# KRYSTAL-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$^{G12C}$ Mutation

Poster #200

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## Background

### KRAS-Driven CRC

- KRAS$^{G12C}$ mutations act as oncogenic drivers and occur in approximately 3-4% of colorectal cancers (CRC)[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 CRC harboring KRAS$^{G12C}$ mutations[6]

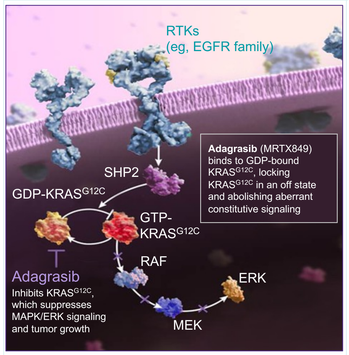
### Adagrasib in KRAS$^{G12C}$ Cancers

- Adagrasib (MRTX849) is a covalent inhibitor of KRAS$^{G12C}$ that irreversibly and selectively binds to 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:
  - 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

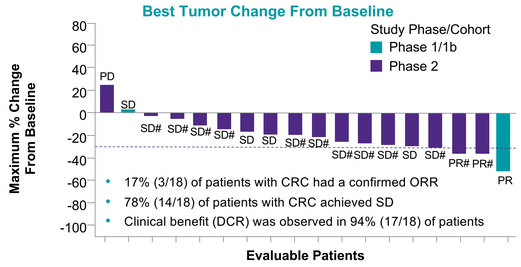
- Initial results from KRYSTAL-1, a Phase 1/2 study, demonstrated the preliminary antitumor activity and tolerability of adagrasib monotherapy across multiple tumor types harboring KRAS$^{G12C}$ mutations, including in patients with CRC who were heavily pretreated. (**Figure 2**)[6]
- In a safety analysis 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 kinase; MEK, mitogen-activated kinase kinase; RAF, rapidly accelerated fibrosarcoma; RTKs, receptor tyrosine kinases; SHP2, Src homology phosphatase 2.

**Figure 2.** Preliminary Activity of Adagrasib 600 mg BID in Patients With Pretreated CRC[a] (KRYSTAL-1)[6]




- 17% (3/18) of patients with CRC had a confirmed ORR
- 78% (14/18) of patients with CRC achieved SD
- Clinical benefit (DCR) was observed in 94% (17/18) of patients

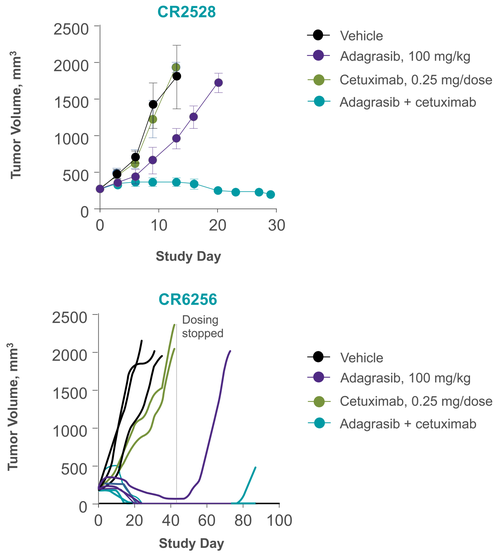
BID, twice daily; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease. # Denotes ongoing treatment.
[a]Patients received a median of 4 prior lines of therapy, including treatment with a fluoropyrimidine-based chemotherapy regimen containing either oxaliplatin or irinotecan. Data as of 30 August 2020.

## Background

### Preclinical Data For Adagrasib + Cetuximab

- Despite this observed clinical activity of KRAS$^{G12C}$ inhibition, reactivation of RAS/MAPK pathway signaling may occur through adaptive feedback mediated 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
- Preclinical data in KRAS$^{G12C}$ human xenograft CRC mouse models suggest the possible synergistic activity of adagrasib and cetuximab, showing that the combination leads to increased antitumor activity and more durable tumor regression compared to either single agent treatment (**Figure 3**)[7]

**Figure 3.** Adagrasib + Cetuximab Results in Deep, Durable Regression in PDX Models[7]




Mice bearing CR2528 and CR6256 PDXs were treated with vehicle PO QD, adagrasib at 100 mg/kg PO QD, cetuximab at 0.25 mg IP Q3D, or the combination for the duration of the study. Data shown as average tumor volume ± SEM, or individual tumor volumes, n=3/group.

IP, intraperitoneal; PDX, patient-derived xenograft; PO, orally; Q3D, every 3 days; QD, once daily; SEM, standard error of the mean.

## Methods

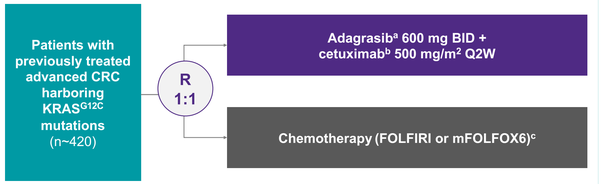
### Study Design

- KRYSTAL-10 is a multicenter, open-label, randomized Phase 3 study evaluating the efficacy of adagrasib + cetuximab vs chemotherapy (FOLFIRI or mFOLFOX6)[a] in patients with CRC harboring a KRAS$^{G12C}$ mutation who have progressed during or after treatment with a standard first-line fluoropyrimidine-based chemotherapy regimen containing either oxaliplatin or irinotecan (**Figure 4**)
- Approximately 420 patients will be randomized in a 1:1 ratio to receive adagrasib + cetuximab or chemotherapy, stratified by:
  - Region (United States/Canada vs other countries)
  - Time to disease progression after initiation of first-line treatment (<6 months vs ≥6 months)

FOLFIRI, folinic acid, fluorouracil, and irinotecan hydrochloride; mFOLFOX6, fluorouracil, folinic acid, and oxaliplatin;.
[a]A vascular endothelial growth factor/vascular endothelial growth factor receptor (VEGF/VEGFR) inhibitor may be used in combination with chemotherapy in the comparator arm at the investigator's discretion.

## Methods

**Figure 4.** KRYSTAL-10 Study Design




IV, intravenously; Q2W, every 2 weeks.
[a]Adagrasib administered orally in 4-week cycles 600 mg BID on a continuous basis until disease progression. [b]Cetuximab administered Q2W by IV 500 mg/m2. [c]A VEGF/VEGFR inhibitor may be given per investigator discretion.

### 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 CRC harboring a KRAS$^{G12C}$ mutation
- Availability of tumor specimen (primary or metastatic, archival or newly obtained) for central laboratory testing of KRAS$^{G12C}$ mutation status
- Prior receipt of first-line treatment with a fluoropyrimidine-based chemotherapy regimen containing either oxaliplatin or irinotecan in the advanced disease setting and radiographically documented disease progression on or after treatment
  - Maintenance therapy given in the metastatic setting is not considered a separate regimen
  - Patients experiencing disease relapse during or within 6 months following the completion of adjuvant treatment are eligible
- Presence of evaluable or measurable disease per RECIST 1.1
- Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1
- Adequate organ function

### Key Exclusion Criteria

- Prior treatment with an agent targeting KRAS$^{G12C}$
- Prior treatment with an anti-EGFR antibody (eg, cetuximab or panitumumab)
- Prior treatment with both an oxaliplatin- and irinotecan-based regimen for CRC in the adjuvant and/or later treatment settings
- Active brain metastases; patients are eligible if brain metastases are adequately treated and they are neurologically stable

### Assessments

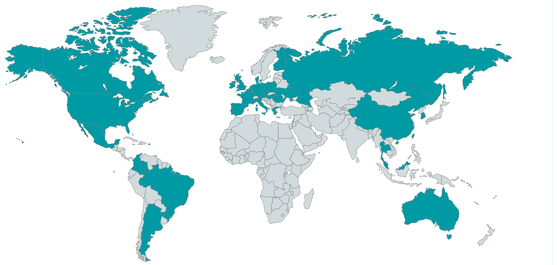
- Tumor assessments will be performed at 8-week intervals beginning from randomization until objective disease progression is documented by the investigator or subsequent anticancer therapy has begun

### Statistical Methods

- With the planned sample size, the trial is sufficiently powered to detect the hypothesized treatment effect on 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 300 global sites across 34 countries are planned for this study
- Enrollment is planned at sites from the countries highlighted below
  - The study is currently open for enrollment at sites in the United States



## Summary

- Adagrasib is a covalent inhibitor of KRAS$^{G12C}$ that irreversibly and selectively binds to KRAS$^{G12C}$ and locks it in its inactive, GDP-bound state
- Initial results from KRYSTAL-1 have demonstrated the preliminary antitumor activity and tolerability of adagrasib monotherapy in patients with CRC harboring a KRAS$^{G12C}$ mutation who were heavily pretreated[6]
- Although adagrasib monotherapy has shown clinical activity in inhibiting KRAS$^{G12C}$, reactivation of RAS/MAPK pathway signaling may occur through adaptive feedback mediated by EGFR; treatment with adagrasib + cetuximab may enhance inhibition of this KRAS-dependent signaling to overcome adaptive feedback and improve clinical outcomes
- KRYSTAL-10 is a multicenter, open-label, randomized Phase 3 study evaluating the efficacy of adagrasib in combination with cetuximab vs chemotherapy in patients with previously treated advanced CRC harboring a KRAS$^{G12C}$ mutation
- Clinical trial registry number: NCT04793958

## References

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