in Table 2. Every effort will be made to collect PK samples at the exact nominal times relative to dosing. A variation window is allowed for each time point as outlined in Table 2. If MRTX849 treatment is interrupted on a scheduled PK collection day, a pre-dose PK sample should still be collected. However, if MRTX849 is being held or has been discontinued prior to the scheduled PK collection day, then no PK samples are required to be collected. If MRTX849 has been held or discontinued for ≥ 3 days, Unscheduled PK collections are not required. 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. Full details on sample collection, processing, storage and shipment will be provided in the Study Laboratory Manual.

All plasma PK samples will be measured for concentrations of MRTX849 using a validated bioanalytical method(s).

7.5.2. Circulating Tumor DNA

Blood samples for ctDNA analysis will be collected as outlined in Table 2. Whole 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 mutation profiling utilizing ctDNA samples will be determined using NGS performed by a central laboratory. Full details on sample collection, processing, storage and shipment will be provided in the Study Laboratory Manual.

7.5.3. Correlative Molecular Analysis in Tumor Tissue

Evidence is emerging that in advanced NSCLC patients, certain recurrent mutations may independently impact prognosis or response to therapy. Therefore, tumor tissue sent to determine or confirm *KRAS* G12C status will be analyzed for tumor mutations of other genes, such as *STK11*, *KEAP1, NF1, CDKN2A,* and *TP53* for an exploratory analysis of correlation of mutations with prognosis and efficacy endpoints. In addition (except in Germany), collection of tumor samples at the time of disease progression in patients with an objective tumor response or prolonged stable disease (> 4 months) on study is requested. Individual genetic alterations in target genes, including mutations, gene amplifications, deletions, and rearrangements, as well as tumor mutation burden (TMB), will be evaluated utilizing the Sponsor-provided NGS assay performed by the central laboratory.

Tumor tissue for profiling selected genetic alterations that are present in patients harboring *KRAS* G12C mutations will be collected as outlined in Table 2. Full details on sample collection, processing, storage and shipment will be provided in the Study Laboratory Manual.

7.5.4. Patient Reported Outcomes

Patient reported outcomes (PROs) will evaluate lung cancer-specific symptoms and health-related quality of life using 2 validated measures: the LCSS (Hollen, 1993), (Hollen, 1994), (Hollen, 1995), (Hollen, 2004) and the European Quality of Life Five Dimensions Questionnaire (EQ-5D-5L) (EuroQoL, 2020), (Herdman, 2011).

The LCSS is a disease specific measure of quality of life. The patient version of the LCSS includes 9 questions and utilizes visual analogue scales (VAS) to score the degree of impairment as reported by patients (range 0-100) across 6 symptoms (appetite loss, fatigue, cough, dyspnea, hemoptysis, pain) and 3 summary global items (symptom distress, activity level, overall quality of life). This patient version will be used in the assessment of health-related quality of life.

The EQ-5D-5L questionnaire includes 2 components – the EQ-5D-5L descriptive assessment of 5 dimensions (inclusive of mobility, self-care, usual function status, pain and/or discomfort, and anxiety and/or depression) with 5 possible response levels (no problems, slight problems,

moderate problems, severe problems or unable to/extreme problems), and the EQ VAS for the patient's self-rated overall health based on a vertical visual analogue scale, which ranges from 0 (worst imaginable) to 100 (best imaginable).

PRO assessments will be collected as outlined in Table 2. EQ-5D-5L questionnaires should always be completed before LCSS.

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 AE events will include type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE, Version 5.0]), timing, seriousness, and relatedness to study treatment. A treatment-emergent AE (TEAE) is an AE that occurs after the first dose of any study treatment or any pre-existing 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 5.4.2.3).

8.2.2. Severity Assessment

AEs occurring during this study will be graded in accordance with the NCI CTCAE v5.0. 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 pre-existing 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.

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 1 month prior to or around the time 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

Special guidance is provided in Appendix 5 for reporting AEs and SAEs impacted by documented or suspected COVID-19 infection during the public health emergency.

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). During the pre-screening period (ie, after pre-screening informed consent and before the main study informed consent), reporting of SAEs is limited to events associated with study required assessments (eg, biopsies for tumor genotype testing). Beginning at the time of signing the main study informed consent to begin clinical eligibility screening, reporting of all SAEs is required. SAE reporting continues for 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 in a patient after the active reporting period has ended should be reported to the Sponsor if the Investigator becomes aware of them and if the Investigator assesses at least a reasonable possibility of being related to study drug. These SAEs should be followed until resolved or stabilized to a chronic condition.

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

8.4.2. Reporting Requirements

All SAEs must be reported within 24 hours of Investigator/site knowledge of the event, irrespective of the extent of available AE information, by faxing the SAE report to the Sponsor's pharmacovigilance representative designated in the Study Manual. The 24 hour timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports and to the initial and follow-up reporting of exposure during pregnancy and exposure via breastfeeding. For sites in Germany, all SAEs must be reported immediately, without undue delay, upon Investigator/site knowledge of the event, irrespective of the extent of available AE information. In Germany, this timeframe requirement 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.

The Sponsor's Safety Management Team (SMT) is responsible for monitoring and evaluation of safety data for the study treatment to assess the benefit-risk to decide appropriate actions for patient safety and to mitigate risk. All AEs (including SAEs) must be documented in source documents. Beginning on the first day of study treatment, all AEs (including SAEs) are to be reported in the CRF. Please note that the CRF and SAE report forms may collect information in somewhat different formats. Where the requested data overlap in different formats, the information should be consistent between the two forms.

9. STATISTICS

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

9.1. Phase 3 Hypothesis and Sample Size

Study 849-012 is adequately powered for the PFS endpoint with an overall 0.05 (2-sided) level of significance. The study plans to randomize approximately 450 patients in a 2:1 ratio to receive MRTX849 or docetaxel, respectively. The sample size of 450 for the study is primarily estimated from the secondary endpoint of OS, which is also adequately powered under the assumption of proportional hazards.

For the PFS endpoint, the study has 90% power to detect a HR of 0.645 (under an assumed median PFS for docetaxel arm of approximately 4 months compared to 6.2 months for the MRTX849 arm) at a 2-sided level of significance of 0.05 based on 246 PFS events.

For the secondary endpoint OS, the study has 80% power to detect a HR of 0.72 (under an assumed median OS for docetaxel arm of approximately 10 months compared to 13.9 months in the MRTX849 arm) at a 2-sided level of significance of 0.05 based on 334 death events. Assuming an enrollment duration of approximately 37 months at an average rate of 12 patients per month (approximately 450 patients), and an additional 15 months of follow-up will be required to reach the number of required death events.

There will be one analysis for the PFS endpoint and an interim analysis of OS (~50% of the expected death events), and one final analysis for the OS endpoint. The enrollment into the study is anticipated to be completed when the PFS analysis occurs. A group sequential design will be used with the O'Brien-Fleming boundary as implemented by the Lan-DeMets alpha spending method. A nonbinding futility boundary using the Rho family spending function with parameter of 3.0 is also constructed for OS (see Section 9.7 for further detail). If the OS endpoint is statistically significant at interim, the formal OS final analysis will not be conducted per group sequential design, but a subsequent survival update may be conducted as warranted.

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 part of a dose of study medication (ie, MRTX849 or docetaxel). The safety population will be used for all safety analyses.

9.3.3. Pharmacokinetic Evaluable Population

The PK evaluable population will consist of all patients who received treatment with MRTX849 and have adequate and reliable data for the evaluation of MRTX849 PK. For patients who were noncompliant with respect to of MRTX849 administration, or for patients with incomplete data, a decision as to their inclusion in the analysis will be made on a case-by-case basis.

9.4. Efficacy Endpoint Definitions and Analyses

9.4.1. Progression-Free Survival

Progression-free survival (PFS) is defined as the time from randomization to the date of PD or death due to any cause, whichever occurs first. The distribution of PFS will be estimated using the Kaplan-Meier method. The stratified log-rank test will be used to compare the PFS between the 2 treatment arms. Due to the shift of region stratification factor in protocol version 4 (USA/Canada versus other to non-Asia-Pacific versus Asia-Pacific), the stratification factors for analysis will be based on the actual region (non-Asia-Pacific versus Asia-Pacific) and the prior treatment administration of last prior platinum-based chemotherapy and anti-PD-1/PD-L1 antibody (sequential versus concurrent).

Censoring for the PFS 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. If PD or

death occurs following ≥ 2 consecutive missed tumor assessments, PFS will be censored at the last tumor assessment date prior to the PD or death. For patients who start a subsequent anticancer therapy prior to PD or death, PFS will be censored at the date of the last tumor assessment prior to the start of the new therapy. For patients without a tumor assessment after randomization, PFS will be censored on the date of randomization with duration of 1 day. If a patient discontinues from the study before PD, PFS will be censored on the date of last tumor assessment prior to discontinuation. Additional details are provided in the SAP.

9.4.2. Overall Survival

Overall survival is defined as the time from date of randomization to date of death due to any cause. The distribution of OS will be estimated using the Kaplan-Meier method. The stratified log-rank test will be used to compare the OS between the 2 treatment arms. Due to the shift of region stratification factor in protocol version 4 (USA/Canada versus other to non-Asia-Pacific versus Asia-Pacific), the stratification factors for analysis will be based on the actual region (non-Asia-Pacific versus Asia-Pacific) and the prior treatment administration of last prior platinum-based chemotherapy and anti-PD-1/PD-L1 antibody (sequential versus concurrent). The Kaplan-Meier method will be used to estimate the median OS and 1-year survival rate; the 95% CI of the median OS and 1-year survival rate will also be reported. Censoring for the survival endpoint will be assigned on the date of the last known survival date.

With the allowance of patients in the docetaxel arm to crossover and receive MRTX849, sensitivity analysis adjusting for the crossover will also be carried out for the OS endpoint. If a substantial proportion of patients in the docetaxel arm were to crossover to receive MRTX849 treatment, a weighted log-rank test may be carried out to account for non-proportional hazards due to treatment crossover (Lin, 2020), (Therneau, 2000); Restricted Mean Survival Time (RMST) method may also be considered (Uno, 2014). Additional analyses may be conducted to account for treatment crossover and to elucidate the non-proportional hazards assumption. Details will be provided in the SAP.

9.4.3. Objective Response Rate

Objective disease response will be categorized in accordance with RECIST v1.1 (Appendix 4). Objective Response Rate 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 Cochran-Mantel-Haenszel (CMH) test will be used to compare the response rates between the 2 treatment arms. In the event some cells have low frequency count (eg, < 5), a Chi-square test may be used instead of CMH.

9.4.4. Duration of Response

Duration of Response (DOR) is defined as the time from date of the first documentation of objective tumor response (CR or PR) to the first documentation of either Progression of Disease (PD) or death due to any cause, whichever occurs first. The DOR analysis only applies to those patients who have confirmed objective response per RECIST v1.1. The distribution of DOR will be estimated using the Kaplan-Meier method.

Censoring for the DOR endpoint will be assigned on the date of the last evaluable tumor assessment if no assessment of tumor progression is recorded and the patient does not die while on study. If PD or death occurs after a documentation of response followed by ≥ 2 consecutive missed tumor assessments, DOR will be censored at the last evaluable tumor assessment date prior to the PD or death. For patients who start a subsequent anticancer therapy prior to PD or death, DOR will be censored at the date of the last evaluable tumor assessment prior to the start of the new therapy. If a patient discontinues from the study before PD, DOR will be censored on the date of last evaluable tumor assessment prior to discontinuation. Additional details are provided in the SAP.

9.4.5. Progression-Free Survival-2

Exploratory analysis of Progression-Free Survival-2 (PFS2) is defined as the time from randomization to disease progression on the next-line of therapy, or death from any cause, whichever first. The distribution of PFS will be estimated using the Kaplan-Meier method. The non-stratified log-rank test will be used to compare the PFS2 between the 2 treatment arms. Additional details are provided in the SAP as needed.

9.4.6. Time to CNS Progression

Time to CNS progression is defined as the time from randomization to newly developed CNS metastases or progression of pre-existing brain lesions, whichever presents first. The distribution of time to CNS progression will be estimated using the Kaplan-Meier method. The non-stratified log-rank test will be used to compare the time to CNS progression between the 2 treatment arms. Additional details are provided in the SAP.

9.4.7. Intracranial activity using CNS RECIST 1.1 endpoints in patients with brain metastases

Intracranial activity using CNS RECIST 1.1 endpoints in patients with brain metastases at baseline, including icORR, icDOR, icPFS and icTTP, will be analyzed in patients with brain metastases only. Additional details are provided in the SAP.

9.4.8. Subgroup Analyses

Baseline characteristics to be evaluated in subgroup analyses include:

- Gender
- Age
- Race
- ECOG status (0 vs 1)
- Smoking history (lifetime non-smoker, past smoker, vs current smoker)
- Region (non-Asia-Pacific vs Asia-Pacific)

- Prior treatment administration of last prior platinum-based chemotherapy and anti-PD-1/PD-L1 antibody (sequential vs concurrent)
- Number of prior lines of therapy in advanced disease (1 vs 2 vs > 2)
- Brain metastasis at baseline (yes vs no)
- Liver metastasis at baseline (yes vs no)
- Bone metastasis at baseline (yes vs no)
- Tumor proportion score (PD-L1 protein expression) (< 1% vs 1-49% vs ≥ 50%)
- Best overall response of the last prior therapy in advanced/metastatic setting

Efficacy endpoints of OS and PFS will be presented descriptively per each subgroup. Forest plots will be used to present the results of the subgroup analysis for OS and PFS. Additional subgroup analyses will be provided in the SAP.

9.5. Safety Data Presentations and Summaries

9.5.1. Adverse Events

Adverse events will be classified using the medical dictionary for regulatory activities (MedDRA) classification system. Listings will include the verbatim term, preferred term, and system organ class (SOC). The number of patients with treatment-emergent AEs and the incidence of TEAEs by SOC and preferred term will be summarized. TEAEs will be summarized by maximum intensity and relationship to study therapy. Separate summaries will be provided for TEAEs, TESAEs, treatment-related AEs, treatment -related SAEs, and other significant AEs (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, thyroid function tests and chemistry), vital signs, MUGA or ECHO and 12-lead ECGs.

Clinical laboratory results will be listed by patient and, as appropriate, summarized descriptively, which will include a display of change from baseline. Selected parameters will be presented in shift tables of baseline against worst grade test result. Laboratory values outside of the normal ranges will be identified. Laboratory values that meet Grade 3 or 4 criteria according to NCI CTCAE v5.0 will be listed and summarized.

Electrocardiogram assessments will be evaluated for change of QTc from baseline. 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, MUGA or ECHO and, ECG measurements will be listed for each patient at each visit. Descriptive statistics of observed values and changes from baseline will be summarized by treatment group.

9.5.4. Patient Demographics, Baseline Characteristics and Disposition

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

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

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

9.5.5. Analysis of Study Treatment Dosing

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

9.6. Other Study Endpoints

9.6.1. Pharmacokinetic Analysis

Descriptive summary statistics of MRTX849 concentrations will be reported.

Sparse PK data from this study will be included with other MRTX849 studies for population PK analysis to identify potential covariates. Results of population PK analysis will be issued in a separate report. Exposure-response analysis for safety and efficacy endpoints will be explored and results will be issued in a separate report.

9.6.2. Patient Reported Outcomes Analysis

For the LCSS, change from baseline scores in the overall, symptom and three-item global components will be compared between treatment arms using mixed effect model repeated measurement (MMRM) analysis. The least-squares mean differences between treatments will be presented. Descriptive statistics will be reported by visit, as well as the change from baseline for the overall, diseases-associated symptom and three-item global components of the LCSS.

For the EQ-5D-5L descriptive system, patient health states will be converted into a single dimension descriptive health utility index (UI). The EQ-5D UI and VAS will be analyzed using a

MMRM analysis as described above. Descriptive statistics will also be reported for both the EQ-5D UI and VAS scores as well as change from baseline scores.

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

9.6.3. Exploratory Analyses

No formal statistical analysis of exploratory endpoints will be performed. Possible relationships between correlative endpoints, PK parameters, safety, and efficacy may be examined if appropriate.

9.7. Interim Analysis

For the secondary endpoint OS, a group sequential design will be utilized with one interim analysis and one final analysis. The interim analysis for OS is conducted at the time when the required PFS events (ie, ~246 PFS events) is observed. The exact alpha spend for OS will be adjusted according to the observed number of events (ie, death) at the time of analysis. The enrollment into the study is anticipated to be completed by the time of the interim analysis. If the number of death events for the interim analysis for OS is maturing slower than expected at the time of the PFS analysis, a decision will be made if PFS analysis will proceed as planned or the analysis will be delayed until an appropriate number of death events has occurred. A nonbinding futility boundary for OS is also constructed using a Rho family spending function with parameter 3.0.

The fixed-sequence testing procedure to control the familywise error rate (FWER) will be used for testing of the primary endpoint PFS and the secondary efficacy endpoints in this study. Initially, PFS hypothesis will be tested at $\alpha = 0.05$ (2-sided). If PFS test is statistically significant, the ORR hypothesis will be tested at $\alpha = 0.05$ (2-sided). If the ORR test is statistically significant, the OS hypothesis will be tested at $\alpha = 0.05$ (2-sided) with the Lan-DeMets O'Brien-Fleming spending function at the interim analysis. Further details will be provided in the SAP.

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 approximate 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 (IRB/EC/REB)

Prior to the shipment of clinical supplies or initiation of the study, the clinical trial protocol along with the 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 (R2)) 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 (not applicable in

France) in CDISC SDTM (SDTM Implementation Guide v.3.2) format, 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 his/her personal data, the right to define guidelines for the storage, deletion and communication of the data after his/her death and the right to the portability of his/her 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 and Data

Source documents to be used for verification of data in the CRF (electronic data capture system) include hospital or clinical patient charts, pertinent historical medical records, local 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.

In addition, source data for this study will be obtained from the IWRS, web-based portals for clinician reported outcomes, mobile electronic applications for patient reported outcomes, central laboratories, specialty laboratories, the central radiology review laboratory, and/or other vendors specified by the Sponsor.

11.2. Study Files and Records Retention

A CRF must be completed for each patient for whom informed consent for the study is obtained. The CRFs must be maintained by properly trained and delegated site representatives. The Principal Investigator has responsibility for ensuring the authenticity, accuracy, completeness and timeliness of all data collected in the CRF. CRFs must be signed by the Principal Investigator or by an authorized Sub-Investigator to attest that the information included is true.

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

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

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. Monitoring Procedures

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

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

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

12.2. Auditing and Inspection Procedures

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

13. CHANGES IN STUDY CONDUCT

13.1. Protocol Amendments

Changes to the study protocol, except those intended to reduce immediate risk to study patients, may be made only by the Sponsor. A protocol change intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRB/EC/REB is notified within 5 days. Any urgent safety measures taken by the Investigator to protect the study patients against any immediately life-threatening hazard must be reported immediately to the Sponsor.

Any permanent change to the protocol must be handled as a protocol amendment. The change and the justification will be documented in writing by the Sponsor, as an Administrative Letter or amended protocol. Protocol amendments will include a list of all changes. 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 ICF 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. Plan for Communication of Study Decisions and Protocol Changes

This Phase 3 trial includes multiple points at which decisions will be made concerning direction of the study. Table 16 lists decision makers, initial communication methods and ultimate documentation of decisions and protocol amendments.

Table 16: Communication of Study Decisions and Protocol Amendments

Study Decision or Protocol Change	Decision Maker	Documentation for Implementation	Ultimate Documentation
Protocol change to address serious safety concern	Sponsor	Administrative Letter to Investigators	Reiteration in next protocol amendment
Change in formulation of MRTX849	Sponsor	Administrative Letter to Investigators	Reiteration in next protocol amendment
Update of fed/fasted dosing instructions	Sponsor	Administrative Letter to Investigators	Reiteration in next protocol amendment
Update AE management guidelines	Sponsor	Administrative Letter to Investigators	Reiteration in next protocol amendment
Update list of medications to use with caution	Sponsor	Administrative Letter to Investigators	Reiteration in next protocol amendment

13.3. 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 MRTX849 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 DURING TREATMENT WITH MRTX849

Examples are provided for QT-prolonging medications to **avoid** (Table 17), and medications and substances to avoid with MRTX849 treatment (Table 18). Refer to Section 5.9 for additional information on concomitant use of medications and substances during the study.

Table 17: Examples of QT-Prolonging Medications to Avoid

Examples of Medications to Avoid	Potential Effect
Amiodarone, anagrelide, azithromycin, chloroquine, chlorpromazine, ciprofloxacin, citalopram, clarithromycin, cocaine, disopyramide, domperidone, donepezil, erythromycin, escitalopram, fluconazole, gatifloxacin, haloperidol, hydroxychloroquine, levofloxacin, loperamide[1], methadone, moxifloxacin, ondansetron[1], oxaliplatin, pentamidine, propofol, quinidine, sotalol, terfenadine, thioridazine, vandetanib	Known risk of QT-prolongation and Torsades de Pointes

Source: Compiled from https://www.crediblemeds.org/druglist (accessed July 2021). This list of examples is not exhaustive; refer to the source for additional examples.

[1] Refer to Section 5.9 for additional guidance related to concomitant use of loperamide and ondansetron.

Table 18: Examples of Medications and Substances to Avoid with MRTX849 Treatment

Characteristic	Examples of Medications/Substances to Avoid	Potential Effect
Effect of MRTX849 on other medications or substances		
Sensitive CYP3A4 substrates[1]	Alfuzosin, alprazolam, aprepitant, avanafil, budesonide (oral), carbamazepine, conivaptan, daridorexant, dihydroergotamine, dronedarone, eletriptan, eplerenone, ergotamine, everolimus, finerenone, isavuconazole, ivabradine, lomitapide, lonafarnib, lopinavir, lovastatin, lurasidone, midazolam, mitapivat, naloxegol, nisoldipine, rivaroxaban, sildenafil (for pulmonary arterial hypertension), simeprevir, simvastatin, sirolimus, ticagrelor, tipranavir, tolvaptan, triazolam, ubrogepant, vardenafil, voclosporin	Increased exposure of CYP3A4 substrates, potentially increasing risk of SAEs associated with con med
Sensitive CYP2D6 substrates with narrow therapeutic index[1]	Eliglustat, pimozide, propafenone, thioridazine	Increased exposure of CYP2D6 substrate, potentially increasing risk of toxicities associated with con med
Sensitive CYP2C9 substrates with narrow therapeutic index[1]	Warfarin[2]	Increased exposure of CYP2C9 substrate, potentially increasing risk of toxicities associated with con med
P-gp substrates with narrow therapeutic index[3]	Colchicine, dabigatran, digoxin	Increased exposure of P-gp substrates, potentially increasing risk of SAEs associated with con medication
Effect of other medications or substances on MRTX849		
Strong Inhibitor of CYP3A4[4]	Boceprevir, clarithromycin, cobicistat, danoprevir, itraconazole, ketoconazole, lopinavir, nefazodone, nelfinavir, posaconazole, ritonavir, telaprevir, telithromycin, troleandomycin, voriconazole	Increased exposure of MRTX849, potentially increasing risk of SAEs associated with MRTX849 (only avoid until MRTX849 reaches steady state after approximately 8 days of continuous dosing)
Strong Inducer of CYP3A4	Carbamazepine, mitotane, phenobarbital, phenytoin, rifampin, St. John's wort	Decreased exposure of MRTX849, potentially reducing efficacy
Inhibitor of BCRP	Eltrombopag, curcumin, cyclosporine	Increased exposure of MRTX849, potentially increasing risk of SAEs associated with MRTX849
Proton pump inhibitors	Dexlansoprazole, esomeprazole, ilaprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole	Decreased exposure of MRTX849, potentially reducing efficacy

Abbreviations: BCRP = breast cancer resistance protein; con med = concomitant medication, CYP = cytochrome P450 enzyme; P-gp = P-glycoprotein; SAE = serious adverse event.

Sources: Compiled from the University of Washington Drug Interaction Database (https://didb.druginteractionsolutions.org/), https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers (accessed February 2023). This list of examples is not exhaustive and excludes anti-neoplastic agents; refer to the sources for additional examples.
For other sensitive substrates not listed in the examples, refer to their Prescribing Information for recommended use.

[1] For other sensitive substrates not listed in the examples, refer to their Prescribing Information for recommended use.

[2] In certain cases, warfarin may be used after approval from the Sponsor and with additional international normalized ratio (INR) monitoring.

[3] Some concomitant medications, upon approval by the Sponsor, may be used in accordance with the Prescribing Information for these medications.

[4] Concomitant use of strong inhibitors of CYP3A4 do not need to be avoided once MRTX849 has reached steady-state (eg, approximately 8 days after continuous MRTX849 dosing).

APPENDIX 3. MEDICATIONS OR SUBSTANCES TO BE AVOIDED DURING TREATMENT WITH DOCETAXEL

Based on information presented in approved product label, concomitant use of docetaxel and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. The potential for drug-drug interactions during use of docetaxel is further discussed in approved product label. Specific concomitant medications to be avoided during docetaxel use are listed in Table 19. Note that strong inducers of CYP3A4 may decrease exposure to docetaxel and should also be generally avoided.

Table 19: Specific Concomitant Medications to Avoid with Docetaxel

Drug Name	Characteristic	Potential DDI Effect	Usage
Atazanavir	Strong CYP3A4 Inhibitor	Increased Exposure of Docetaxel	Avoid
Boceprevir	Strong CYP3A4 Inhibitor	Increased Exposure of Docetaxel	Avoid
Clarithromycin	Strong CYP3A4 Inhibitor	Increased Exposure of Docetaxel	Avoid
Cobicistat	Strong CYP3A4 Inhibitor	Increased Exposure of Docetaxel	Avoid
Danoprevir and Ritonavir	Strong CYP3A4 Inhibitor	Increased Exposure of Docetaxel	Avoid
Darunavir and Ritonavir	Strong CYP3A4 Inhibitor	Increased Exposure of Docetaxel	Avoid
Elvitegravir and Ritonavir	Strong CYP3A4 Inhibitor	Increased Exposure of Docetaxel	Avoid
Grapefruit Juice	Strong CYP3A4 Inhibitor	Increased Exposure of Docetaxel	Avoid
Idelalisib	Strong CYP3A4 Inhibitor	Increased Exposure of Docetaxel	Avoid
Indinavir and Ritonavir	Strong CYP3A4 Inhibitor	Increased Exposure of Docetaxel	Avoid
Itraconazole	Strong CYP3A4 Inhibitor	Increased Exposure of Docetaxel	Avoid
Ketoconazole	Strong CYP3A4 Inhibitor	Increased Exposure of Docetaxel	Avoid
Lopinavir and Ritonavir	Strong CYP3A4 Inhibitor	Increased Exposure of Docetaxel	Avoid
Nefazodone	Strong CYP3A4 Inhibitor	Increased Exposure of Docetaxel	Avoid
Nelfinavir	Strong CYP3A4 Inhibitor	Increased Exposure of Docetaxel	Avoid

Drug Name	Characteristic	Potential DDI Effect	Usage
Paritaprevir and Ritonavir and (Ombitasvir and/or Dasabuvir)	Strong CYP3A4 Inhibitor	Increased Exposure of Docetaxel	Avoid
Posaconazole	Strong CYP3A4 Inhibitor	Increased Exposure of Docetaxel	Avoid
Ritonavir	Strong CYP3A4 Inhibitor	Increased Exposure of Docetaxel	Avoid
Saquinavir and Ritonavir	Strong CYP3A4 Inhibitor	Increased Exposure of Docetaxel	Avoid
Telaprevir	Strong CYP3A4 Inhibitor	Increased Exposure of Docetaxel	Avoid
Telithromycin	Strong CYP3A4 Inhibitor	Increased Exposure of Docetaxel	Avoid
Tipranavir and Ritonavir	Strong CYP3A4 Inhibitor	Increased Exposure of Docetaxel	Avoid
Troleandomycin	Strong CYP3A4 Inhibitor	Increased Exposure of Docetaxel	Avoid
Voriconazole	Strong CYP3A4 Inhibitor	Increased Exposure of Docetaxel	Avoid

APPENDIX 4. ABBREVIATED PRESENTATION OF RECIST VERSION 1.1 GUIDELINES

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

Categorizing Lesions at Baseline

Measurable Lesions

- Not previously irradiated, unless disease progression in the lesion was documented after completion of radiotherapy.
- Accurately measured in at least one dimension.
- When assessed by CT or MRI, longest diameter at least 10 mm or greater (slice thickness 5-8 mm), measured in the axial plane. If the slice thickness is greater than 5 mm (including any inter-slice gap), the longest diameter must be at least twice the slice thickness.
- Malignant lymph nodes with a short axis (defined as the largest measurement perpendicular to the longest diameter of the lesion) 15 mm or greater when assessed by CT or MRI.

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

Non-Measurable Disease

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

Normal Lesions

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

Tumor Assessments

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

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

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to look for PR 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.
- Patients who receive palliative locoregional treatment such as complete resection or radiotherapy to target lesions after initiating study treatment will be censored from response evaluation in the efficacy analyses at the time the patient receives the palliative locoregional treatment.

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 indeterminate.

Target Disease

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

Non-Target Disease

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

New Lesions

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

Lesion Changes That May Be Transient

Potential exists for individual tumor lesions to develop necrosis, cavitate, have a flare response to treatment, demonstrate pseudoprogression or become otherwise difficult to evaluate for a period of time as the result of study treatment impact. For example, tumor necrosis, cavitation, flare or pseudoprogression may result in increase in overall size of individual lesions, unclear tumor margins, or observation of apparently new lesions prior to recovery to smaller lesions, development of scar tissue, or complete resolution. The true tumor measurements of lesions should be recorded but the conclusion of progressive disease may be suspended until continued assessment clarifies the nature of the tumor change. If repeat assessments indicate progression of disease, then PD should be recorded on the date of the first assessment giving the impression of progression. If repeat assessments indicate that the change was a process of transition, then NE should be recorded during the period of transition, and PR or CR may be recorded for subsequent evaluations. The CRF will collect information on the observations during the period of transition to support the assessment conclusions.

Supplemental Investigations

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

Best Objective Response

Target Lesions	Non-Target Lesions	New Lesion	Point in Time Response	Best Response
CR	CR	No	CR	CR and PR require confirmation at least 4 weeks after first observation
CR	Non-CR/Non-PD	No	PR	
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	SD requires an on-study assessment after at least 6 weeks on treatment. 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. GUIDANCE TO STUDY SITES ON STUDY AND PATIENT MANAGEMENT DURING COVID-19 PUBLIC HEALTH EMERGENCY

The content of this appendix is consistent guidance issued by the US FDA in March 2020 and updated 30 August 2021 (FDA, 2021). Addressed are issues in study conduct impacted by the COVID-19 public health emergency such as patient visits, documentation of deviations to the protocol and recording of data. The changes made to the protocol and clinical trial conduct are temporary and will remain in effect until a future Administrative Letter to Investigators notifies study sites to resume study conduct in accordance with the full protocol and normal practices.

Adjustments to Visit Windows and Study Assessments

Study assessments associated with ± 2-day visit windows are assigned a ± 5-day window. Visits conducted within the expanded window are not considered protocol deviations. Visits outside of the expanded window may be considered protocol deviations. Data should be recorded on the CRF associated with the nominal visit day.

Imaging assessments may be performed using an alternative modality and will not be reported as protocol deviations if the Sponsor is made aware in advance.

Study procedures that cannot be conducted due to institutional restrictions will not be reported as protocol deviations if the Sponsor is made aware in advance on a case-by-case basis. Such procedures may include PK blood sample collection and corresponding ECGs at timepoints of 4 hours and later, and collection of tumor tissue sample at the time of disease progression.

Remote Patient Visits

- If permitted by institutional guidelines, remote patient visits may be conducted with site staff by telephone or using video technology and/or with a visit by a home health care professional. Depending on local IRB/EC/REB policy, a revised ICF may be needed to allow remote patient visits.
- If new local laboratories are used during remote visits for safety laboratory assessments (eg, hematology and chemistry), ensure all test results, laboratory certifications, and reference normal laboratory values are collected and documented in the site records consistent with institutional guidelines. The laboratory normal ranges should be provided to the Sponsor for entry into the clinical database.
- Ensure all details of remote patient visits are documented in patient site records.

Shipment of MRTX849 Clinical Trial Material to Patients

MRTX849 tablets may be shipped to the homes of study participants being visited by home health professionals under 3 conditions: 1) such clinical trial material shipment is permitted by local institution policy, 2) shipment is by a secure, trackable method and documentation of shipment and receipt is retained with the patient or pharmacy records, and 3) the material is shipped in packaging that monitors and records internal package temperature. Clinical trial material exposed to temperature excursions should be replaced. In the patient's home, clinical

trial material must be stored under the conditions stated on the container labels and the Pharmacy Study Manual. Unused material and empty containers should be returned to the study site to enable the pharmacy to maintain accountability records.

Study Drug Administration Delay or Interruption

If study drug administration is delayed or interrupted due to inability to obtain study drug during the COVID-19 public health emergency, this reason should be recorded in the patient site record and reported in the CRF as the reason for delay or interruption. Such delays and interruptions will be documented as a protocol deviation.

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

Study Treatment

- Patients in Screening for Study Entry – Patients who exhibit symptoms consistent with COVID-19 infection or have recent COVID-19 test results consistent with active viral replication should delay study entry and start of study treatment until resolution of symptoms and evaluation by the Investigator. Questions should be directed to the Sponsor's Medical Monitor.
- Patients in Study Treatment – For patients on study treatment exhibiting symptoms consistent with COVID-19 infection, contact the Sponsor's Medical Monitor as soon as feasible.

Reporting in CRF

- Adverse Events Involving COVID-19
  - "COVID-19" should be recorded as an AE in the AE CRF form for patients diagnosed with COVID-19.
  - "COVID-19 PCR test positive" should be recorded in the AE CRF for asymptomatic patients with positive PCR testing.
  - "COVID-19 serology test positive" should be recorded in the AE CRF for asymptomatic patients with positive serology testing.
  - "COVID-19 pneumonia" should be recorded in the AE CRF for patients experiencing pneumonia due to SARS-CoV-2 infection (the virus that causes COVID-19).
  - Any other COVID-19 related complications that meet the definition of an AE/SAE should also include "COVID-19" in the CRF entry/SAE report, eg, multiple-organ failure due to COVID-19.
  - Any AEs meeting any of the seriousness criteria should also be reported as SAEs.
- COVID-19 Testing – Record "COVID-19 testing" PCR test or antibody test in the concomitant procedure CRF.

APPENDIX 6. PATIENT CROSSOVER SCHEDULE OF ASSESSMENTS

	Crossover Baseline Assessments[1]	**Crossover Cycles 1-4**		**Crossover Cycles 5 + Day 1 (± 2 days)**[18]	**End of Treatment Visit**[2] **28-35 Days After Last Dose**	**Long Term Follow-up Every 2 Months (± 14 days)**
		Day 1 C1 (- 2) C2-C4 (± 2)	**Day 15 (± 2 days)**			
Crossover Informed Consent[3]	X					
ctDNA[4]		C1	At disease progression (optional)			
ECOG	X					
Physical Exam[5] - Full (F), Abbrev (A)	F	A	A	A	F	
Vital Signs[6]	X	X	X	X	X	
Hematology[7]	X	X	X	X	X	
Chemistry[7]	X	X		X	X	
TSH[7]		C3		C5	X	
Pregnancy Test[8]	X	As clinically indicated except where required routinely[8]			X	
Single 12 Lead ECG[9]		As clinically indicated			X	
ECHO or MUGA (preferred except in Germany)[10]	X			C5 & C9 (- 7 to + 2 day window)		
Disease Evaluation[11]	X	Every 6 weeks (± 10 days) until Week 26, then every 12 weeks				
PK Sampling[12] & Triplicate ECGs[13]		C1 & C2 – Predose & Peak; C3 – Predose		C5 & C7 Predose		

	Crossover Baseline Assessments[1]	**Crossover Cycles 1-4**		**Crossover Cycles 5 + Day 1 (± 2 days)**[18]	**End of Treatment Visit**[2] **28-35 Days After Last Dose**	**Long Term Follow-up Every 2 Months (± 14 days)**
		Day 1 C1 (- 2) C2-C4 (± 2)	**Day 15 (± 2 days)**			
MRTX849 Dispensing (D) & Reconciliation (R)[14]		D, R (C2-4)		D, R	R	
PRO Questionnaires[15]		X	X	X	X	
AEs[16] & Concomitant Medications	Throughout					
Survival & Anticancer Therapies[17]						X

Abbreviations: A =abbreviated, symptom directed evaluation; C = cycle; D = dispense; F =full physical examination; R = reconcile.

[1] The window for all Crossover baseline assessments is within 28 days of MRTX849 treatment initiation except for laboratory requirements (Section 4.1 and Section 4.3), which must be performed at least 7 days after the last administration of docetaxel, and MUGA or ECHO, which may be performed within 45 days of MRTX849 treatment initiation.

[2] End of Treatment: Visit occurs 28-35 days after last dose of study treatment. Repeat of assessments completed in the previous 4 weeks is not required with the exception of assessment of AEs, hematology, chemistry and pregnancy test as applicable.

[3] Informed consent to crossover using the crossover ICF is required after BICR confirmed progression of disease and prior to first MRTX849 administration.

[4] Blood samples for ctDNA: Blood samples for ctDNA are to be obtained at crossover Cycle 1 Day 1.

[5] Physical Examinations: A full physical examination (F) required at Crossover Screening and End of Treatment only. All other evaluations will be abbreviated, symptom directed evaluations (A). Allowed time windows permit evaluation within two calendar days (Friday assessments allowed for Monday dosing) in advance of busy days, eg, PK profile collection.

[6] Vital Signs: Weight, temperature, blood pressure, pulse rate, and respiratory rate to be assessed prior to dosing as indicated. Vital signs are to be performed in the semi-recumbent position. Height is not required if recorded at main study screening.

[7] Safety Laboratory Assessments: Laboratory assessments for Crossover Screening and Eligibility (Section 4.1 and Section 4.3) must have been performed at least 7 days after the last administration of docetaxel on study. Hematology, chemistry, and thyroid function will be performed using local laboratories. Parameters to be assessed are presented in Table 15. Repeat baseline assessment not required if assessment performed within 7 days before the first dose. Allowed time windows permit evaluation within two calendar days (Friday assessments allowed for Monday dosing) in advance of busy days, eg, PK profile collection. Additional assessments of any laboratory parameters may be performed according to standard of care or as clinically indicated.

[8] Pregnancy Test: If the patient is a woman of childbearing potential, negative urine or serum pregnancy test performed by the local laboratory at time of crossover baseline assessments and End of Treatment will be required (in the United Kingdom and Germany, screening test required ≤ 7 days and ≤ 72 hours, respectively, before first dose of MRTX849). In addition, in regions where required by regulation (eg, European Union), monthly pregnancy testing will be performed until the end of systemic exposure to MRTX849 (testing may be performed at the beginning of each 3-week treatment cycle for convenience). At study sites in Austria, Belgium, France, Italy, and Spain and as required at other sites, pregnancy testing will be performed at the beginning of every treatment cycle and the same frequency (approximately monthly) for at least 1 month after the last dose of MRTX849. Additional pregnancy testing is to be performed whenever pregnancy is suspected during the study.

[9] Single 12-lead ECGs to be performed unless otherwise stated. In addition, ECGs are to be performed as clinically indicated. ECGs are to be performed in the semi-recumbent position. Assessments will include an evaluation of heart rate, PR, QRS, RR, QT, and QTc intervals.

[10] MUGA or ECHO: MUGA is preferred (except in Germany where it is not an option); the same modality should be used throughout a patient's participation when possible. For patients in crossover, if a MUGA or ECHO has been performed within 45 days of MRTX849 treatment initiation, then the crossover screening MUGA/ECHO is not required.

[11] Disease Evaluations: To be performed as part of the crossover eligibility criteria and every 6 weeks from the date of first MRTX849 administration (± 10-day window for all other assessments except crossover eligibility) until week 26 (~6 months) and then every 12 weeks. If an on-study disease evaluation was performed within 35 days of MRTX849 treatment initiation, then an additional crossover eligibility disease evaluation is not required. Assessment locations to be included are listed in Table 13 and recommended imaging modalities are listed in Table 14. BICR scans submission is not required after patient has crossed over. More detailed guidance on assessments to be performed and exceptional circumstances is provided in Section 7.3.

[12] Pharmacokinetic Sampling: Predose samples should be collected up to 30 minutes prior to dosing in clinic. Peak samples should be collected 4 to 6 hours after dosing unless logistically infeasible. In addition to the scheduled samples, an unscheduled pre-dose PK blood sample (along with a triplicate ECG, see below) should be collected as soon as possible after an SAE, immediately prior to treatment interruption or dose reduction for a treatment-related nonserious AE, and at a clinic visit at least one week following a dose reduction of MRTX849. If MRTX849 has been held or discontinued for ≥ 3 days, Unscheduled PK collections are not required.

[13] Triplicate ECGs: To be performed after the patient has rested in the supine position for at least 5 minutes. All ECGs will be obtained prior to and as close as possible to PK sample collection. Three individual ECG tracings should be obtained as closely as possible in succession, between 1 and 2 minutes apart. The full set of triplicates should be completed in approximately 4 minutes or less.

[14] Patients should have a minimum of 7 days from last docetaxel administration prior to MRTX849 treatment initiation. Patients who crossover will initiate MRTX849 at a dose of 600 mg BID.

[15] PRO Questionnaires: Generally, to be performed prior to other assessments during clinic visits. Exceptions include assessments that are scheduled in other departments prior to the clinic visit, and vital signs if they are performed during patient check-in. EQ-5D-5L questionnaires should always be completed before LCSS. After six months, perform every other cycle on Day 1 and conclude after one year.

[16] Adverse Events: Must continue to be reported for crossover patients until the End of Treatment visit.

[17] Long-term Follow-up: Survival status and subsequent anticancer therapies will be collected as described in Section 6.4 every 2 months (± 14 days) from the End of Treatment visit until death or lost to follow-up.

[18] Patients on MRTX849 for at least 12 months whom the PI believes are clinically stable on current dose regimen, may reduce frequency of clinic visits from every cycle to every other cycle (ie, Day 1 visits required every 6 weeks vs. 3 weeks).

APPENDIX 7. DOCUMENT HISTORY

Document	Version Date	Summary of Changes
Original Protocol, Version 1.0	24 August 2020	NA
Amendment 1, Version 2.0	16 November 2020	[redacted] • Added that patients with known hypersensitivity to docetaxel or polysorbate 80 are excluded from this study. • Changed the designation of the MRTX849 600 mg BID dose level from 'highest planned dose level' to 'starting dose level.' • Changed AE management guideline in the event of MRTX849-related pneumonitis to require dose reduction rather than consider dose reduction. • Cautioned against use of infusion equipment containing PVC for docetaxel administration. To ensure greater clarity and consistency across the MRTX849 program – • Explicitly stated that central radiology reviewers will be blinded to treatment assignment. • Clarified that the timeframe for several exclusion criteria is relative to randomization. • Reiterated within the Concomitant Medications section that strong CYP3A4 inhibitors be avoided in both treatment arms and strong CYP3A4 inducers should be avoided in the MRTX849 treatment arm. • Reiterated within the Concomitant Medications section that substrates of CYP2C9, CYP3A4 and CYP2B6 with low therapeutic index should be used with caution for patients in the MRTX849 treatment arm. • Clarified guidance for study treatment discontinuation in the event of increased bilirubin in the MRTX849 treatment arm. • Deleted use of the stratified log-rank test to compare the two treatment arms for the secondary efficacy endpoint DOR. • Clarified when irradiated lesions can be chosen as target lesions, and the impact of on-study locoregional treatment of target lesions on response evaluation. Country specific details added to meet regulatory requirements in participating regions – • Specified that pregnancy testing in women of child-bearing potential be performed monthly where required by regulation. • Specified that in the United Kingdom, screening pregnancy test required ≤ 7 days before first dose of study treatment.

Document	Version Date	Summary of Changes
		• Added HIV, HBV and HCV serology testing during study screening in Germany and Czech Republic. • Added detail to entry criteria concerning HIV, HBV and HCV to address regulations in Germany. • Specified that in Germany, ECHO examination is to be used rather than MUGA. • Added locally approved docetaxel product labels to the reference list. • Clarified definition of End of Trial in European Union Member State.
Amendment 2, Version 3.0	09 March 2021	• Updated the study population to include patients with unresectable, locally advanced disease in addition to patients with metastatic disease. Treatment setting retained; patients are to have previously received treatment with a platinum-based chemotherapy regimen and an immune checkpoint inhibitor. • Updated nonclinical MRTX849 pharmacokinetics and metabolism background. • Updated nonclinical toxicology background to include 13-week studies and additional genotoxicity studies. • Updated MRTX849 clinical safety and pharmacokinetics background sections. • Updated guidance on use of concomitant medications based on preliminary clinical pharmacokinetic data. • Clarified circumstances under which presence of *KRAS* G12C mutation should undergo confirmatory testing. • Updated minor errors in the text of the document.
Amendment 3, Version 4.0	17 November 2021	• Updated the study endpoints to specify PFS as the sole primary endpoint and OS as a secondary endpoint. • Added the option of crossover for patients in the comparator arm (docetaxel) who experience disease progression as defined by RECIST 1.1 by blinded independent central review to receive MRTX849. • Updated the statistical considerations and region stratifications. Revised the Phase 3 hypothesis and sample size estimates, decreased the estimated sample size to 340, added statistical considerations if a substantial proportion of patients in the comparator (docetaxel) arm were to crossover to receive MRTX849 treatment. • Added Appendix 6, Patient crossover schedule of assessments. • Changed MRTX849 administration instructions to allow dosing with or without food. • Removed HIV, HBV and HCV serology testing during study screening in Czech Republic.

Document	Version Date	Summary of Changes
		• Added exclusion criteria of hypersensitivity to any component of the MRTX849 drug product and administration of a life/attenuated vaccine within 30 days before the first dose of study treatment. • Updated Reproductive Health sections for men and women. • Added benefit/risk of MRTX849 treatment. • Updated the address for Mirati Therapeutics, Inc. • Updated nonclinical PK and metabolism section. • Updated clinical PK section. • Updated concomitant medication sections. • Added ethnic factors to the Confidentiality and Privacy Protection section. • Updated country specific requirements. • Updated guidelines for MRTX849 dose modification and adverse event management.
Amendment 4, Version 5.0	31 May 2022	• Update of In Vitro Activity data for MRTX849. • Updated MRTX849 clinical pharmacokinetics sections including DDI's. • Updated guidance on the use of concomitant medication in Section 5.9.1 and Appendix 2 and dietary restrictions in Section 4.5.1. • Added exploratory endpoints of Time to CNS Progression and intracranial activity using CNS RECIST endpoints in patients with brain metastases. • Added exclusionary text regarding prior docetaxel use. • Updated creatinine clearance inclusion criteria. • Updated HIV, Hepatitis B and C eligibility criteria. • Updated the minimum number of slides to 7. • Clarified age of consent for participation in countries where the legal age of consent is higher than 18 years of age. • Clarified stratifications used for statistical analyses. • Decreased interruption time for MRTX849 with major surgery to align with program. • Updated dose modification tables to align with MRTX849 program and IB. • Added ORR into the testing sequence. • Updated Section 7.1 to clarify percentage of indeterminate or discordant KRAS G12C results necessary before requiring central mutation detection prior to enrollment. • Updated Section 7.5.1.1 for PK sampling if dose modification.

Document	Version Date	Summary of Changes
		• Updated Section 8.4.2 Reporting Requirements. • Updated minor errors in the text of the document.
Amendment 5, Version 6.0	19 December 2022	• Removed requirement of live (on-study) central confirmation of local KRAS mutation and discordance ICF • Clarified that stratification of sequential versus concurrent prior treatment is based on the administration of the last prior platinum-based chemotherapy and anti-PD-1/PD-L1 antibody. • Specified that in UK and Germany, screening pregnancy test required ≤ 7 days and <72 hours before first dose of study treatment. • Clarified that patients enrolled at sites in Germany will not undergo tumor lesion biopsy after the Screening period. • Clarified that if MRTX849 has been held or discontinued for ≥ 3 days, unscheduled PK collections are not required. • Clarified exclusion criterion #2 for active brain metastases • Added an exception for hemoglobin and transfusion of red blood cells in the inclusion criteria for crossover treatment. • Updated guidance on diarrhea management and the use of loperamide as concomitant medication in Section 5.9.1 and Appendix 2. • Clarified Table 15 glucose chemistry as non-fasted preferred • Removed requirement to perform fractionation in patients who have abnormal creatine kinase laboratory results. • Allow urea to be tested when blood urea nitrogen is not available to be tested. • Updated minor errors in the text of the document. • Clarified Exclusion Criteria #9 to refer to Appendix 3 for medications to be avoided with docetaxel (strong CYP3A4 inhibitors). • Added footnote to Table 2 and Appendix 6 to allow patients on MRTX849 for at least 12 months, whom the PI believes are clinically stable on current dose regimen, to reduce frequency of clinic visits from every cycle to every other cycle (ie, Day 1 visits required every 6 weeks vs. 3 weeks). • Updated the primary and secondary endpoints to dual primary endpoints (PFS and OS). Updated statistical considerations and sample size estimates, increased the sample size to 589. • Updated crossover design to allow only upon positive PFS readout for patients enrolled in version 6.0 or later • Revised secondary PK endpoint for accuracy. Characterization of metabolites was removed because

Document	Version Date	Summary of Changes
		human Absorption, Metabolism and Excretion study showed no major pharmacologically active metabolites associated with MRTX849 PK. • Updated Exclusion #8, Nonclinical PK and metabolism data (Section 1.3.3) Concomitant medications (Section 5.9.1) and Appendix 2 impacted by updated PK data • Updated *KRAS* G12C tumor mutation and the documentation of disease progression (Section 7.1 and Section 7.2, respectively) to clarify the testing of tumor samples and CRF requirements for radiographic evaluation for disease progression determination following platinum-based chemotherapy and checkpoint inhibitor therapy. • Clarified Table 2 footnote 15 Docetaxel Administration that patients who are pending crossover should continue to send in imaging to BICR and collect EOT information but not complete EOT visit nor enter into long-term follow-up.
Amendment 6, Version 7.0	24 March 2023	• Updated the primary and secondary endpoints making PFS a single primary endpoint and Overall Survival a secondary endpoint. Updated statistical considerations and sample size estimates, decreased the sample size to 450. • Clarified that disease assessments should continue to be sent to BICR until BICR confirms disease progression in patients treated beyond Investigator assessed (local) progression. • Reverted crossover design to Version 5.0 which allows crossover for patients in the comparator arm (docetaxel) who experience disease progression as defined by RECIST 1.1 by blinded independent central review to receive MRTX849 and meet all other crossover criteria. • Updated Exclusion Criteria #8 to align with new concomitant medication guidance. • In Section 5.8 Clarified options if locally assessed PD but not confirmed by BICR for patients on docetaxel. • Updated guidance on the use of concomitant medication in Section 5.9.1 and Appendix 2. • Exempted patients enrolled at sites in Germany from the optional tumor lesion biopsy at the time of disease progression or prolonged stable disease. • Changed guidance for sites in Germany to require immediate (without undue delay) SAE reporting to the Sponsor. • Added baseline characteristics for subgroup analyses in Section 9.4.8.