**BACKGROUND**

**KRAS MUTATIONS IN CANCER**
- RAS proteins are part of the family of small GTPases which regulate intracellular signaling pathways responsible for cell growth, migration, survival, and differentiation
- Oncogenic point mutations involving RAS family at codons 12, 13, and 61 occur in up to 25% of all human cancers and result in constitutive activation of RAS signaling
- Constitutive RAS signaling plays an important role in uncontrolled cellular growth and malignant transformation

**KRAS<sup>G12C</sup> MUTATION**
- Detected in ~25 different tumor types
- Represents the most common mutation in lung adenocarcinoma (14%)
- Occurs in ~4% of colorectal cancer (CRC)
- Identified in other cancers including pancreatic ductal adenocarcinoma, cancer of unknown primary, gastric cancer, and endometrial cancer

**KRAS<sup>G12C</sup> is Frequently Mutated in Lung Adenocarcinoma**

**MRTX849**
- Orally available, mutation-selective small molecule inhibitor of KRAS<sup>G12C</sup>
- Irreversible, covalent binding to KRAS<sup>G12C</sup>
  - KRAS cycles between an active GTP-bound form and an inactive GDP-bound form
  - MRTX849 irreversibly binds to Cysteine 12 in the inducible Switch II pocket of KRAS<sup>G12C</sup> and locks it in an inactive GDP-bound state
  - MRTX849 inactivates KRAS<sup>G12C</sup> and prevents oncogenic signaling in KRAS<sup>G12C</sup> mutant tumor cells but has no effect on normal cells
- Highly selective
  - Does not bind wild-type KRAS, other mutant KRAS species, or any of ~6000 peptides from 2490 proteins
  - In cell lines, MRTX849 inhibits growth and viability of cells harboring KRAS<sup>G12C</sup> mutations, but not in cells with other mutant forms or of wild-type KRAS
- In animal models, MRTX849 demonstrated antitumor activity in a broad range of KRAS<sup>G12C</sup> positive tumors

**MRTX849 Inhibits KRAS<sup>G12C</sup> - Mediated Oncogenic Signaling**
- RTK signaling normally activates the RAS/MAP kinase pathway by facilitating GTP-loading of KRAS which induces a conformation change in KRAS that activates the pathway
- KRAS<sup>G12C</sup> mutations prevent GAP-stimulated GTP hydrolysis, leaving KRAS<sup>G12C</sup> in the active state
- MRTX849 covalently binds to a defined pocket within the GTP-binding domain of KRAS<sup>G12C</sup>, inactivating the pathway, and leading to tumor growth inhibition

**MRTX849 Binding is Highly Selective for KRAS<sup>G12C</sup>**

**MRTX849 Demonstrates Broad Spectrum Tumor Regression in KRAS<sup>G12C</sup> Nonclinical Tumor Growth Models**

**STUDY OBJECTIVES**

**PRIMARY OBJECTIVE**
- To characterize the safety and tolerability of MRTX849 in patients with solid tumor malignancies with KRAS<sup>G12C</sup> mutation
- To evaluate the pharmacokinetics (PK) of MRTX849

**PHASE 1/1B OBJECTIVES**
- To establish the maximum tolerated dose (MTD) in one or more regimens
- To evaluate biologically relevant dose levels
- To identify the recommended Phase 2 dose (RP2D) and regimens of MRTX849
- To evaluate the clinical activity

**PHASE 2 OBJECTIVES**
- To evaluate the clinical activity of MRTX849 in cohorts of patients having selected tumor malignancies with KRAS<sup>G12C</sup> mutation

**EXPANSION COHORT SUB-STUDIES & EXPLORATORY OBJECTIVES**
- To evaluate the PK of new formulations, with food and in combination sub-studies
- To explore correlations between exposure and patient outcomes, evaluate population PK, characterize metabolites, evaluate the utility of detection of KRAS<sup>G12C</sup> mutations in plasma, explore potential pharmacodynamic markers of KRAS inhibition, and explore correlations between baseline tumor biomarkers, gene alterations and clinical activity

**METHODS**

- This multi-center Phase 1/2 first-in-human, multiple expansion cohort trial evaluates the safety, PK, metabolomics, pharmacodynamics, and clinical activity of MRTX849 in patients with advanced solid tumor malignancies with KRAS<sup>G12C</sup> mutation
- The study begins with an exploration of dose using both the accelerated titration and modified Toxicity Probability Interval statistical designs to determine the MTD and possible RP2D and regimen
- Phase 1b dose expansion cohorts may be implemented to ensure sufficient safety experience, PK information, and early evidence of clinical activity
- In Phase 2, separate cohorts of patients stratified by histological diagnosis will be evaluated for clinical activity

**STUDY DESIGN**

**STATISTICAL METHODS**

**Phase 1**
- Accelerated Titration (AT) Design:
  - Dose escalation is initiated with single patient cohorts and 100% dose escalation until moderate toxicity and/or target plasma exposure is observed
  - Modified Toxicity Probability Interval Design (mtPPI):
    - Completion of dose escalation is conducted using a Bayesian approach for establishing the MTD defined as the dose with a 30%/55% probability of DLT

**Phase 2**
- Each of the four Phase 2 cohorts is evaluated independently
- Predictive Probability Design (PPD) is used to establish stopping rules for futility
- Statistical assumptions: p<0.10; p<0.05
- Sample size of N=40 for each Phase 2 cohort
- Type I error (α) < 0.05, and Power (1-β) ≥ 0.90

**KEY INCLUSION CRITERIA**
- Histologically confirmed diagnosis of solid tumor malignancy with KRAS<sup>G12C</sup> mutation
- Unresectable or metastatic disease
- No available treatment with curative intent, no available standard-of-care, patient is ineligible or declines treatment
- Presence of tumor lesions to be evaluated per RECIST 1.1
- ECOG performance status in 0 or 1
- Adequate organ function

**KEY EXCLUSION CRITERIA**
- Active brain metastases
- Carcinomatous meningitis
- Cardiac abnormalities within the last 6 months
- History of stroke or transient ischemic attack within the previous 6 months
- Known or suspected presence of another malignancy
- Prior treatment with a therapy targeting KRAS<sup>G12C</sup> (applicable for Phase 2 cohorts)

**MRTX849 DOSING REGIMENS AND ASSESSMENTS**
- Patients receive MRTX849 orally, once daily in a continuous 3-week cycles
- Other regimens may be evaluated based on emerging results
- During Phase 1, PK sampling will follow a lead-in dose and after repeated dosing
- Treatment will continue until disease progression, intolerable toxicity, patient refusal, or death
- Routine safety assessments performed throughout the study
- Disease assessments using RECIST version 1.1 every 6 weeks
- Other assessments include safety, tolerability, PK, and biomarker sample collection

**REFERENCES**

1. Bunn PA, 13th International Lung Cancer Congress, 2012; Huntington Beach, CA

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