Targeting the genetic and immunological drivers of cancer

A phase 1 clinical trial evaluating the pharmacokinetics (PK), safety, and clinical activity of MRTX849, a mutant-selective small molecule KRAS G12C inhibitor, in advanced solid tumors

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MRTX849 Demonstrates Near Complete Target Inhibition and Broad Spectrum Antitumor Activity In Nonclinical Models

Modification of KRAS<sup>G12C</sup> Protein and Inhibition of pERK

- MRTX849 demonstrates near-complete modification of KRAS<sup>G12C</sup> protein and inhibition of pERK – and is well tolerated – at 100 mg/kg
- Protein binding-corrected plasma exposure in human exceeds levels in mouse at 100 mg/kg
- Response rate in nonclinical CDX and PDX models is 65% in all models and 75% in NSCLC models

Antitumor Activity of MRTX849 in Cancer Models

Concomitant mutations in TP53, KEAP1, or STK11 do not predict MRTX849 therapeutic response
Study Population
• Solid tumor with KRAS (p.G12C) mutation based on Sponsor-approved test
• Unresectable or metastatic disease
• No available treatment with curative intent
• No active brain metastases

Study Endpoints
• Safety
• PK/PD
• Clinical Activity

Expansion Criteria
• Dose expansion decisions prior to MTD will be based on PK, PD, and safety

Doses Evaluated (as of 11-Oct-2019)

- 150 mg (QD) N=1
- 300 mg (QD) N=2
- 600 mg (QD) N=1
- 600 mg (BID) N=1
- 1200 mg QD N=1
- 600 mg BID N=1
- Further dose escalation to MTD may continue

ClinicalTrials.gov Identifier: NCT03785249
Patient Disposition

**Enrolled Patients**
(received ≥ 1 dose MRTX849)

- N=17
- 10 NSCLC, 4 CRC, 2 Appendiceal, 1 Duodenal

**Evaluable Patients**
(received ≥ 1 scan)

- N=12
- 6 NSCLC, 4 CRC, 2 Appendiceal

**Non-Evaluable Patients**

- Yet to have 1st scan
  - N=3
- Off treatment prior to 1st scan
  - N=2*

* 1 patient withdrew consent prior to 1st scan (1200 mg QD);
  1 patient discontinued treatment due to an unrelated AE prior to 1st scan (600 mg QD)

Data cut-off date: 11-Oct-2019
## Patient Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>N=17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – median (range), years</td>
<td>60 (44-76)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White, n (%)</td>
<td>15 (88)</td>
</tr>
<tr>
<td>Black, n (%)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Asian, n (%)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>9 (53)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>8 (47)</td>
</tr>
<tr>
<td>ECOG Performance Status</td>
<td></td>
</tr>
<tr>
<td>0, n (%)</td>
<td>10 (59)</td>
</tr>
<tr>
<td>1, n (%)</td>
<td>7 (41)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Non-Small Cell Lung Cancer, n (%)</td>
<td>10 (59)</td>
</tr>
<tr>
<td>Colorectal Cancer, n (%)</td>
<td>4 (24)</td>
</tr>
<tr>
<td>Other Tumor Type, n (%)</td>
<td>3 (18)</td>
</tr>
</tbody>
</table>

Data cut-off date: 11-Oct-2019
## Patient Population

<table>
<thead>
<tr>
<th></th>
<th>All Patients N=17</th>
<th>NSCLC N=10</th>
<th>CRC N=4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Smoking History</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime Never Smoker</td>
<td>5 (29)</td>
<td>0</td>
<td>3 (75)</td>
</tr>
<tr>
<td>Former Smoker</td>
<td>12 (71)</td>
<td>10 (100)</td>
<td>1 (25)</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>16 (94)</td>
<td>10 (100)</td>
<td>3 (75)</td>
</tr>
<tr>
<td><strong>No. Prior Regimens</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1, n (%)</td>
<td>4 (24)</td>
<td>2 (20)</td>
<td>0</td>
</tr>
<tr>
<td>2, n (%)</td>
<td>1 (6)</td>
<td>1 (10)</td>
<td>0</td>
</tr>
<tr>
<td>≥3, n (%)</td>
<td>12 (71)</td>
<td>7 (70)</td>
<td>4 (100)</td>
</tr>
<tr>
<td>Median (Range)</td>
<td>3 (1-9)</td>
<td>3 (1-9)</td>
<td>4 (3-5)</td>
</tr>
<tr>
<td><strong>Type of Prior Regimens</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Checkpoint Inhibitor¹, n (%)</td>
<td>10 (59)</td>
<td>9 (90)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Cisplatin or Carboplatin, n (%)</td>
<td>10 (59)</td>
<td>10 (100)</td>
<td>0</td>
</tr>
<tr>
<td>Oxaliplatin, n (%)</td>
<td>5 (29)</td>
<td>0</td>
<td>4 (100)</td>
</tr>
<tr>
<td>Irinotecan, n (%)</td>
<td>6 (35)</td>
<td>1 (10)</td>
<td>4 (100)</td>
</tr>
</tbody>
</table>

¹Includes pembrolizumab, nivolumab, atezolizumab regimens

Data cut-off date: 11-Oct-2019
Mean MRTX849 Plasma Concentrations Following Single and Multiple Oral Dose Administration QD and BID

The cave achieved at 600 mg BID at steady-state is:

- 2-fold above concentration associated with maximal efficacy in resistant models (1450 ng/ml)
- 5-fold above concentration associated with maximal efficacy in sensitive models (600 ng/ml)

### 600 mg BID GeoMean (CV%)

<table>
<thead>
<tr>
<th>Period</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</th>
<th>AUC&lt;sub&gt;0-24&lt;/sub&gt; (ug*h/mL)</th>
<th>C&lt;sub&gt;ave&lt;/sub&gt; (ng/mL)</th>
<th>t&lt;sub&gt;½&lt;/sub&gt; (h)</th>
<th>t&lt;sub&gt;½_eff&lt;/sub&gt; (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 (N=12)</td>
<td>513 (101.0)</td>
<td>12.1 (69.5)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>318 (79.8)</td>
<td>24.7&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>Steady State (N=10)</td>
<td>3180 (50.4)</td>
<td>69.8 (58.6)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2880 (51.4)</td>
<td>-</td>
<td>63.2 (76.6)</td>
</tr>
</tbody>
</table>

Median (Min-Max); *N=9; *N=1 (Only 1 patient contributed to the lead-in 96 hours post-dose sampling); Data Source: Interim Pharmacokinetic Data (14 October 2019)
Patient Incidence of Treatment Related AEs (>10%)
The MTD has not yet been established

<table>
<thead>
<tr>
<th>Treatment-Related AEs (N=17)</th>
<th>Grade 1 n</th>
<th>Grade 2 n</th>
<th>Grade 3 n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>6</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>AST Increased</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ALT Increased</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Creatinine Increased</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal Distension</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alkaline Phosphatase Increased</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment-Related AEs (N=17)</th>
<th>Grade 1 n</th>
<th>Grade 2 n</th>
<th>Grade 3 n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Dehydration</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>QT Prolonged</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Dose limiting toxicities observed: 1200 QD capsule burden intolerable (12 capsules), limited dose exposure <80%; 600 mg BID grade 3/4 amylase/lipase increase, isolated enzyme elevation without pancreatitis (only treatment related Grade 4 AE observed)

Data cut-off date: 11-Oct-2019
All Evaluable Patients: Best Tumor Response* (N = 12)

-70% -60% -50% -40% -30% -20% -10% 0% 10% 20% 30%

Maximum % Change from Baseline

Dose: 150 mg (QD) 300 mg (QD) 600 mg (QD) 600 mg (BID)

**CRC**
- SD 5%

**NSCLC**
- SD 1%
- PR 1%
- SD 0%
- SD 0%
- SD -1%
- SD -2%
- SD -7%
- SD -14%
- SD -21%
- SD -36%
- SD -43%
- SD -47%
- SD -62%
- SD -70%

**Evaluable Patients at All Doses**

<table>
<thead>
<tr>
<th>Disease</th>
<th>ORR</th>
<th>DCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>3/6</td>
<td>6/6</td>
</tr>
<tr>
<td>CRC</td>
<td>1/4</td>
<td>3/4</td>
</tr>
<tr>
<td>Append</td>
<td>0/2</td>
<td>2/2</td>
</tr>
</tbody>
</table>

- DCR: Disease Control Rate (SD+PR at 6 weeks)

* Based on local radiographic scans every 6 weeks using RECIST 1.1 criteria
† Confirmed response (1st scan: -37%, 2nd scan: -47%); ‡ Response yet to be confirmed (on study but only 1 scan)
§ Patient had confirmed PR post data cut-off (1st scan: -33%, 2nd scan: -43%)
○ Patient on study (off study patients: 1 progressive disease, 1 global deterioration of health, 1 patient withdrawal of consent)

Data cut-off date: 11-Oct-2019
600 mg BID Dose Patients: Best Tumor Response* (N = 9)

- Based on local radiographic scans every 6 weeks using RECIST 1.1 criteria
- Confirmed response (1st scan: -37%, 2nd scan: -47%); † Response yet to be confirmed (on study but only 1 scan);
- § Patient had confirmed PR post data cut-off (1st scan: -33%, 2nd scan: -43%)
- ○ Patient on study (off study patient: 1 patient withdrawal of consent)

Data cut-off date: 11-Oct-2019
Case Study #1: NSCLC

Demographics
61 year old female with metastatic NSCLC, former smoker

Molecular Characteristics
• KRAS G12C mutation (c.34G>T), High mutant allele freq
• High TMB: 16.7 mut/megabase, no additional notable mutations

Treatment History
• Cisplatin/pemetrexed with concurrent chemoradiation
• RLL wedge resection and LLL lobectomy
• 8 chemotherapy regimens for recurrent disease, including carboplatin/pemetrexed, selumetinib, carboplatin/gemcitabine, gemcitabine monotherapy, pembrolizumab, vinorelbine, irinotecan, and paclitaxel, all without an objective response.

Best Response
PR: 62% reduction at first scan. The patient remains on study.
Prominent neck mass noted smaller by week 1 and no longer detectable by week 2. Notable increase in energy and activity during continued treatment.
Case Study #2: NSCLC

Demographics
45 year old female with metastatic lung adenocarcinoma, former smoker

Molecular Characteristics
• KRAS G12C mutation (c.34G>T)
• KEAP1 (K97M)
• STK11 (E223*)

Treatment History
• Carboplatin/pemetrexed/pembrolizumab
• Docetaxel
• Investigational treatment with binimetinib plus palbociclib
• Best response on prior regimens is SD

Best Response
PR: 33% reduction at first scan. A 43% reduction was observed at the second scan, after the data cut-off. The patient remains on study.

Marked clinical improvement within 2 weeks, including complete resolution of baseline cough and oxygen dependency.

§ This patient had confirmed PR post data cut-off (1st scan: -33%, 2nd scan: -43%)
Case Study #3: CRC

Demographics

47 year old KRAS (p.G12C) female with adenocarcinoma of the left colon with extensive metastases involving the liver, peritoneum, ovaries and lymph nodes, never smokers

Treatment History

• FOLFOX/bevacizumab, partial response
• Capecitabine monotherapy, no response
• FOLFIRI/bevacizumab, no response
• Investigational antibody drug conjugate, no response

Best Response

PR: 37% reduction at first scan, confirmed PR with 47% reduction at second scan. The patient remains on study.

Marked clinical improvement within 3 weeks and a visible decrease in size of her umbilical Sister Mary Joseph’s nodule
Duration of Treatment by Tumor Types and Responses (N=12)

CRC Appendiceal Tumor Type:
- NSCLC (N=6): 6.7 – 38.6 weeks
- CRC (N=4): 9.9 – 30.1 weeks
- Appendiceal (N=2): 10.7 – 20.7 weeks

Data cut-off date: 11-Oct-2019

Dose:  
- a. 150 mg QD  
- b. 300 mg QD  
- c. 600 mg QD  
All other patients received 600 mg BID
Conclusions

• MRTX849 is rationally designed, potent, mutant-selective inhibitor of KRAS$^{G12C}$ that irreversibly binds to and locks KRAS$^{G12C}$ in its inactive, GDP-bound state

• MRTX849 is orally bioavailable and demonstrates linear pharmacokinetics with extensive tissue distribution and a half-life of approximately 25 hours after a single dose (effective $t_{1/2}$ at SS is 63 h)

• MRTX849 is associated with a favorable safety profile and clinical expansion is being pursued at 600 mg BID
  • Expansion cohorts for NSCLC, CRC, and multi-tumor basket underway

• MRTX849 has demonstrated significant clinical activity in heavily pretreated patients, with objective responses observed in patients without responses to prior treatment regimens

• Clinical activity supports the role for inhibition of mutant KRAS in cancer treatment
With Thanks to Patients, Caregivers, Research Staff, and Investigators

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