KRYSTAL-1: Activity and Safety of Adagrasib (MRTX849) in Patients with Colorectal Cancer (CRC) and Other Solid Tumors Harboring a KRAS G12C Mutation

Melissa L. Johnson
Sai-Hong Ignatius Ou
Minal Barve
Igor I. Rybkin

Henry Ford Health, irybkin1@hfhs.org

Kyriakos P. Papadopoulos

See next page for additional authors

Follow this and additional works at: https://scholarlycommons.henryford.com/hematologyoncology_mtgabstracts

Recommended Citation

This Conference Proceeding is brought to you for free and open access by the Hematology-Oncology at Henry Ford Health Scholarly Commons. It has been accepted for inclusion in Hematology Oncology Meeting Abstracts by an authorized administrator of Henry Ford Health Scholarly Commons.
Authors
Melissa L. Johnson, Sai-Hong Ignatius Ou, Minal Barve, Igor I. Rybkin, Kyriakos P. Papadopoulos, Ticiana A. Leal, Karen Velastegui, James G. Christensen, Thian Kheoh, Richard C. Chao, and Jared Weiss

This conference proceeding is available at Henry Ford Health Scholarly Commons:
https://scholarlycommons.henryford.com/hematologyoncology_mtgabstracts/73
KRYS TAL-1: Activity and Safety of Adagrasib (MRTX849) in Patients With Colorectal Cancer (CRC) and Other Solid Tumors Harboring a KRAS$^{G12C}$ Mutation

Melissa L. Johnson$^{1}$; Sai-Hong Ignatius Ou$^{2}$; Minal Barve$^{3}$; Igor I. Rybkin$^{4}$; Kyriakos P. Papadopoulos$^{5}$; Tician A. Leal$^{6}$; Karen Velastegui$^{7}$; James G. Christensen$^{7}$; Thian Kheoh$^{7}$; Richard C. Chao$^{7}$; Jared Weiss$^{8}$

$^{1}$Sarah Cannon Research Institute Tennessee Oncology, Nashville, Tennessee, USA. $^{2}$University of California, Irvine, Chao Family Comprehensive Cancer Center, Orange, California, USA. $^{3}$Mary Crowley Cancer Research, Dallas, Texas, USA. $^{4}$Henry Ford Cancer Institute, Detroit, Michigan, USA. $^{5}$START Center for Cancer Care, San Antonio, Texas, USA. $^{6}$University of Wisconsin Carbone Cancer Center, Madison, Wisconsin, USA. $^{7}$Mirati Therapeutics, Inc., San Diego, California, USA. $^{8}$Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, North Carolina, USA.
Disclosures

• Sponsored Research (Paid to Institution):
  - AstraZeneca; Boehringer-Ingelheim; Calithera Bioeciences; EMD Serono; Roche/Genentech; GlaxoSmithKline; Gritstone Oncology; Guardant Health; Incyte; Janssen R&D; Eli Lilly and Company; Merck; Novartis; Pfizer; Sanofi-Aventis; AbbVie; Acerta Pharma; Adaptimmune; Amgen; Apexigen Array BioPharma; BeiGene; Checkpoint Therapeutics; Corvus Pharmaceuticals; CytoX; Daiichi Sankyo; Dynavax Technologies; Genmab; Genocea Biosciences; Hengrui Therapeutics; Immunocore; Jounce Therapeutics; Kadmon Pharmaceuticals; Loxo Oncology; Lycera; Mirati Therapeutics, Inc; Neovia Oncology; OncoMed Pharmaceuticals; Regeneron Pharmaceuticals; Shattuck Labs; Stem CentRx; Syndax Pharmaceuticals; Takeda Pharmaceuticals; Tarveda; University of Michigan; WindMIL Therapeutics; TCR2 Therapeutics; Arcus Biosciences; Ribon Therapeutics; Seven and Eight Biopharmaceuticals; BerGenBio; Foundation Medicine; Atreca; Rubius Therapeutics; Tmunity Therapeutics

• Consulting Fees (Paid to Institution):
  - Achilles Therapeutics; AstraZeneca; Atreca, Boehringer Ingelheim; Bristol-Myers Squibb; Daiichi Sankyo; EMD Serono; G1 Therapeutics; GlaxoSmithKline; Gritstone Oncology; Incyte; Janssen; Eli Lilly and Company; Merck; Mirati Therapeutics, Inc.; Novartis; Pfizer; Ribon Therapeutics; Roche/Genentech; Sanofi-Aventis and WindMIL Therapeutics

• Other:
  - Astellas Pharmaceuticals and Otsuka Pharmaceuticals (spouse)
**Adagrasib (MRTX849) Is a Differentiated and Selective Inhibitor of KRAS<sub>G12C</sub>**

- **KRAS<sub>G12C</sub>** mutations act as oncogenic drivers and occur in approximately 14% of NSCLC (adenocarcinoma), 3-4% of CRC, and 1-2% of several other cancers<sup>1-3</sup>

- The KRAS protein cycles between GTP-On and GDP-Off states and has a protein resynthesis half-life of ~24 h<sup>4,5</sup>

- Adagrasib is a covalent inhibitor of KRAS<sub>G12C</sub> that irreversibly and selectively binds KRAS<sub>G12C</sub> in its inactive, GDP-bound state<sup>6</sup>

- Adagrasib was optimized for desired properties of a KRAS<sub>G12C</sub> inhibitor:
  - Potent covalent inhibitor of KRAS<sub>G12C</sub> (cellular IC<sub>50</sub>: ~5 nM)
  - High selectivity (>1000X) for the mutant KRAS<sub>G12C</sub> protein vs wild-type KRAS
  - Favorable PK properties, including oral bioavailability, long half-life (~24 h), and extensive tissue distribution

**Hypothesis:** Maintaining continuous exposure of adagrasib above a target threshold enables inhibition of KRAS-dependent signaling for the complete dose interval and maximizes depth and duration of antitumor activity

---

For Phase 2 NSCLC cohorts, patients must have received prior treatment with platinum-based chemotherapy and a PD-1/PD-L1 inhibitor. CRC/other solid tumor cohort eligibility based on tissue or plasma test; KRAS<sup>G12C</sup> testing for entry was performed locally or centrally using a sponsor preapproved test. CRC=Phase 1/1b (n=2) and Phase 2 (n=22); ClinicalTrials.gov. NCT03785249.

### Phase 1 Endpoints
- **Primary:** Safety, MTD, PK, RP2D
- **Secondary:** Objective Response (RECIST 1.1), DOR, PFS, OS

### Phase 2 Endpoints
- **Primary:** ORR (RECIST 1.1)
- **Secondary:** Safety

### Key Eligibility Criteria
- Solid tumor with KRAS<sup>G12C</sup> mutation
- Unresectable or metastatic disease
- No available treatment with curative intent or available standard of care<sup>a</sup>

### Data
- Previously reported data from Phase 1 demonstrated clinical activity with adagrasib (MRTX849) in patients with pretreated KRAS<sup>G12C</sup> CRC and NSCLC
- 600 mg BID was chosen as the RP2D
- Here we report data for 31 patients, evaluating adagrasib 600 mg BID in patients with previously treated CRC (n=24)<sup>c</sup> or other solid tumors (n=7); median follow-up, 4.3 mo for patients with CRC and not calculated for patients with other solid tumors
- Data as of 30 August 2020

<sup>a</sup>For Phase 2 NSCLC cohorts, patients must have received prior treatment with platinum-based chemotherapy and a PD-1/PD-L1 inhibitor. <sup>b</sup>CRC/other solid tumor cohort eligibility based on tissue or plasma test; KRAS<sup>G12C</sup> testing for entry was performed locally or centrally using a sponsor preapproved test. <sup>c</sup>CRC=Phase 1/1b (n=2) and Phase 2 (n=22); ClinicalTrials.gov. NCT03785249.
## Patient Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>CRC (Pooled), 600 mg BID (n=24)</th>
<th>“Other” Cohort, 600 mg BID (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, y (range)</strong></td>
<td>59 (37-79)</td>
<td>64 (25-80)</td>
</tr>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>12 (50%)</td>
<td>2 (29%)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>18 (75%)</td>
<td>5 (71%)</td>
</tr>
<tr>
<td>Black</td>
<td>4 (17%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (8%)</td>
<td>1 (14%)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0%)</td>
<td>1 (14%)</td>
</tr>
<tr>
<td><strong>ECOG PS, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>9 (38%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>1</td>
<td>15 (63%)</td>
<td>7 (100%)</td>
</tr>
<tr>
<td><strong>Tumor type, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRC</td>
<td>24 (100%)</td>
<td></td>
</tr>
<tr>
<td>Pancreatic ductal adenocarcinoma</td>
<td></td>
<td>2 (29%)</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>1 (14%)</td>
<td>1 (14%)</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>1 (14%)</td>
<td>1 (14%)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>1 (14%)</td>
<td>1 (14%)</td>
</tr>
<tr>
<td>Appendiceal cancer</td>
<td>2 (29%)</td>
<td></td>
</tr>
<tr>
<td><strong>Prior lines of anticancer therapy, median (range)</strong></td>
<td>4 (1-9)</td>
<td>2 (1-5)</td>
</tr>
</tbody>
</table>

Data as of 30 August 2020. Pooled includes Phase 1/1b (n=2) and Phase 2 (n=22) 600 mg BID.
## Incidence of Treatment-Related Adverse Events

### All Cohorts Pooled, 600 mg BID<sup>a</sup> (n=110)

<table>
<thead>
<tr>
<th>TRAEs&lt;sup&gt;b,c&lt;/sup&gt;, %</th>
<th>Any Grade</th>
<th>Grades 3-4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TRAEs</td>
<td>85%</td>
<td>30%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Most frequent TRAEs&lt;sup&gt;a,d&lt;/sup&gt;, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>54%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>51%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>35%</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32%</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>20%</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Increased AST</td>
<td>17%</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Increased blood creatinine</td>
<td>15%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>15%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>QT prolongation</td>
<td>14%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>Anemia</td>
<td>13%</td>
<td>2%</td>
<td>0%</td>
</tr>
</tbody>
</table>

- Grade 5 TRAEs included pneumonitis in a patient with recurrent pneumonitis (n=1) and cardiac failure (n=1)
- 7.3% of TRAEs led to discontinuation

---

<sup>a</sup>Includes patients pooled from Phase 1/1b and Phase 2 NSCLC (n=79), and CRC and Phase 2 other tumor cohorts (n=31).<br>
<sup>b</sup>Includes events reported between first dose and 30 August 2020.<br>
<sup>c</sup>The most common treatment-related SAEs (2 patients each) reported were diarrhea (grade 1, grade 2) and hyponatremia (both grade 3).<br>
<sup>d</sup>Occurred in ≥10%. Data as of 30 August 2020.

**Presented at the 32nd EORTC-NCI-AACR Symposium, October 24-25, 2020**
Adagrasib in Patients With CRC: Best Overall Response and Disease Control Rate

- Confirmed ORR 17% (3/18) of patients; SD 78% (14/18)
- Disease control observed in 94% (17/18) of patients

*aAll results based on investigator assessments.
Data as of 30 August 2020. Pooled includes Phase 1/1b and Phase 2 600 mg BID.
**Adagrasib in Patients With Advanced CRC: Duration of Treatment**

- **Evaluable Patients**
  - Duration of Treatment, wk
  - Median time to response 12.9 wk
  - At time of analysis, 67% (12/18) of patients remain on treatment
  - 55% (10/18) of patients have been on treatment for ≥4 mo

Data as of 30 August 2020. Pooled includes Phase 1/1b and Phase 2 600 mg BID.

Presented at the 32nd EORTC-NCI-AACR Symposium, October 24-25, 2020
Adagrasib in Patients With Other Advanced Solid Tumors: Best Overall Response

Best Tumor Change From Baseline

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Evaluable Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucinous appendiceal</td>
<td>80</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>60</td>
</tr>
<tr>
<td>Ovarian</td>
<td>40</td>
</tr>
<tr>
<td>Endometrial</td>
<td>20</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>0</td>
</tr>
</tbody>
</table>

All results based on investigator assessments. At the time of the 30 August 2020 data cut off, the cholangiocarcinoma patient had unconfirmed PR; the response was subsequently confirmed by scans that were performed after the 30 August 2020 data cut off. Data as of 30 August 2020. All patients treated at 600 mg BID.
Adagrasib in Patients With Other Advanced Solid Tumors: Duration of Treatment

- All patients remain on treatment

Data as of 30 August 2020. All patients treated at 600 mg BID.
Patient Case: Ovarian Cancer

- 25-year-old female
- Ovarian cancer diagnosed June 2019
- Treatment history
  - TAH/BSO, July 2019
  - Adjuvant carboplatin/docetaxel/bevacizumab, August-December 2019
  - Letrozole, January-May 2020

- TRAEs: Grade 1 peripheral edema
- Currently on cycle 6

Baseline

Adagrasib
600 mg BID

Scan 2,
 uPR (-46%)
August 2020

Data as of 25 September 2020.
63-year-old female
Endometrial cancer diagnosed June 2016
Treatment history
- TAH/BSO June 2016
- Carboplatin/paclitaxel, October 2016-June 2017
- Local radiation, April-June 2017
- Investigational agent (tinostamustine), March-October 2019
- Pelvic radiation, March 2020

Molecular analysis by expanded NGS panel
- KRAS\textsuperscript{G12C}, PTEN\textsuperscript{R130Q}, PTEN\textsuperscript{T319fs}
- MSS (microsatellite stable) and p53 WT

TRAEs
- Grade 1 vomiting

Currently in cycle 8

Data as of 25 September 2020.
Conclusions

- Adagrasib is a KRAS\textsuperscript{G12C}-selective covalent inhibitor with a long half-life, and extensive predicted target coverage throughout the dosing interval
- Adagrasib is well tolerated
- Adagrasib provides durable benefit to patients with CRC harboring KRAS\textsuperscript{G12C} mutations
  - Durable responses were observed
  - Broad disease control rate was observed
- Adagrasib demonstrated clinical activity in various KRAS\textsuperscript{G12C}-mutated solid tumors, including pancreatic, ovarian, and endometrial cancers, and cholangiocarcinoma
- Enrollment in the CRC and other solid tumor monotherapy Phase 2 cohorts is ongoing
- Evaluation of adagrasib in combination with cetuximab (CRC) at full dose of each agent is ongoing\(^a\); a Phase 3 trial of adagrasib in combination with cetuximab is planned

\(^a\)ClinicalTrials.gov. NCT03785249

Durable responses observed in NSCLC (n=23/51; 45%); See Jänne PA et al., abstract LBA-03.
Acknowledgements

• The patients and their families who make this trial possible
• The clinical study teams for their work and contributions
• This study is supported by Mirati Therapeutics, Inc.
• All authors contributed to and approved this presentation; writing and editorial assistance were provided by Rohan Gidvani of Axiom Healthcare Strategies, funded by Mirati Therapeutics, Inc.
Investigators

Harshad Amin
Boca Raton Clinical Research
Global USA

Daniel Anderson
Metro-Minnesota Community
Oncology Research Consortium

Minal Barve
Mary Crowley Cancer Center

Bruno R. Bastos
Miami Cancer Institute and
Baptist Health of South Florida

Lyudmila Bazhenova
Moore’s Cancer Center,
University of California
San Diego

Tanios Bekaii-Saab
Mayo Clinic

David Berz
Beverly Hills Cancer Center

Alberto Bessudo
California Cancer Associates for
Research and Excellence

Alejandro Calvo
Kettering Cancer Center

Patrick Cobb
Sisters of Charity of
Leavenworth Health St. Mary’s

Mike Cusnir
Mount Sinai Comprehensive
Cancer Center

Keith Eaton
Seattle Cancer Care Alliance

Yousuf Gaffar
Maryland Oncology Hematology

Navid Hafez
Yale Cancer Center

David Hakimian
Illinois Cancer Specialists

Rebecca S. Heist
Massachusetts General Hospital

Pasi A Jänne
Dana-Farber Cancer Institute

Melissa L. Johnson
Sarah Cannon Research Institute

Han Koh
Kaiser Permanente

Scott Kruger
Virginia Oncology Associates

Timothy Larson
Minnesota Oncology

Ticiana A. Leal
University of Wisconsin Carbone
Cancer Center

Konstantinos Leventakos
Mayo Clinic

Yanyan Lou
Mayo Clinic

Steven McCune
Northwest Georgia Oncology Centers

Jamal Misleh
Medical Oncology

Suresh Nair
Lehigh Valley Physician Group

Sujatha Nallapareddy
Rocky Mountain Cancer Center

Marcelo Negro
MD Anderson Cancer Center

Gregg Newman
Ridley-Tree Cancer Center

Sai-Hong Ignatius Ou
University of California, Irvine,
Chao Family Comprehensive
Cancer Center

Rami Owera
Woodlands Medical Specialists

Jose M. Pacheco
University of Colorado Anschutz
Medical Campus

Kyriakos P. Papadopoulos
START Center for Cancer Care

David Park
Virginia K. C. Crosson Cancer Center

Scott Paulson
Texas Oncology, USOR

Nathan Pennell
Cleveland Clinic Lerner College

Muhammad Riaz
University of Cincinnati Health

Barrett Cancer Center

Donald Richards
Texas Oncology, USOR

Gregory J. Riely
MSKCC, Weill Cornell

Medical College

Francisco Robert
University of Alabama at
Birmingham School of Medicine

Richard Rosenberg
Arizona Oncology

Peter Rubin
MaineHealth Cancer Care

Robert Ruxer
Texas Oncology

Igor I. Rybkin
Henry Ford Cancer Institute

Joshua Sabari
New York University Langone
Health, New York University

Perlmutter Cancer Center

Alexander I. Spira
Virginia Cancer Specialists,
US Oncology Research

Caesar Tin-U
Texas Oncology

Anthony Van Ho
Compass Oncology

Jared Weiss
Lineberger Comprehensive

Cancer Center, University of North Carolina

John Wrangle
Medical University of

South Carolina

Edwin Yau
Roswell Park Comprehensive

Cancer Center

Jeffrey Yorio
Texas Oncology

Jun Zhang
University of Kansas

Medical Center
Abbreviations

ALT = alanine aminotransferase
AST = aspartate aminotransferase
BID = twice daily
CRC = colorectal cancer
DCR = disease control rate
DOR = duration of response
ECOG = Eastern Cooperative Oncology Group
MTD = maximum tolerated dose
nM = nanomolar
NSCLC = non–small-cell lung cancer
ORR = objective response rate
OS = overall survival
PD = progressive disease
PFS = progression-free survival
PK = pharmacokinetics
PR = partial response
PS = performance status
QD = once daily
RP2D = recommended Phase 2 dose
SAE = serious adverse event
SD = stable disease
TAH/BSO = total abdominal hysterectomy with bilateral salpingo-oophorectomy
TRAE = treatment-related adverse event
uPR = unconfirmed partial response