KRYSITL-1: Updated Activity and Safety of Adagrasib (MRTX849) in Patients (Pts) With Unresectable or Metastatic Pancreatic Cancer (PDAC) and Other Gastrointestinal (GI) Tumors Harboring a KRAS\textsuperscript{G12C} Mutation

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Adagrasib (MRTX849) is a Differentiated, Selective Inhibitor of KRAS$^{G12C}$

- KRAS mutations occur in approximately 90% of pancreatic cancer$^1$; ~2% of these are KRAS$^{G12C}$ mutations$^2$
- The KRAS protein cycles between GTP-on and GDP-off states and has a protein resynthesis half-life of ~24 hours$^3,4$
- Adagrasib, a covalent inhibitor of KRAS$^{G12C}$, irreversibly and selectively binds KRAS$^{G12C}$ in its inactive, GDP-bound state
- Adagrasib was optimized for desired properties of a KRAS$^{G12C}$ inhibitor$^5$:
  - Long half-life of ~24 hours
  - Dose-dependent PK
  - CNS penetration
- 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

CNS, central nervous system; EGFR, epidermal growth factor receptor; PK, pharmacokinetics; RTK, receptor tyrosine kinase.
KRYS TAL-1 (849-001) Study Design

**Key Eligibility Criteria**
- Solid tumor with KRAS\(^{G12C}\) mutation
- Unresectable or metastatic disease
- Treated and/or stable brain metastases\(^a\)

**Phase 1**
- Dose Escalation\(^b\)
  - 600 mg BID Expansion
  - 1200 mg QD\(^c\)
  - 600 mg QD\(^c\)
  - 300 mg QD\(^c\)
  - 150 mg QD\(^c\)

**Phase 1b**
- Dose Expansion and Combination\(^b\)
  - Adagrasib monotherapy in solid tumors
  - Adagrasib brain metastases in solid tumors
  - Adagrasib NSCLC treatment-naïve
  - Adagrasib NSCLC prior KRAS\(^{G12C}\) inhibitor
  - Adagrasib + pembrolizumab in NSCLC
  - Adagrasib + afatinib in NSCLC
  - Adagrasib + cetuximab in CRC
  - Adagrasib + cetuximab in NSCLC / PDAC
  - Adagrasib in NSCLC (tablet formulation)

**Phase 2**
- Monotherapy and Combination Treatment
  - NSCLC
    - Adagrasib
  - CRC
    - Adagrasib
  - Other solid tumors (N=42)\(^b,d\)
    - (GI tumors, n=30)
      - Adagrasib
  - Treatment-Naïve NSCLC
    - Adagrasib: KRAS\(^{G12C}\) and STK11 mutation
  - CRC
    - Adagrasib +/- cetuximab

**Phase 2 Endpoints**
- **Primary:** ORR (RECIST 1.1)
- **Secondary:** DOR, PFS, OS, safety

**Previously reported data demonstrated clinical activity with adagrasib in patients with various KRAS\(^{G12C}\)-mutated solid tumors, including NSCLC, CRC and other tumors such as PDAC, ovarian and endometrial cancers, and cholangiocarcinoma\(^1-3\)**

**Here we report preliminary data from a Phase 2 cohort evaluating adagrasib 600 mg BID in patients with previously-treated GI tumors (n=30), excluding CRC, with a focus on PDAC (n=12) and other GI cancers (n=18), with a KRAS\(^{G12C}\) mutation**

CRC, colorectal cancer; ctDNA, circulating tumor deoxyribonucleic acid; GI, gastrointestinal; NSCLC, non–small-cell lung cancer; PDAC, pancreatic ductal adenocarcinoma.


*Most cohorts allow patients with brain metastases if adequately treated and stable; additional phase 1/1b cohort allows limited brain metastases; \(^a\)KRAS\(^{G12C}\) mutation detected in tumor tissue and/or ctDNA; \(^b\)Patients subsequently dose escalated up to 600 mg BID; \(^c\)Solid tumors included GI tumors (n=30) and non-GI tumors (n=12).

Data as of 10 September 2021. ClinicalTrials.gov. NCT03785249.
## Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>PDAC (n=12)</th>
<th>Other GI cancers (n=18)</th>
<th>Overall GI cancers(^a) (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, y (range)</strong></td>
<td>66.5 (40–80)</td>
<td>64.0 (54–89)</td>
<td>65.5 (40–89)</td>
</tr>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>4 (33)</td>
<td>8 (44)</td>
<td>12 (40)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>7 (58)</td>
<td>13 (72)</td>
<td>20 (67)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>1 (8)</td>
<td>2 (11)</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Asian / Other</td>
<td>1 (8) / 3 (25)</td>
<td>1 (6) / 2 (11)</td>
<td>2 (7) / 5 (17)</td>
</tr>
<tr>
<td><strong>ECOG PS, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 / 1</td>
<td>0 (0) / 12 (100)</td>
<td>6 (33) / 12 (67)</td>
<td>6 (20) / 24 (80)</td>
</tr>
<tr>
<td><strong>Tumor type, n</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDAC</td>
<td>12</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Other GI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biliary tract</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Appendiceal</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Gastro-esophageal junction</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Small bowel</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Esophageal</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Prior lines of systemic anticancer therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>2.5 (1–4)(^b)</td>
<td>2.0 (1–5)</td>
<td>2.0 (1–5)</td>
</tr>
<tr>
<td>1 / 2 / 3 / ≥4 / missing, %</td>
<td>8 / 42 / 42 / 8</td>
<td>22 / 39 / 11 / 22 / 6</td>
<td>17 / 40 / 23 / 17 / 3</td>
</tr>
</tbody>
</table>

Percentages may not add up to 100 due to rounding.

ECOG PS, Eastern Cooperative Oncology Group performance status.

\(^a\)Excluding CRC; \(^b\)All patients with PDAC received gemcitabine-based regimen(s), and all but 2 received prior fluoropyrimidine-based regimen(s).
Adagrasib in Patients With PDAC and Other GI Tumors: Objective Response Rate

A total of 30 patients were enrolled: 12 PDAC, 18 Other GI.

Excluding CRC; Based on investigator assessment of the clinically evaluable patients (measurable disease with ≥1 on-study scan); Evaluable population (n=10) excludes 2 patients who had discontinued treatment prior to first scan due to unrelated adverse events and were not evaluable for clinical activity; Evaluable population (n=17) excludes 1 patient who withdrew consent prior to the first scan; Includes 1 unconfirmed PR as of data cut-off; Includes 2 unconfirmed PR as of data cut-off; Includes 3 unconfirmed PR as of data cut-off.

Data as of 10 Sept 2021 (median follow-up: overall, 6.3 months; PDAC, 8.1 months; other GI cancers: 6.3 months).

<table>
<thead>
<tr>
<th>Efficacy outcome</th>
<th>PDAC (n=10)</th>
<th>Other GI cancers (n=17)</th>
<th>Overall GI cancers (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response rate</td>
<td>5 (50)</td>
<td>6 (35)</td>
<td>11 (41)</td>
</tr>
<tr>
<td>Best overall response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>5 (50)</td>
<td>6 (35)</td>
<td>11 (41)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>5 (50)</td>
<td>11 (65)</td>
<td>16 (59)</td>
</tr>
<tr>
<td>Disease control rate</td>
<td>10 (100)</td>
<td>17 (100)</td>
<td>27 (100)</td>
</tr>
</tbody>
</table>
Adagrasib in Patients With Unresectable or Metastatic PDAC: Best Tumor Change From Baseline and Duration of Treatment

- Response rate: 50% (5/10), including 1 unconfirmed PR
- SD: 50% (5/10 patients)
- DCR: 100% (10/10 patients)

- Median TTR: 2.8 months
- Median DOR: 6.97 months
- Median PFS: 6.6 months (95% CI 1.0–9.7)
- Treatment ongoing in 50% (5/10) of patients

Evaluation population (n=10) excludes 2 patients who had discontinued treatment prior to first scan due to unrelated adverse events and were not evaluable for clinical activity; all results are based on investigator assessments; at data cut-off, 1 patient had unconfirmed PR.

Data as of 10 Sept 2021 (median follow-up: 8.1 months).
Adagrasib in Patients With Other GI Tumors:a
Best Tumor Change From Baseline and Duration of Treatment

**Best Tumor Change From Baseline (n=17)b,c**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Evaluable Patients</th>
<th>Maximum % Change From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary Tract (n=8)</td>
<td>GEJ (n=1)</td>
<td>SD, SD, SD, SD, SD, SD, SD, SD</td>
</tr>
<tr>
<td>Appendiceal (n=5)</td>
<td>Esophageal (n=1)</td>
<td>SD, SD, SD, SD, SD, SD, SD, SD</td>
</tr>
<tr>
<td>Small Bowel (n=2)</td>
<td></td>
<td>SD, SD, SD, SD, SD, SD, SD, SD</td>
</tr>
</tbody>
</table>

**Duration of Treatment (n=17)b,c**

- **Response rate:**
  - Biliary tract cancer: 50% (4/8), including 2 unconfirmed PRs
  - GEJ and small bowel cancer: 1 PR each
  - DCR: 100% (17/17 patients)

- **DCR, disease control rate; DOR, duration of response; GEJ, gastro-esophageal junction; PR, partial response; SD, stable disease; TTR, time to response.**

- Data as of 10 Sept 2021 (median follow-up: 6.3 months).

- **Median TTR: 1.3 months**
- **Median DOR: 7.85 months**
- **Median PFS: 7.85 months (95% CI 6.90–11.30)**
- **Treatment ongoing in 65% (11/17) of patients**

*aExcluding CRC and PDAC; bEvaluable population (n=17) excludes 1 patient who withdrew consent prior to the first scan; cAll results are based on investigator assessments; d1 patient with appendiceal cancer and 1 patient with esophageal cancer had maximum % change from baseline of 0; eAt data cut-off, 2 patients had unconfirmed PR.
Adagrasib in Patients With Other Advanced Solid Tumors: \(^a\)
Incidence of Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th>Most Frequent TRAEs(^b)</th>
<th>Overall (N=42)(^c)</th>
<th>Overall GI cancers(^d) (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRAEs, %</td>
<td>Any Grade</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Any TRAEs</td>
<td>91</td>
<td>21</td>
</tr>
<tr>
<td>Most frequent TRAEs, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>48</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>43</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>43</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>29</td>
<td>7</td>
</tr>
<tr>
<td>AST increase</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Blood creatinine increase</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>QT prolongation</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>ALT increase</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

- No Grade 4 or 5 TRAEs
- No TRAEs led to discontinuation

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAE, treatment-related adverse event.
\(^a\)Excluding NSCLC and CRC; \(^b\)Occurring in ≥10% of patients; \(^c\)Overall population included 12 other non-GI cancers (ovarian [n=4], endometrial [n=2], breast [n=1], glioblastoma [n=1], and unknown primary [n=4]); \(^d\)Excluding CRC. Data as of 10 Sept 2021 (median follow-up: 6.3 months).
Conclusions

- Adagrasib is a KRAS\textsuperscript{G12C}-selective covalent inhibitor with a long half-life that enables exposure above a target threshold throughout the dosing interval.

- Adagrasib monotherapy demonstrated promising clinical activity and 100% disease control in previously treated patients with PDAC and other GI (non-CRC) tumors harboring a KRAS\textsuperscript{G12C} mutation.
  - Of the tumor histologies with >5 patients evaluable, response rates for PDAC and biliary tract cancer were 50%.

- Adagrasib has now demonstrated responses across multiple tumor types (NSCLC, CRC, PDAC, biliary tract, GEJ, small bowel, ovarian and endometrial cancers)\textsuperscript{1–3}

- Adagrasib monotherapy is well tolerated and has a manageable safety profile.

- Further exploration of adagrasib is ongoing in the KRYSTAL-1 trial (NCT03785249), and a newly initiated early access program (NCT05162443) is available to this patient population.

Acknowledgments

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