A Randomized Phase 3 Study of Adagrasib in Combination with Cetuximab Versus Chemotherapy in Patients with Advanced Colorectal Cancer with KRAS G12C Mutation with Disease Progression On or After Standard First-Line Therapy

Published: 12-07-2021
Last updated: 19-09-2024

This study has been transitioned to CTIS with ID 2023-506241-30-00 check the CTIS register for the current data. Primary objectives:To compare the efficacy of Adagrasib in combination with cetuximab versus chemotherapy (FOLFIRI or mFOLFOX6)...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Gastrointestinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON54310

Source
ToetsingOnline

Brief title
KRYSTAL-10

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
Colon cancer

Research involving
Human

Sponsors and support

Primary sponsor: Mirati Therapeutics, Inc.
Source(s) of monetary or material Support: Industry

Intervention

Keyword: Advanced Colorectal Cancer, KRAS G12C, Phase 3

Outcome measures

Primary outcome

• Progression-Free Survival (PFS), and

• Overall Survival (OS).

Secondary outcome

• Safety characterized by type, incidence, severity, timing, seriousness and

relationship to study treatment of adverse events, laboratory abnormalities,

and number of patients discontinuing study treatment due to an adverse event.

• Secondary efficacy endpoints:

*- Objective Response Rate (ORR),

*- Duration of Response (DOR), and

*- 1-Year Survival Rate.

• Plasma PK parameters of Adagrasib (and metabolites, if applicable).

• Patient reported outcome (PROs) scores using the following:

- European Organization for Research and Treatment of Cancer (EORTC) Quality of

Life Questionnaire for Cancer Patients (QLQ-C30).

- European Quality of Life Five Dimensions Questionnaire (EQ-5D-5L).

Study description

Background summary

RAS proteins are part of the family of small GTPases that are activated in response to growth factor stimulation and various other extracellular stimuli to regulate intracellular signaling pathways responsible for growth, migration, survival and differentiation of cells. The activation of RAS proteins at the cell membrane by growth factors results in the binding of key effector molecules, formation of signaling complexes, and the initiation of a cascade of intracellular signaling pathways within the cell including the RAF and PI3 kinase pathways. RAS proteins normally alternate between GTP- and GDP-bound conformations, where the GTP-bound conformation represents the *On* and GDP-bound the *Off* state. Dependence of RAS and other GTPases on guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs) to switch them on and off allows both processes to be highly regulated and responsive to multiple signal inputs. In contrast, oncogenic mutants of RAS generally function by preventing hydrolysis of GTP, thereby generating constitutively active GTP-bound RAS molecules with severe consequences for the cell including uncontrolled cellular growth and malignant transformation.
KRAS is the most frequently mutated gene of the RAS family, and KRAS mutations occur in approximately 30% of lung adenocarcinomas, 50% of colorectal cancers, and 90% of pancreatic ductal adenocarcinomas. Mutation of the glycine at residue 12 produces a steric block that prevents GAP proteins from accessing KRAS, thereby inhibiting GTP hydrolysis resulting in a highly activated GTP-bound form of RAS. Mutation of that amino acid residue to cysteine, noted as KRAS G12C (also known as KRAS (p.G12C)), comprise approximately 3% of colorectal cancer (CRC) and defines a unique segment of CRC without a current targeted therapy option.
Adagrasib is a potent and orally available small molecule inhibitor of KRAS G12C. Adagrasib demonstrated potent inhibition of KRAS-dependent signal transduction and cancer cell viability with selectivity for KRAS G12C of over 1000-fold compared to KRAS wild-type. Adagrasib demonstrated broad-spectrum antitumor activity across several KRAS G12C-positive patient- or cell-derived tumor models implanted in mice, including complete tumor responses in a subset of models. Collectively, these results support the evaluation of Adagrasib in patients with malignancies having KRAS G12C mutations. Initial clinical trial observations with Adagrasib include demonstration of confirmed objective responses in NSCLC and colorectal cancer.
The epidermal growth factor receptor (EGFR) is constitutively expressed in many normal epithelial tissues and is also detected in many human cancers including those of the colon and rectum. Cetuximab is a human/mouse chimeric monoclonal antibody (mAb) that binds the extracellular domain of epidermal growth factor receptor (EGFR) and blocks the interaction between EGFR and its ligand, epidermal growth factor (EGF). Cetuximab binds specifically to the EGFR on both

normal and tumor cells, and competitively inhibits the binding of epidermal growth factor (EGF) and other ligands, such as transforming growth factor-alpha. Nonclinical studies have shown that binding of cetuximab to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production. Cetuximab is indicated as monotherapy or in combination with chemotherapy for the treatment of KRAS wildtype metastatic CRC. Signal transduction through EGFR results in activation of wild-type KRAS protein. However, in cells with activating KRAS somatic mutations, the mutant KRAS protein is continuously active and appears independent of EGFR regulation. Retrospective subset analyses of KRAS mutant and wildtype populations across several randomized clinical trials have indicated that cetuximab in patients with KRAS mutations results in no clinical benefit.

The rationale for combining Adagrasib with cetuximab in KRAS G12C mutant CRC stems from various lines of work. Efforts to target the RAS-RAF-MEK pathway in CRC have been hindered by adaptive feedback reactivation of pathway signaling as a mode of therapeutic resistance. For example, BRAF inhibition in BRAF V600 mutant CRC leads to loss of negative feedback signals regulated by the MAPK pathway, leading to receptor tyrosine kinase (RTK)-mediated reactivation of MAPK signaling through wildtype RAS and RAF. Similarly, in KRAS mutant cancers, MEK inhibitor treatment leads to adaptive feedback activation of RAS signaling, often through EGFR or other RTKs, limiting efficacy. Indeed, early preclinical studies with KRAS G12C inhibitors, such as ARS-1620 and AMG510, have suggested a potential role for adaptive feedback as a mechanism of resistance to KRAS G12C inhibition alone.

Therefore, interrupting the adaptive feedback loop following KRAS G12C inhibition may overcome adaptive resistance and improve clinical efficacy in a manner similar to BRAF V600E mutant colorectal cancer, where targeting EGFR*a primary driver of feedback reactivation in CRC*in combination with BRAF inhibition led to an improvement in clinical efficacy. In line with this hypothesis, the addition of an EGFR inhibitor to a KRAS G12C inhibitor resulted in significant improvement in antitumor activity compared to either single agent alone in nonclinical KRAS G12C mutant xenograft models. The combination of Adagrasib and the small molecule EGFR inhibitor afatinib demonstrated significantly greater antitumor efficacy compared with either single agent in all five KRAS G12C mutant xenograft models evaluated, including multiple models exhibiting complete or near-complete responses to the combination. In multiple nonclinical KRAS G12C human xenograft colorectal cancer mouse models, anti-tumor activity was significantly enhanced with the combination of Adagrasib and cetuximab, whereas Adagrasib or cetuximab alone exhibited little to no effect on tumor growth inhibition. These observations suggest the combination may address mechanisms responsible for a limited response to Adagrasib single agent treatment. In summary, these data support the rationale for combining Adagrasib with cetuximab for the treatment of KRAS G12C-mutant CRC.

This Phase 3 study compares the efficacy of Adagrasib in combination with

cetuximab against chemotherapy in patients with CRC with KRAS G12C mutation who have previously experienced radiographic disease progression on or after standard first-line chemotherapy

Study objective

This study has been transitioned to CTIS with ID 2023-506241-30-00 check the CTIS register for the current data.

Primary objectives:
To compare the efficacy of Adagrasib in combination with cetuximab versus chemotherapy (FOLFIRI or mFOLFOX6) administered in the second-line treatment setting to patients with CRC with KRAS G12C mutation.

Secondary objectives:
• To evaluate secondary efficacy endpoints in the study population.
• To evaluate the safety and tolerability in the study population.
• To evaluate the pharmacokinetics (PK) of Adagrasib administered in combination with cetuximab.
• To evaluate health-related quality of life (HRQOL) and cancer-related symptoms in the study population.

Exploratory objectives:
• To explore correlations between tumor biomarkers, gene alterations and efficacy.
• To evaluate the Progression-Free Survival in the next-line of therapy (PFS2) in the study population.

Study design

Study 849-010 is an open-label, randomized Phase 3 clinical trial comparing the efficacy of Adagrasib administered in combination with cetuximab versus chemotherapy (FOLFIRI or mFOLFOX6) in the second-line treatment setting in patients with CRC with KRAS G12C mutation. Patients will have previously experienced radiographic disease progression on or after treatment with a standard first-line fluoropyrimidine-based chemotherapy regimen containing either oxaliplatin or irinotecan. Secondary objectives include evaluation of safety and tolerability, secondary efficacy endpoints, PROs, and Adagrasib PK in the study population. The presence of KRAS G12C mutation in tumor tissue for the purpose of patient eligibility must be established using Sponsor pre-approved methods and laboratories. Presence of tumor KRAS G12C mutation may be established using a Sponsor-approved local test or the Sponsor-provided central laboratory test. Sponsor-approval process includes review of analytical performance and validation of tests to ensure locked-down assay cutoffs (ie, criteria to determine whether subjects are biomarker-positive or negative) before use of the test(s) in the study for patient enrollment. Patient eligibility for study enrollment based on objective disease progression on or after a standard first-line fluoropyrimidine-based chemotherapy regimen (containing either oxaliplatin or irinotecan) will be evaluated by the

Investigator. Data entered into the case report form (CRF) are to include all prior systemic treatment regimens received for colorectal cancer, the date of at least one radiographic evaluation prior to the occurrence of disease progression on first-line treatment, and the date the radiographic evaluation demonstrated disease progression, as well as specifics about organ systems (e.g., lung, liver, lymph node, bone and/or brain) having tumors that increase in size or are new. Eligible patients will be randomized 1:1 to the experimental arm (Adagrasib with cetuximab) or the control arm (FOLFIRI or mFOLFOX6 chemotherapy). Randomization will be stratified by: 1. Region (USA/Canada vs. other), 2. Time to disease progression after beginning first-line treatment (<6 months vs. >=6 months). The requirements for tumor KRAS G12C for determining eligibility are presented in Table 1 and Figure 1. The Schedule of Assessments is presented in Table 2. Study treatment will be expressed in 4-week (28 day) cycles. Patients randomized to the experimental arm will receive Adagrasib 600 mg BID and cetuximab 500 mg/m2 by intravenous (IV) infusion every 2 weeks, i.e., Days 1 and 15 of each treatment cycle. Patients randomized to the chemotherapy control arm will receive FOLFIRI or mFOLFOX6 depending on their first-line treatment regimen. Patients who received prior irinotecan will receive mFOLFOX6; patients who received prior oxaliplatin will receive FOLFIRI. In the chemotherapy control arm, patients will receive appropriate pre-medications followed by either: • FOLFIRI administered on days 1 and 15 of each cycle: - irinotecan 180 mg/m² IV, - folinic acid 400 mg/m² IV, and - fluorouracil 400 mg/m² given as an IV bolus, then 2400 mg/m² given as a continuous infusion over 46-48 hours. OR • mFOLFOX6 administered on days 1 and 15 of each cycle: - oxaliplatin 85 mg/m² IV, - folinic acid 400 mg/m2 IV, and - fluorouracil 400 mg/m2 given as an IV bolus, then 2400 mg/m² given as a continuous infusion over 46-48 hours. AND, OPTIONALLY • A VEGF/VEGFR inhibitor (bevacizumab or locally approved bevacizumab biosimilar, ramucirumab, or ziv-aflibercept, at the discretion of the Investigator) used as local standard-of-care may be given as a concomitant therapy with control arm chemotherapy in accordance to package labeling at the discretion of the Investigator. For an individual patient, the dose of study drug(s) may be reduced or interrupted as appropriate based on protocol-defined treatment modification criteria (Section 5). Disease response and progression will be evaluated in accordance with Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Disease progression as documented by the Investigator in the CRF will be the basis for patient management and supportive statistical analyses of radiology-based study endpoints. Blinded central radiology review for disease response and progression will be performed for the purpose of primary statistical analyses of these study endpoints. Disease assessments must be performed as scheduled according to the calendar to prevent the introduction of bias in the assessment of efficacy based on toxicity. Timely and complete disease assessments and transfer of radiographic documentation to the Central Radiology Laboratory is critical to the integrity of this clinical trial. Patients will receive study treatment as assigned at randomization until disease progression, unacceptable adverse events, investigator decision, patient refusal or death, whichever comes earlier. Patients experiencing clinical benefit in the judgment of the Investigator may continue study treatment beyond disease progression as defined by RECIST 1.1 if specified criteria are met (see Section 3). In the event a patient discontinues study treatment for a reason other than objective disease progression, disease assessments post-treatment should continue until objective disease progression is documented by the Investigator or start of subsequent anti-cancer therapy, whichever is sooner. No crossover to the alternative treatment assignment is provided in this study.

Intervention

The trial will compare the effectiveness of Adagrasib in combination with cetuximab (investigational arm) versus standard of care second-line treatment consisting of either FOLFIRI or mFOLFOX6 chemotherapy (comparator arm). Patients will have a 50% chance of receiving the investigational arm (Adagrasib with cetuximab) and a 50% chance of receiving the comparator arm (FOLFIRI or mFOLFOX6 chemotherapy). This means 1 out of 2 people will get Adagrasib with cetuximab. Patients will receive Adagrasib by mouth and cetuximab as an intravenous infusion.

Study burden and risks

Please see protocol section 7.0 for the study procedure and assessments.
Please see section 6.0 in the ICF for possible side effects and complications.

Contacts

Public
Mirati Therapeutics, Inc.

Cray Court 3545
San Diego 92121
US
Scientific
Mirati Therapeutics, Inc.

Cray Court 3545
San Diego 92121
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Histologically confirmed diagnosis of colorectal carcinoma with KRAS G12C mutation in tumor tissue.
2. Prior receipt of 1st line treatment in the advanced CRC with a fluoropyrimidine-based chemotherapy regimen containing either oxaliplatin or irinotecan, and radiographically documented progression of disease on or after treatment.

Exclusion criteria

1. Prior treatment with both an oxaliplatin-and irinotecan-based regimen for CRC, concurrently or successively, in any setting (neoadjuvant, adjuvant or advanced)
2. Prior treatment with a therapy targeting KRAS G12C mutation (e.g., AMG 510).
3. Prior treatment with an anti-EGFR antibody (e.g., cetuximab or panitumumab).

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	26-01-2023

Enrollment:	7
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ERBITUX
Generic name:	Cetuximab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	FOLFIRI
Generic name:	NA
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	mFOLFOX6
Generic name:	NA
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	MRTX849
Generic name:	Adagrasib

Ethics review

Approved WMO Date:	12-07-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-05-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-06-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	28-06-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-07-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-09-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-10-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-11-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-01-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-05-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-07-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-08-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-506241-30-00
EudraCT	EUCTR2020-004048-27-NL
ClinicalTrials.gov	NCT04793958
CCMO	NL77118.091.21