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KRISTAL-1: Updated efficacy and safety of adagrasib (MRTX849) with or without cetuximab in patients with advanced colorectal cancer (CRC) harboring a KRASG12C mutation

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Background

KRASG12C mutations occur in 3–4% of CRC and are associated with shorter PFS and OS with standard chemotherapy. Adagrasib (ada), a selective and irreversible KRASG12C inhibitor, is optimized for a long half-life (23 h), dose-dependent PK, and CNS penetration. Durable inhibition of KRASG12C may be important in CRC, due to signaling pathways creating susceptibility to feedback reactivation of RAS. Preclinical data suggest dual EGFR/KRASG12C blockade may enhance inhibition of KRAS-dependent signalling and overcome adaptive feedback.

Methods

KRISTAL-1 (NCT03785249) is a multicohort Ph 1/2 study evaluating safety and efficacy of ada in patients (pts) with KRASG12C-mutated advanced solid tumors. Ada (600 mg BID) and ada + cetuximab (cetux; 400 mg/m² followed by 250 mg/m² QW or 500 mg/m² Q2W) were evaluated in pts with previously treated CRC, in Ph 2 and 1b cohorts, respectively. Responses were investigator assessed.

Results

As of Jun 16 2022, 44 pts received ada and 32 pts received ada + cetux. In the ada mono cohort (median follow-up 20.1 mo), median age was 59 yrs, 50% were female, median prior lines of systemic therapy was 3, 52% and 48% were ECOG PS 0 and 1, respectively. In 43 pts evaluable for efficacy, ORR was 19% (8/43), and DCR was 86% (37/43). Median DOR was 4.3 mo (95% CI 2.3–8.3) and median PFS was 5.6 mo (95% CI 4.1–8.3). In the ada + cetux cohort (median follow-up 17.5 mo), median age was 60 yrs, 53% were female, median prior lines of systemic therapy was 3, 44% and 56% were ECOG PS 0 and 1, respectively. In 28 pts evaluable for efficacy, ORR was 46% (13/28) and DCR was 100% (28/28). Median DOR was 7.6 mo (95% CI 5.7–NE) and median PFS was 6.9 mo (95% CI 5.4–8.1). Gr 1–2 and 3–4 TRAEs occurred in 59% and 34% of pts, respectively, in the ada cohort, and 84% and 16% of pts, respectively, in the ada + cetux cohort. No Gr 5 TRAE occurred.

Conclusions

Adagrasib is well tolerated as monotherapy and with cetuximab. Both showed clinical activity in heavily pretreated pts with KRASG12C-mutated CRC, with more sustained responses with the combination. Adagrasib + cetuximab is being investigated in 2L CRC in the Phase 3 KRISTAL-10 trial (NCT04793958).

Clinical trial identification

NCT03785249.

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**Disclosure**


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