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

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KRYSRATL-1: Activity and Safety of Adagrasib (MRTX849) in Patients With Colorectal Cancer (CRC) and Other Solid Tumors Harboring a KRASG12C Mutation

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Adagrasib (MRTX849) Is a Differentiated and Selective Inhibitor of KRAS$^{G12C}$

- KRAS$^{G12C}$ mutations act as oncogenic drivers and occur in approximately 14% of NSCLC (adenocarcinoma), 3-4% of CRC, and 1-2% of several other cancers$^{1-3}$
- The KRAS protein cycles between GTP-On and GDP-Off states and has a protein resynthesis half-life of ~24 h$^{4,5}$
- Adagrasib is a covalent inhibitor of KRAS$^{G12C}$ that irreversibly and selectively binds KRAS$^{G12C}$ in its inactive, GDP-bound state$^{6}$
- Adagrasib was optimized for desired properties of a KRAS$^{G12C}$ inhibitor:
  - Potent covalent inhibitor of KRAS$^{G12C}$ (cellular IC$_{50}$: ~5 nM)
  - High selectivity (>1000X) for the mutant KRAS$^{G12C}$ 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; KRASG12C 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.

**KRYSERAL-1 (849-001) Study Design**

**Key Eligibility Criteria**
- Up to n=391
- Solid tumor with KRASG12C 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
  - 600 mg BID

**Expansion**
- **Adagrasib monotherapy**
- **Adagrasib + pembrolizumab in NSCLC**
- **Adagrasib + afatinib in NSCLC**
- **Adagrasib + cetuximab in CRC**

**Phase 1B**
- Dose Expansion and Combination

**Phase 2**
- Monotherapy Treatment
  - NSCLC
  - CRC
  - Other solid tumors

**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

Previously reported data from Phase 1 demonstrated clinical activity with adagrasib (MRTX849) in patients with pretreated KRASG12C 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) 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.

*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; KRASG12C 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.*

Presented at the 32nd EORTC-NCI-AACR Symposium, October 24-25, 2020
## 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: Treatment-Related Adverse Events (TRAEs)

<table>
<thead>
<tr>
<th>TRAEs[^b,c]</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>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>

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

- 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
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

\(^a\)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

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

- 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

Study Phase
- Phase 1/1b
- Phase 2

First response
- Progression
- Treatment ongoing
- Death

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

- **Best Tumor Change From Baseline**: 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.

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**Tumor Type**
- Mucinous appendiceal
- Pancreatic
- Ovarian
- Endometrial
- Cholangiocarcinoma

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

KRYSTAL-1: Adagrasib (MRTX849) KRAS\textsuperscript{G12C} Inhibitor in CRC and Other Solid Tumors

Adagrasib
600 mg BID

Scan 2,
\textit{uPR} (-46%)
August 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$^{G12C}$, PTEN$^{R130Q}$, PTEN$^{T319fs}$
  - 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<sup>G12C</sup>-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<sup>G12C</sup> mutations
  - Durable responses were observed
  - Broad disease control rate was observed
- Adagrasib demonstrated clinical activity in various KRAS<sup>G12C</sup>-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 Phase 3 trial of adagrasib in combination with cetuximab is planned

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

ClinicalTrials.gov. NCT03785249
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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