KRYSTAL-12: A Randomized Phase 3 Study of Adagrasib (MRTX849) vs Docetaxel in Patients With Previously Treated Non–Small-Cell Lung Cancer (NSCLC) With KRAS^{G12C} Mutation

TPS 9129

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Background

KRAS-Driven NSCLC

- KRAS^{G12C} mutations act as oncogenic drivers and occur in approximately 14% of NSCLC (adenocarcinomas)[1-3]
- Historically, KRAS has been considered undruggable; however, KRAS^{G12C} can now be inhibited covalently[4,5]
- Emerging data demonstrate the clinical activity of KRAS^{G12C} inhibitors in pretreated patients with NSCLC harboring KRAS^{G12C} mutations[6]

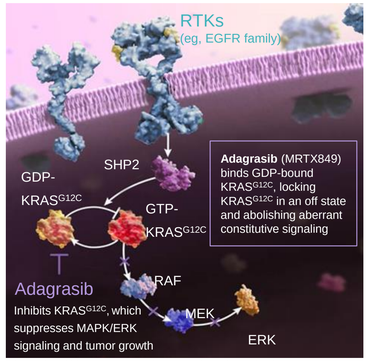
Adagrasib in KRAS^{G12C} Cancers

- Adagrasib (MRTX849) is a covalent inhibitor of KRAS^{G12C} that irreversibly and selectively binds KRAS^{G12C} and locks it in its inactive, GDP-bound state[6] **(Figure 1)**
- Adagrasib was optimized for desired properties of a KRAS^{G12C} inhibitor:
  - Potent covalent inhibitor of KRAS^{G12C} (cellular IC_{50}: ~5 nM)
  - High selectivity (>1000X) for the mutant KRAS^{G12C} protein vs wild-type KRAS
  - Favorable pharmacokinetic (PK) properties, including oral bioavailability, long half-life (~24 hours), and extensive tissue distribution[6]
- Adagrasib maintains continuous exposure above a target threshold, thus enabling inhibition of KRAS-dependent signaling and maximizing depth and duration of antitumor activity

Adagrasib Monotherapy

- Initial results from KRYSTAL-1, a Phase 1/2 study, demonstrated the preliminary antitumor activity and tolerability of adagrasib monotherapy across multiple tumor types harboring KRAS^{G12C} mutations, including patients with NSCLC previously treated with both platinum-based chemotherapy and checkpoint inhibitors (CPIs)[6] **(Figure 2)**[6]
- In a safety analysis of patients (n=110) from KRYSTAL-1, adagrasib was well tolerated, with a low incidence of grade 3-4 treatment-related adverse events (TRAEs)[6]
  - The most common TRAEs included nausea, diarrhea, vomiting, and fatigue

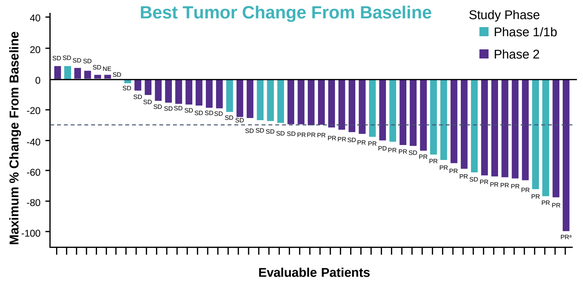
Figure 1. Mechanism of Action (MOA) of Adagrasib



ERK, extracellular signal–regulated kinase; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated kinase kinase; RAF, rapidly accelerated fibrosarcoma; RTKs, receptor tyrosine kinases; SHP2, Src homology phosphatase 2

Background

Figure 2. Adagrasib 600 mg BID in Patients With Pretreated NSCLC (KRYSTAL-1)[6]



- 45% (23/51) of patients with NSCLC had a confirmed ORR
- 51% (26/51) of patients with NSCLC achieved SD
- Clinical benefit (DCR) was observed in 96.1% (49/51) of patients

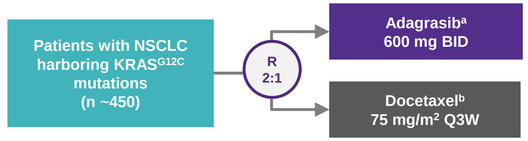
BID, twice daily; CR, complete response; ORR, objective response rate; DCR, disease control rate; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease
[a]In one patient, two timepoint assessments of CR were separated by recurrent disease associated with treatment interruption due to hypoxia; this patient remains on treatment and in 2 consecutive scans (1 after the August 30 data cutoff) demonstrated 100% tumor regression in target and nontarget lesions after resuming treatment.
Data as of 30 August 2020.

Methods

Study Design

- KRYSTAL-12 is a multicenter, open-label, randomized Phase 3 study, evaluating the efficacy of adagrasib (600 mg BID) vs docetaxel in patients with NSCLC harboring a KRAS^{G12C} mutation
- Approximately 450 patients will be randomized in a 2:1 ratio to receive adagrasib or docetaxel, **(Figure 3)** stratified by:
  - Region (United States/Canada vs other countries)
  - Sequential vs concurrent administration of prior platinum-based chemotherapy and anti-programmed death-1 / anti-programmed death ligand-1 (anti–PD-1/L1) therapy

Figure 3. KRYSTAL-12 Study Design



Q3W, every 3 weeks.
[a]Adagrasib, administered in 3-week cycles 600mg BID administered orally on a continuous basis until disease progression.
[b]Docetaxel, administered 75 mg/m^2 Q3W (no crossover allowed)

Methods

Primary Endpoints

- Progression-free survival (PFS)
- Overall survival (OS)

Secondary Endpoints

- Safety
- Objective response rate (ORR) per RECIST 1.1
- Duration of response (DOR)
- 1-year survival rate
- Plasma PK parameters of adagrasib
- Patient-reported outcomes (PROs)

Exploratory Endpoints

- Gene alterations in tumor tissue and circulating tumor DNA (ctDNA)
- Progression-free survival-2 (PFS2)

Key Inclusion Criteria

- Histologically or cytologically confirmed diagnosis of NSCLC harboring KRAS^{G12C} mutation
- Unresectable, locally advanced or metastatic disease
- Prior treatment with a platinum-containing regimen and a CPI (ie, anti–PD-1/L1 inhibitor) for advanced or metastatic disease with objective disease progression on or after treatment
- Presence of evaluable or measurable disease per RECIST version 1.1
- Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1
- Availability of tumor specimen (primary or metastatic, archival or newly obtained) for central laboratory testing of KRAS^{G12C} mutation status and correlative gene alterations

Key Exclusion Criteria

- Prior treatment with an agent targeting KRAS^{G12C}
- Active brain metastases; patients are eligible if brain metastases are adequately treated and patients are neurologically stable

Assessments

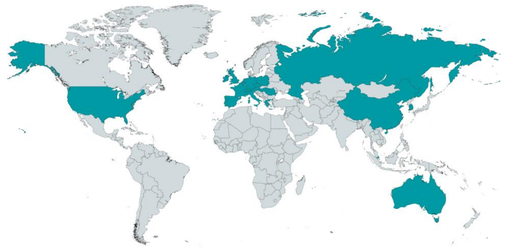
- All patients enrolled in the study are to undergo tumor assessments at screening, while on study, and at response confirmation, using the imaging modalities recommended
- Disease assessments will be performed at 6-week intervals beginning from randomization, until objective disease progression is documented by the investigator, or subsequent anticancer therapy has begun (with optional sample collection at progression)

Statistical Methods

- With the planned sample size, the trial is sufficiently powered to detect the hypothesized treatment effect of the primary endpoints (OS and PFS) at an overall alpha of 0.05. A group sequential design will be utilized to control the inflation of type I error

Trial Progress

- Approximately 257 global sites across 23 countries are planned for this study
- Enrollment is currently planned at sites from the following countries highlighted below, including:
  - United States, China, South Korea, France, Germany, Italy, Russia, Spain, United Kingdom



Summary

- Adagrasib (MRTX849) is a covalent inhibitor of KRAS^{G12C} that irreversibly and selectively binds KRAS^{G12C} and locks it in its inactive, GDP-bound state
- Maintaining continuous exposure of adagrasib above a target threshold enables inhibition of KRAS-dependent signaling for the complete dose interval and maximizes depth and duration of antitumor activity
- Initial results from KRYSTAL-1, a Phase 1/2 study, have demonstrated antitumor activity and tolerability of adagrasib monotherapy in patients with NSCLC harboring a KRAS^{G12C} mutation
- KRYSTAL-12 is a global, multicenter, randomized Phase 3 study with the primary objective of evaluating the efficacy of adagrasib vs docetaxel in patients with NSCLC harboring KRAS^{G12C} mutation who have received prior treatment with a platinum-based regimen and CPI
- Clinical trial registry number: NCT04685135

References

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