MRTX0902: A SOS1 inhibitor for therapeutic intervention of KRAS-driven cancers

Jacob R. Haling, Director or Biology
Mirati Therapeutics, San Diego, CA
Disclosure Information

Jacob Haling

I have the following relevant financial relationships to disclose:

Employee of: Mirati Therapeutics
Stockholder in: Mirati Therapeutics
Dysregulation of KRAS/MAPK pathway is one the most frequent causes of cancer
>200K deaths in the US due to NSCLC, CRC, and PDAC (2021 Estimated Deaths – NCI)

Targeted KRAS G12C inhibitors will improve the outcome for a subset of these patients

Additional therapies that enhance KRAS inhibition and/or target additional mutations may increase durability of response or expand the spectrum of targetable patients
Son of Sevenless homolog 1 (SOS1) Directly Binds and Activates KRAS

- SOS1 is a guanine nucleotide exchange factor (GEF) that binds to KRAS and promotes the exchange of KRAS-bound GDP for GTP and facilitates activation of the RAF-MEK-ERK kinases
- SOS1 mediates negative feedback inhibition upon RAF-MEK-ERK activation
RTK-mediated Acquired Resistance may be Sensitive to SOS1 Inhibition

• RTK amplification and/or mutations are clinically relevant mechanisms of acquired resistance
• SOS1 represents a potential universal node in cases of RTK-mediated resistance
SOS1 Inhibition Shifts KRAS<sup>G12C</sup> into an Inactive State and Augments MRTX849 Activity

**SOS1 Activates KRAS<sup>G12C</sup>**

- RTKs (EGFR Family) → SOS1 → GDP-KRAS<sup>G12C/D</sup> → GTP-KRAS<sup>G12C</sup> → MRTX849

**Combination Strategy**

- RTKs (EGFR Family) → SOS1 → MRTX0902 → GDP-KRAS<sup>G12C</sup> → GTP-KRAS<sup>G12C</sup> → MRTX849

- **KRAS G12C covalent inhibitors such as adagrasib bind to KRAS-GDP**

- **SOS1 inhibition has synergistic antitumor activity when combined with MRTX849; synergy also observed with additional KRAS inhibitors**

- **MRTX0902 represents a potential best-in-class SOS1 inhibitor with efficacy comparable to literature molecules**
Discovery team utilized a structure-enabled approach to design Mirati SOS1 inhibitors that push into the SOS1:KRAS interface, thereby disrupting the protein-protein interaction (PPI).
SOS1 Inhibitor Optimization to MRTX0902

MRTX7496
pERK IC_{50} = 134 nM

MRTX9528
pERK IC_{50} = 87 nM

MRTX9416
pERK IC_{50} = 39 nM

MRTX0902
pERK IC_{50} = 33 nM

- Designed and elaborated a novel series of phthalazine based SOS1 inhibitors
- Addition of C4-substituent blocked AO metabolism without loss of cellular potency
- Azaphthalazine core increased permeability and potency, while minimizing time-dependent inhibition of CYP3A4
- Installation of nitrile on the right-hand side of the molecule further lowered CYP3A4 inhibition
### MRTX0902 Meets Development Candidate Criteria

<table>
<thead>
<tr>
<th>Assay</th>
<th>Criteria</th>
<th>MRTX0902</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOS1 Binding / Cell pERK IC&lt;sub&gt;50&lt;/sub&gt; (nM)</td>
<td>Potent binder with good cell activity</td>
<td>2 / 33</td>
</tr>
<tr>
<td>SOS2 Binding IC&lt;sub&gt;50&lt;/sub&gt; (nM)</td>
<td>Weak binder</td>
<td>&gt; 100,000</td>
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<tr>
<td>In vivo Pharmacology: KRAS G12C TGI</td>
<td>Improved efficacy in combination with adagrasib</td>
<td>✓</td>
</tr>
<tr>
<td>Pharmacokinetic Profile (m/r/d/cy): Bioavailability (lowest doses)</td>
<td>High projected human oral bioavailability &amp; exposure</td>
<td>69% / 83% / 38% / 20%</td>
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<tr>
<td>CYP3A4 Induction</td>
<td>Low CYP Induction risk</td>
<td>✓</td>
</tr>
<tr>
<td>Toxicity Assessment in Rat and Dog</td>
<td>≥ 1-fold safety margin</td>
<td>✓</td>
</tr>
<tr>
<td>Predicted human dose</td>
<td>&lt; 1 g/day</td>
<td>✓</td>
</tr>
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**Co-Crystal Structure of SOS1:MRTX0902**

- MRTX0902 exhibits promising potency, selectivity, and exposure in preclinical species
- Regulatory toxicology (GLP) studies have completed with minimal gross observations or clinical signs at top dose levels enabling starting doses approaching efficacious dose range
MRTX0902 Demonstrates Strong In Vivo Efficacy and PD Target Modulation

MIA PaCa-2 (KRAS$^{G12C}$)

- Combination of MRTX0902 + MRTX849 results in -92% regression, tumor free animals and correlative PD modulation
- Plasma concentration of MRTX849 remains unchanged when co-dosed with MRTX0902
MRTX0902 in Combination with MRTX849 Demonstrates Durable Regression in KRAS\textsuperscript{G12C} NSCLC and CRC PDX Models

- Combination of MRTX0902 + MRTX849 results in sustained tumor regression in LU11692 (-57%) and CR6256 (-80%) and early onset of tumor free animals in the CR6256 model
- 100 mg/kg QD MRTX849 is the maximally efficacious preclinical dose
Combination Treatment with MRTX0902 and MRTX849 Leads to Broad Antitumor Activity in KRAS<sup>G12C</sup>-Mutant Human Tumor Xenograft Models

**MRTX0902/MRTX849 Efficacy**

Study day ~28

- Improved efficacy observed with combination of MRTX0902 + MRTX849 in 8 of 10 models tested

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Model</th>
<th>In vivo effect: MRTX849</th>
<th>In vivo effect: MRTX0902 + MRTX849</th>
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<tbody>
<tr>
<td>MIA PaCa-2</td>
<td>CDX</td>
<td>94% TGI*</td>
<td>-92% Regression*</td>
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<tr>
<td>LU99</td>
<td>CDX</td>
<td>99% TGI*</td>
<td>-91% Regression*</td>
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<tr>
<td>CR6256</td>
<td>PDX</td>
<td>99% TGI</td>
<td>-80% Regression</td>
</tr>
<tr>
<td>LU11692</td>
<td>PDX</td>
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<td>H2122</td>
<td>CDX</td>
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<td>LU2512</td>
<td>PDX</td>
<td>95% TGI</td>
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<td>KYSE-410</td>
<td>CDX</td>
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<td>75% TGI</td>
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<td>SW1573</td>
<td>CDX</td>
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<td>71% TGI</td>
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<tr>
<td>CR2528</td>
<td>PDX</td>
<td>27% TGI</td>
<td>53% TGI</td>
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*Sub-ailfieacious dose of 10 or 30 mg/kg QD MRTX849 was tested. Max-effieacious dose of 100 mg/kg QD MRTX849 was tested in combination with MRTX0902 unless otherwise annotated. TGI = tumor growth inhibition.
Rational MAPK Combinations with MRTX0902 Demonstrate Improved Efficacy

- Combination of 50 mg/kg MRTX0902 BID with osimertinib (EGFRi), VS-6766 (RAF/MEKc), or VS-6766 + MRTX849 improves depth of response in MAPK addicted tumor models
- Triple combination prevents feedback-mediated reactivation of the MAPK pathway
SOS1 Inhibition Prevents Feedback-mediated Reactivation of the MAPK Pathway

• SOS1 inhibition prevents pathway reactivation mediated by RAF/MEK and KRAS inhibition

• Additional KRAS\textsuperscript{MT} models are being evaluated using a similar approach with MRTX0902 combinations
SOS2, the paralog of SOS1 has some functional redundancy but is largely viewed as having a minimal role in KRAS activation.

In vitro and in vivo data suggests that SOS2 can compensate for the loss/inhibition of SOS1.
Summary

• MRTX0902 was selected as the development candidate and is currently in IND-enabling studies; IND filing anticipated in 2H 2022

• MRTX0902 exhibits promising potency, selectivity, and oral exposure in preclinical species
  • Please see John Ketcham’s e-poster for more; abstract # LB505

• The combination of MRTX0902 with MRTX849 enhances the depth and durability of an anti-tumor response when compared to MRTX849 alone in pre-clinical KRAS\textsuperscript{G12C} tumor models

• Clinical development plan is to initially pursue MRTX0902/MRTX849 combination followed by additional MAPK combinations pending pre-clinical evaluations

• Compensatory role for SOS2 identified in functional genomics studies
  • Please see Shilpi Khare’s poster on Wednesday April 13 for more; abstract # LB193
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