A Phase 1/2 Multiple Expansion Cohort Trial of MRTX849 in Patients with Advanced Solid Tumors with *KRAS* G12C Mutation

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BACKGROUND

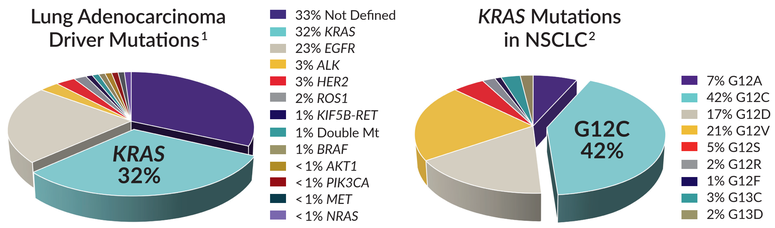
KRAS MUTATIONS IN CANCER

- 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^{G12C} MUTATION

- Detected in >25 different tumor types
- Represents the most common mutation in lung adenocarcinoma (14%) and has also been reported in large cell neuroendocrine and sarcomatoid non-small cell lung cancer (NSCLC)
- 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 is Frequently Mutated in Lung Adenocarcinoma

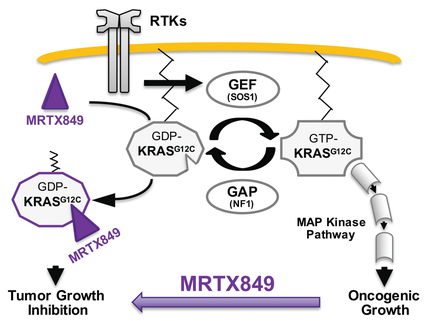


MRTX849

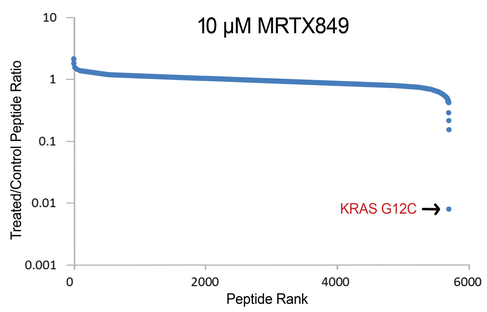
- Orally available, mutation-selective small molecule inhibitor of KRAS^{G12C}
- Irreversible, covalent binding to KRAS^{G12C}
  - KRAS cycles between an active GTP-bound form and an inactive GDP-bound form
  - MRTX849 irreversibly binds to Cysteine 12 in the inducible Switch II pocket of KRAS^{G12C} and locks it in an inactive GDP-bound state
  - MRTX849 inactivates KRAS^{G12C} and prevents oncogenic signaling in KRAS^{G12C} 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^{G12C} 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^{G12C} positive tumors

MRTX849 Inhibits KRAS^{G12C} – Mediated Oncogenic Signaling

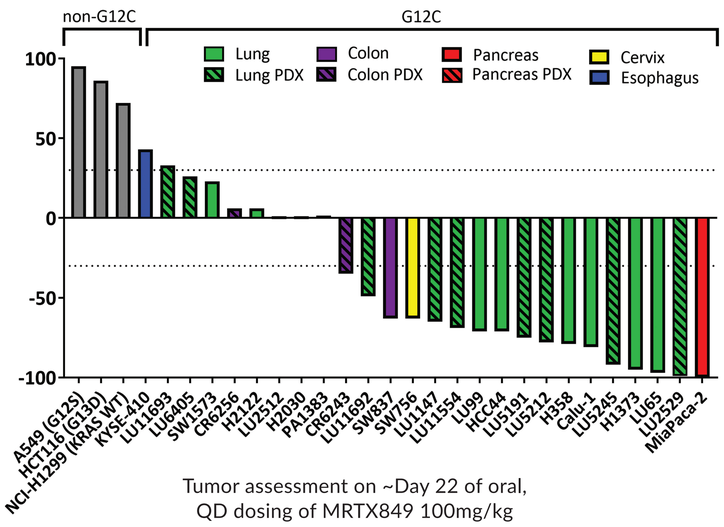
- RTK signaling normally activates the RAS/MAP kinase pathway by facilitating GTP-loading of KRAS which induces a conformation change in KRAS that activates the pathway
- KRAS^{G12C} mutations prevent GAP-stimulated GTP hydrolysis, leaving KRAS^{G12C} in the active state
- MRTX849 covalently binds in a defined pocket to the Cys residue of inactive, GDP-bound KRAS^{G12C}, inactivating the pathway, and leading to tumor growth inhibition



MRTX849 Binding is Highly Selective for KRAS^{G12C}



MRTX849 Demonstrates Broad Spectrum Tumor Regression in KRAS^{G12C} Nonclinical Tumor Growth Models



Tumor assessment on ~Day 22 of oral, QD dosing of MRTX849 100mg/kg

STUDY OBJECTIVES

PRIMARY OBJECTIVE

- To characterize the safety and tolerability of MRTX849 in patients with solid tumor malignancies with *KRAS*^{G12C} 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*^{G12C} mutation

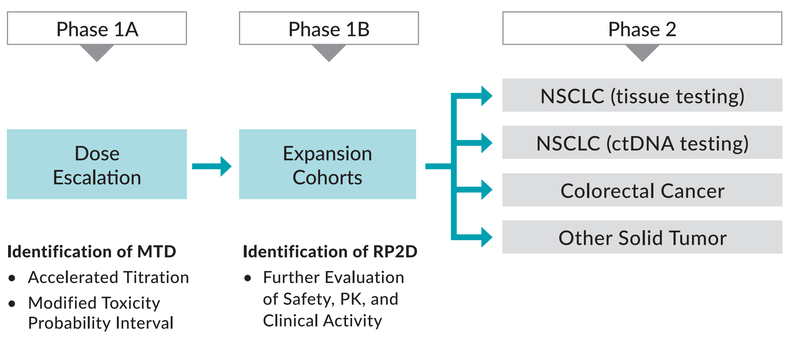
EXPANSION COHORT SUB-STUDIES & EXPLORATORY OBJECTIVES

- 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*^{G12C} 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, metabolites, pharmacodynamics, and clinical activity of MRTX849 in patients with advanced solid tumor malignancies with *KRAS*^{G12C} mutation
- The study begins with an exploration of dose using both the accelerated titration and modified Toxicity Probability Interval Phase 1 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 (mTPI):
  Completion of dose escalation is conducted using a Bayesian approach for establishing the MTD defined as the dose with a 30%±5% 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=0.10; p_1=0.30
- 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*^{G12C} 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^{G12C} (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

SUMMARY

- KRAS^{G12C} plays a critical role in carcinogenesis NSCLC, CRC, and other tumors
- MRTX849 is an highly selective and oral small molecule inhibitor of KRAS^{G12C}
- Binding of MRTX849 to KRAS^{G12C} is covalent and irreversible
- This multiple expansion cohort Phase 1/2 study evaluates the safety, pharmacokinetics, and clinical activity of MRTX849 in patients with solid tumor malignancies harboring a *KRAS*^{G12C} mutation
- Enrollment began in January, 2019 and the study is actively accruing patients
- Clinical Trial Information: NCT03785249

REFERENCES

1. Bunn PA, 13th International Lung Cancer Congress, 2012; Huntington Beach, CA
2. Karachaliou, et.al. *Clin Lung Canc* 2013; **14** (3):205-214