Adagrasib (MRTX849) as monotherapy or combined with cetuximab (Cetux) in patients (Pts) with colorectal cancer (CRC) harboring a KRASG12C mutation


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Background

KRASG12C mutations, which occur in 3%-4% of CRC, are a negative predictor of cetux efficacy. Adagrasib, an investigational agent, is a KRASG12C inhibitor that irreversibly and selectively binds KRASG12C, locking it in its inactive state; it was optimized for favorable PK properties, including a long half-life (24 hours). Durable inhibition of KRASG12C may be particularly important in CRC due to signaling pathways which create a susceptibility to feedback reactivation of KRAS. EGFR signaling is implicated in this reactivation, providing a rational co-targeting strategy for KRAS-mutant CRC.

Methods

KRYSTAL-1 (NCT03785249) is a multicohort Phase 1/2 study evaluating adagrasib in pts with KRASG12C-mutant advanced solid tumors. CRC cohorts include adagrasib 600 mg BID monotherapy (Phase 1/2) and adagrasib 600 mg BID + cetux 400 mg/m² followed by 250 mg/m² QW; or 500 mg/m² Q2W (Phase 1b). Endpoints include safety, PK, and clinical activity. Here we report preliminary monotherapy and cetux combination data.

Results

As of 25 May 2021, 46 pts with CRC (50% female; median age 58 years; 3 median prior lines of therapy) had received adagrasib monotherapy (median follow-up 8.9 months). TRAEs of any grade (gr) occurred in 91% and gr 3/4 events in 30% of pts, with no gr 5 events. Among the 45 pts evaluable for clinical activity, the response rate was 22% (10/45, including 1 unconfirmed PR who remains on study) and DCR was 87% (39/45). Median DOR was 4.2 months; median PFS was 5.6 months. As of 9 July 2021, 32 pts with CRC (53% female; median age 60 years; 3 median prior lines of therapy) were treated with adagrasib + cetux (median follow-up 7 months). TRAEs of any gr occurred in 100% and gr 3/4 events in 16% of pts, with no gr 5 events. Among the 28 pts evaluable for clinical activity, the response rate was 43% (12/28, including 2 unconfirmed PRs who remain on study) and DCR was 100%.

Conclusions

Adagrasib is well tolerated as monotherapy and combined with cetux and demonstrates promising clinical activity in heavily pretreated pts with KRASG12C-mutant CRC. Adagrasib + cetux is currently being evaluated in the 2L setting in a Phase 3 trial of pts with KRASG12C-mutant CRC (NCT04793958).

Clinical trial identification

NCT03785249.

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Legal entity responsible for the study

Mirati Therapeutics, Inc.

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Disclosure

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