KRYSFACE-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\textsuperscript{1}; Sai-Hong Ignatius Ou\textsuperscript{2}; Minal Barve\textsuperscript{3}; Igor I. Rybkin\textsuperscript{4}; Kyriakos P. Papadopoulos\textsuperscript{5}; Ticiane A. Leal\textsuperscript{6}; Karen Velastegui\textsuperscript{7}; James G. Christensen\textsuperscript{7}; Thian Kheoh\textsuperscript{7}; Richard C. Chao\textsuperscript{7}; Jared Weiss\textsuperscript{8}

\textsuperscript{1}Sarah Cannon Research Institute Tennessee Oncology, Nashville, Tennessee, USA. \textsuperscript{2}University of California, Irvine, Chao Family Comprehensive Cancer Center, Orange, California, USA. \textsuperscript{3}Mary Crowley Cancer Research, Dallas, Texas, USA. \textsuperscript{4}Henry Ford Cancer Institute, Detroit, Michigan, USA. \textsuperscript{5}START Center for Cancer Care, San Antonio, Texas, USA. \textsuperscript{6}University of Wisconsin Carbone Cancer Center, Madison, Wisconsin, USA. \textsuperscript{7}Mirati Therapeutics, Inc., San Diego, California, USA. \textsuperscript{8}Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, North Carolina, USA.
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Adagrasib (MRTX849) Is a Differentiated and Selective Inhibitor of KRAS<sup>G12C</sup>

- KRAS<sup>G12C</sup> 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<sup>G12C</sup> that irreversibly and selectively binds KRAS<sup>G12C</sup> in its inactive, GDP-bound state<sup>6</sup>
- Adagrasib was optimized for desired properties of a KRAS<sup>G12C</sup> inhibitor:
  - Potent covalent inhibitor of KRAS<sup>G12C</sup> (cellular IC<sub>50</sub>: ~5 nM)
  - High selectivity (>1000X) for the mutant KRAS<sup>G12C</sup> 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\text{G12C} 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

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**Key Eligibility Criteria**
- Solid tumor with KRAS\text{G12C} mutation
- Unresectable or metastatic disease
- No available treatment with curative intent or available standard of care

**Phase 1**
- **Dose Escalation**
  - 150 mg QD
  - 300 mg QD
  - 600 mg QD
  - 1200 mg QD

**Phase 1B**
- Dose Expansion and Combination
  - 600 mg BID

**Phase 2**
- **Monotherapy Treatment**
  - Adagrasib monotherapy
    - Adagrasib + pembrolizumab in NSCLC
    - Adagrasib + afatinib in NSCLC
    - Adagrasib + cetuximab in CRC

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Presented at the 32nd EORTC-NCI-AACR Symposium, October 24-25, 2020

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\(^1\) For Phase 2 NSCLC cohorts, patients must have received prior treatment with platinum-based chemotherapy and a PD-1/PD-L1 inhibitor. \(^2\) CRC/other solid tumor cohort eligibility based on tissue or plasma test; KRAS\text{G12C} testing for entry was performed locally or centrally using a sponsor preapproved test. \(^3\) 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></td>
<td>1 (14%)</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td></td>
<td>1 (14%)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td></td>
<td>1 (14%)</td>
</tr>
<tr>
<td>Appendiceal cancer</td>
<td></td>
<td>2 (29%)</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

<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).
<sup>b</sup>Includes events reported between first dose and 30 August 2020.
<sup>c</sup>The most common treatment-related SAEs (2 patients each) reported were diarrhea (grade 1, grade 2) and hyponatremia (both grade 3).
<sup>d</sup>Occurred in ≥10%.
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

All results based on investigator assessments. Data as of 30 August 2020. Pooled includes Phase 1/1b and Phase 2 600 mg BID.

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Adagrasib in Patients With Advanced CRC: Duration of Treatment

Duration of Treatment

- 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.
Adagrasib in Patients With Other Advanced Solid Tumors: Best Overall Response

Best Tumor Change From Baseline\textsuperscript{a}

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Evaluable Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucinous appendiceal</td>
<td>SD</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>SD</td>
</tr>
<tr>
<td>Ovarian</td>
<td>PR</td>
</tr>
<tr>
<td>Endometrial</td>
<td>uPR</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>PR\textsuperscript{b}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}All results based on investigator assessments. \textsuperscript{b}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

Data as of 25 September 2020.
Patient Case: Endometrial Cancer

- 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}, PTENT\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\textsuperscript{a}; a Phase 3 trial of adagrasib in combination with cetuximab is planned

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

\textsuperscript{a}ClinicalTrials.gov. NCT03785249
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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  
Institute Tennessee Oncology

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 Hematology Consultants

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. Crosson Cancer Center

Scott Paulson  
Texas Oncology, USOR

Nathan Pennell  
Cleveland Clinic Lerner College Of Medicine

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

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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