2021 ESMO congress

LBA6

KRYSTAL-1: Adagrasib (MRTX849) as monotherapy or combined with cetuximab (Cetux) in patients (Pts) with colorectal cancer (CRC) harboring a KRASG12C mutation

J. Weiss[1], R.D. Yaeger[2], M.L. Johnson[3], A. Spira[4], S.J. Klempner[5], M.A. Barve[6], J.G. Christensen[7], A. Chi[7], H. Der-Torossian[7], K. Velastegui[7], T. Kheoh[7], S-H.I. Ou[8]

[1] Lineberger Comprehensive Cancer Center, University of North Carolina-Chapel Hill, Chapel Hill, NC, USA, [2] Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [3] Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN, USA, [4] Virginia Cancer Specialists, US Oncology Research, Fairfax, VA, USA, [5] Mass General Cancer Center, Massachusetts General Hospital, Boston, MA, USA, [6] Mary Crowley, Cancer Center, Dallas, TX, USA, [7] Clinical Discovery, Mirati Therapeutics, Inc., San Diego, CA, USA[8] Chao Family Comprehensive Cancer Center, University of California Irvine, Orange, CA, USA

Background

$KRAS^{G12C}$ mutations, which occur in 3%-4% of CRC, are a negative predictor of cetux efficacy. Adagrasib, an investigational agent, is a $KRAS^{G12C}$ inhibitor that irreversibly and selectively binds $KRAS^{G12C}$, locking it in its inactive state; it was optimized for favorable PK properties, including a long half-life (⊠24 hours). Durable inhibition of $KRAS^{G12C}$ 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 $KRAS^{G12C}$ -mutant advanced solid tumors. CRC cohorts include adagrasib 600 mg BID monotherapy (Phase 1/2) and adagrasib 600 mg BID + cetux 400 mg/m^2 followed by 250 mg/m^2 QW; or 500 mg/m^2 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 $KRAS^{G12C}$-mutant CRC. Adagrasib + cetux is currently being evaluated in the 2L setting in a Phase 3 trial of pts with $KRAS^{G12C}$-mutant CRC (NCT04793958).

Clinical trial identification

NCT03785249.

Editorial acknowledgement

Editorial and writing support was provided by Robin Serody of Axiom Healthcare Strategies.

Legal entity responsible for the study

Mirati Therapeutics, Inc.

Funding

Mirati Therapeutics, Inc.

Disclosure

J. Weiss: Financial Interests, Personal, Stocks/Shares: Nektar; Financial Interests, Personal, Stocks/Shares: Vesselon; Financial Interests, Personal, Advisory Board: AstraZeneca; Financial Interests, Personal, Advisory Board: EMD Serono; Financial Interests, Personal, Advisory Board: AstraZeneca; Financial Interests, Personal, Advisory Board: Genentech; Financial Interests, Personal, Advisory Board: Inivata; Financial Interests, Personal, Advisory Board: Celgene; Financial Interests, Personal, Advisory Board: G1 Therapeutics; Financial Interests, Personal, Advisory Board: Jounce Therapeutics; Financial Interests, Personal, Advisory Board: AbbVie; Financial Interests, Personal, Advisory Board: Rakuten Medical; Financial Interests, Personal, Advisory Board: Nanobiotix; Financial Interests, Personal, Advisory Board: Azitra; Financial Interests, Personal, Advisory Board: Lilly; Financial Interests, Personal, Advisory Board: Blueprint Medicines; Financial Interests, Personal, Advisory Board: Pfizer; Financial Interests, Personal, Advisory Board: Jazz Pharmaceuticals; Financial Interests, Personal, Advisory Board: Boehringer Ingelheim; Financial Interests, Personal, Advisory Board: Regeneron; Financial Interests, Personal, Advisory Board: Genmab. R.D. Yaeger: Financial Interests, Personal, Advisory Board: Array Biopharma; Financial Interests, Personal, Advisory Board: Natera. M.L. Johnson: Financial Interests, Institutional, Advisory Board: Genentech/Roche; Financial Interests, Institutional, Advisory Board: Boehringer Ingelheim; Financial Interests, Institutional, Advisory Board: Calithera; Financial Interests, Institutional, Advisory Board: AstraZeneca; Financial Interests, Institutional, Advisory Board: Merck; Financial Interests, Institutional, Advisory Board: Loxo; Financial Interests, Institutional, Advisory Board: Sanofi; Financial Interests, Institutional, Advisory Board: Mirati Therapeutics; Financial Interests, Institutional, Advisory Board: Pfizer; Financial Interests, Institutional, Advisory Board: Guardant Health; Financial Interests, Institutional, Advisory Board: Ribon Therapeutics; Financial Interests, Institutional, Advisory Board: Incyte; Financial Interests, Institutional, Advisory Board: AbbVie; Financial Interests, Institutional, Advisory Board: GlaxoSmithKline; Financial Interests, Institutional, Advisory Board: Janssen; Financial Interests, Institutional, Advisory Board: Lilly; Financial Interests, Institutional, Advisory Board: Novartis; Financial Interests, Institutional, Advisory Board: Amgen; Financial Interests, Institutional, Advisory Board: BMS; Financial Interests, Institutional, Advisory Board: Daichi-Sankyo; Financial Interests, Institutional, Advisory Board: EMD Serono; Financial Interests, Institutional, Advisory Board: G1 Therapeutics; Financial Interests, Institutional, Advisory Board: Checkpoint Therapeutics; Financial Interests, Institutional, Advisory Board: Eisai. A. Spira: Financial Interests, Personal, Stocks/Shares: Lilly; Financial Interests, Personal, Advisory Board: Array Biopharma; Financial Interests, Personal, Advisory Board: Incyte; Financial Interests, Personal, Advisory Board: Amgen; Financial Interests, Personal, Advisory Board: Novartis; Financial Interests, Personal, Advisory Board: AstraZeneca/MedImmune; Financial Interests, Personal, Advisory Board: Mirati Therapeutics; Financial Interests, Personal, Advisory Board: Gritstone Oncology; Financial Interests, Personal, Advisory Board: Jazz Pharmaceuticals; Financial Interests, Personal, Advisory Board: Merck; Financial Interests, Personal, Advisory Board: BMS; Financial Interests, Personal, Other: CytomX Therapeutics; Financial Interests, Personal, Other: Takeda; Financial Interests, Personal, Other: Amgen; Financial Interests, Personal, Other: Janssen; Financial Interests, Personal, Other: Bayer. S.J. Klempner: Financial Interests, Personal, Advisory Board: Lilly; Financial Interests, Personal, Advisory Board: Boston Biomedical; Financial Interests, Personal, Advisory Board: Astellas Pharma; Financial Interests, Personal, Advisory Board: Foundation Medicine; Financial Interests, Personal, Advisory Board: BMS; Financial Interests, Personal, Advisory Board: Pieris Pharmaceuticals; Financial Interests, Personal, Advisory Board: Merck; Financial Interests, Personal, Advisory Board: Daichi Sankyo/UCB Japan; Financial Interests, Personal, Speaker's Bureau: Foundation Medicine; Financial Interests, Personal, Stocks/Shares: TP Therapeutics. J.G. Christensen: Financial Interests, Personal, Full or part-time Employment: Mirati Therapeutics, Inc; Financial Interests, Personal, Advisory Role: BridgeBio; Financial Interests, Personal, Leadership Role: Mirati Therapeutics; Financial Interests, Personal, Leadership Role: BCTG Acquisition Corporation; Financial Interests, Personal, Stocks/Shares: Mirati Therapeutics; Financial Interests, Personal, Stocks/Shares: Bluebird Bio; Financial Interests, Personal, Stocks/Shares: BCTG Acquisition Corp. A. Chi: Financial Interests, Personal, Full or part-time Employment: Mirati Therapeutics, Inc; Financial Interests, Personal, Stocks/Shares: Mirati Therapeutics, Inc. H. Der-Torossian: Non-Financial Interests, Personal, Full or part-time Employment: Mirati Therapeutics, Inc. K. Velastegui: Other, Personal, Full or part-time Employment: Mirati Therapeutics, Inc. T. Kheoh: Financial Interests, Personal, Full or part-time Employment: Mirati Therapeutics, Inc; Financial Interests, Personal, Stocks/Shares: Mirati Therapeutics, Inc; Financial Interests, Personal, Stocks/Shares: Tocagen. S.I. Ou: Financial Interests, Personal, Advisory Role: Pfizer; Financial Interests, Personal, Advisory Role: Roche/Genentech; Financial Interests, Personal, Advisory Role: Takeda; Financial Interests, Personal, Advisory Role: Janssen Oncology; Financial Interests, Personal, Speaker's Bureau: AstraZeneca; Financial Interests, Personal, Speaker's Bureau: Roche/Genentech; Financial Interests, Personal, Stocks/Shares: Turning Point Therapeutics; Financial Interests, Personal, Stocks/Shares: Elevation Oncology. All other authors have declared no conflicts of interest.