Design and Discovery of MRTX0902, a Potent, Selective, and Orally Bioavailable SOS1 Inhibitor

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Background:

- Activating mutations of KRAS lead to hyperproliferation and aberrant signaling within the MAPK pathway.
- Many of these mutations are single codon mutations (G12, Q61, G61, etc.) and are the most common driver mutations in human cancers.
- The Son of Sevenless (SOS) protein is a guanine nucleotide exchange factor (GEF) that facilitates the ability of KRAS to turnover from its GDP-bound state to its GTP-bound “on” state.
- Two mechanisms of SOS exist (SOS1 and SOS2) that impact GEF activity onto KRAS, however, only SOS1 is involved in the negative feedback loop of the KRAS pathway.
- Functional genomic screens have identified cancer cell lines addicted to KRAS signaling that are particularly sensitive to generic perturbation of SOS1.
- Gain-of-function mutations of SOS1 are reported in Noonan’s syndrome and hereditary gingival fibromatosis (HGFI) and are less prevalent in human cancer.
- With the promising clinical activity of our CR001/500 inhibitor adelapag (MRTX849), a combination approach with a SOS1 inhibitor could help to address this SOS1-driven state.
- Additionally, SOS1 inhibition can be an indirect approach to targeting other KRAS-mutated cancers.

Role of SOS1 in the RAS/MAPK Pathway

SOS1 Activates KRAS

RTKs (EGFR Family)

HSP90

Activation

GTP

SOS1

SOS1

Deletion

SOS1

Inhibitor

GTP

KRAS

Quasi

SOS1

SOS1

Inhibitor

GTP

KRAS

Combination Strategy

SOS1 Inhibitor

RTKs (EGFR Family)

HSP90

GTP

SOS1

SOS1

Deletion

SOS1

Inhibitor

GTP

KRAS

Quasi

SOS1

SOS1

Inhibitor

GTP

KRAS

Designing a New Class of SOS1 Inhibitors

- 2-12 quinazolines have been the primary focus of SOS1 inhibitor design.
- Newly designed phthalazine scaffold can provide distinct physicochemical properties when compared to previously reported inhibitors.
- Phthalazines block EGFR binding without the need for 2-ethyl substituent.

Initial SAR for Simplified Phthalazines

<table>
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<th>Compound</th>
<th>IC50 (nM)</th>
<th>Activity</th>
<th>EGFR IC50 (nM)</th>
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Representative SAR leading to MRTX0902

- Deletion of the C8-methyl ether and installation of a C7-piperazine resulted in increased cellular potency.
- Combination of the arylpiperazine core with a C7-morpholine led to high potency.
- Replacing the 3-CF3 phenyl substituent with a 3-cyano resulted in lower DD risk.
- Phthalalene core shares 95% matching similarity with MRTX849.
- Not from the C8-carboxyl amine substituent creates a crucial hydrogen bond with Tyr884.
- Chiral benzyl benzylic amine core fits a small hole and facilitates into the hydrophobic back pocket.
- Proteolipid N-terminus within the phthalazine conveys a salt bridge with the carboxylate of Glu890.
- C7-morpholine pushes into the KRAS-SOS1 interface and blocks the protein-protein interaction.

MRTX0902 with MRTX849 Results in Complete Regression in KRAS<sup>G12D</sup> MIA PaCa-2 Model

- Co-Crystal Structure of SOS1-MRTX0902

MRTX0902 Pharmacokinetic Profile

- MRTX0902 displays clearance less than 22% of hepatic blood flow and bioavailability of 38-65% across species.

MRTX0902 in Vitro Profile

- C4-methyl blocks AO metabolism without loss in timing and cellular potency.

Conclusions:

- Through rational design, we have discovered MRTX0902—a potent, selective, and orally bioavailable inhibitor of SOS1 that is brain penetrant.
- MRTX0902 in combination with our KRAS<sup>G12D</sup> inhibitor MRTX849 yields enhanced MAPK pathway inhibition and combined tumor regression in the KRAS<sup>G12D</sup> MIA PaCa-2 Model.
- MRTX0902 is currently in IND-enabling studies, planned submission in 2H 2020.

Acknowledgements and References