KRYSAL-10: A Randomized Phase 3 Study of Adagrasib (MRTX849) in Combination With Cetuximab vs Chemotherapy in Patients (Pts) With Previously Treated Advanced Colorectal Cancer (CRC) With KRAS<sup>G12C</sup> Mutation

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<sup>Abstract</sup>

**Background**

KRAS<sup>G12C</sup>-Driven Cancers

- KRAS<sup>G12C</sup>-mutated actors as oncogenic drivers and occur in approximately 3-4% of colorectal cancers (CRC).<sup>1</sup>
- Historically, KRAS has been considered undruggable; however, KRAS<sup>G12C</sup> can now be inhibited clinically<sup>2</sup>.
- Emerging data demonstrate the clinical activity of KRAS<sup>G12C</sup>-inhibited in pretreated patients with CRC harboring KRAS<sup>G12C</sup>-mutated<sup>3</sup>.

**Adagrasib in KRAS<sup>G12C</sup>-Cancers**

- Adagrasib (MRTX849) is a covalent inhibitor of KRAS<sup>G12C</sup> that irreversibly and selectively binds to KRAS<sup>G12C</sup>-mutated<sup>4</sup> and both G12D and G12V (Figure 1).
- Adagrasib was optimized for preclinical properties for KRAS<sup>G12C</sup>-mutated:
  - High selectivity (~1000x) for the mutant KRAS<sup>G12C</sup> protein vs wild-type KRAS.
- Favorable pharmacokinetic (PK) properties, including oral bioavailability, long half-life (24 hours), and extensive tissue distribution.
- Adagrasib maintains continuous exposure above a target threshold, thus enabling inhibition of KRAS-signaling and maintaining 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<sup>G12C</sup>-mutated<sup>5</sup>, including patients with CRC who were heavily pretreated (Figure 2).
- In a safety analysis of patients (n = 40), adagrasib was well-tolerated, with a median duration of grade 3-treatment-related adverse events (TRAEs) of 2 months.
- The most common TRAEs included diarrhea, dermatitis, vomiting, and fatigue.

**Figure 1. Mechanism of Action (MoA) of Adagrasib (MRTX849)**

**Figure 2. Preliminary Activity of Adagrasib 600 mg/m² CI in Patients With Pretreated CRC (KRYSTAL-17)**

**Clinical Data For Adagrasib + Cetuximab**

- Despite this observed clinical activity of KRAS<sup>G12C</sup>-inhibition, reactivation of RAS/MAPK pathway signaling may occur through adaptive feedback mechanisms by the epidermal growth factor receptor (EGFR), which is expressed in a variety of human tumors including CRC.
- Combining adagrasib with cetuximab, an EGFR inhibitor, may enhance inhibition of KRAS-dependent signaling or overcome adaptive feedback and improve clinical outcomes.
- Preliminary data in KRAS<sup>G12C</sup>-human xenograft CRC mouse models suggest the possible synergy of activity of adagrasib and cetuximab, showing that the combination leads to a longer duration of tumor regression compared to either single agent treatment (Figure 3).

**Figure 3. Adagrasib + Cetuximab Results in Deep, Durable Regression in PDX Models**

**Methods**

**Key Exclusion Criteria**

- Prior treatment with an agent targeting KRAS<sup>G12C</sup>.
- Prior treatment with an EGFR inhibitor (e.g., cetuximab or panitumumab).
- Prior treatment with both an oral phosphatidylinositol 3-kinase (PI3K) inhibitor and a covalent EGFR inhibitor.
- Prior treatment with a covalent EGFR inhibitor and a noncovalent anti-EGFR monoclonal antibody.
- Active brain metastases; patients are eligible if brain metastases are adequately treated and they have no signs or symptoms of brain involvement.
- Increase of target lesion size >25% from baseline.
- Progression during previous line treatment with a fluoropyrimidine-containing regimen or within 6 months of previousline treatment.
- History of previous CRC treatment with a fluoropyrimidine-containing regimen or within 6 months of previousline treatment.
- Presence of any uncontrolled intercurrent medical condition that places the patient at unacceptable risk for treatment with adagrasib.
- Combination of adagrasib with cetuximab has not been shown to be effective in the advanced CRC setting.
- In combination with adagrasib, cetuximab may enhance inhibition of this KRAS-dependent signaling to overcome adaptive feedback and improve clinical outcomes.

**Trial Progress**

- Approximately 300 global sites across 34 countries are planned for this study.
- Enrollment is planned to start at sites from the countries highlighted below:
  - The study is currently open for enrolment at sites in the United States.

**References**


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