Development of MRT-2359, an orally bioavailable GSPT1 molecular glue degrader, for the treatment of lung cancers with MYC-induced translational addiction

Gerald Gavory, Ph.D.
Monte Rosa Therapeutics, Boston MA & Basel Switzerland
Disclosure Information

Gerald Gavory

I have the following relevant financial relationships to disclose:

   Employee of Monte Rosa Therapeutics
   Stockholder in Monte Rosa Therapeutics
Targeting MYC-driven Tumors and Their Addiction to Protein Translation

1. Addiction
   To sustain growth, MYC-driven tumors are addicted to protein translation.

2. Dependency
   This addiction creates a dependency on the translation termination factor GSPT1.

3. Therapeutic vulnerability
   GSPT1 is a therapeutic vulnerability of MYC-driven tumors which can be targeted using molecular glue degrader (MGD).
MRT-2359 is a Highly Selective, Orally Bioavailable GSPT1 MGD with a Favorable ADMET Profile

**Biochemical and cellular data**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRBN binding (HTRF; $K_i$)</td>
<td>113 nM</td>
</tr>
<tr>
<td>Ternary complex (HTRF; $EC_{50}$)</td>
<td>7 nM</td>
</tr>
<tr>
<td>CRBN dependency (KO, multiple lines)</td>
<td>Yes</td>
</tr>
<tr>
<td>G-loop dependency (G575N mut., multiple lines)</td>
<td>Yes</td>
</tr>
<tr>
<td>Selectivity (proteomics)</td>
<td>GSPT1 / GSPT2</td>
</tr>
<tr>
<td>Degradation DC$<em>{50}$/D$</em>{max}$ (in disease relevant lines)</td>
<td>1-20 nM / 100%</td>
</tr>
<tr>
<td>Viability EC$_{50}$ (in disease relevant MYC high lines)</td>
<td>2-80 nM</td>
</tr>
</tbody>
</table>

**ADMET profile**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP DDIs (7 isoforms)</td>
<td>&gt; 30 µM</td>
</tr>
<tr>
<td>CEREP (Safety panel 44)</td>
<td>None</td>
</tr>
<tr>
<td>hERG inhibition (patch clamp)</td>
<td>EC$_{50}$ &gt; 30 µM</td>
</tr>
<tr>
<td>Oral bioavailability (all species)</td>
<td>~50%</td>
</tr>
</tbody>
</table>
MRT-2359 is a Highly Selective Recruiter and Degrader of GSPT1

MRT-2359 is a potent inducer of GSPT1-cereblon proximity

MRT-2359 is highly selective against common neosubstrates of CRBN

100 nM MRT-2359, 1hr post treatment

6hr post treatment in MM1S and Kelly (SALL4)
MRT-2359 Shows Preferential Activity in MYC High or Neuroendocrine (NE) Positive Lung Cancer Lines

**N-MYC - NSCLC lines**

![Graph showing viability vs MRT-2359 concentration for N-MYC high and low lines.](image)

- **High N-MYC**
  - NCI-H1155
  - ABC-1
- **Low N-MYC**
  - NCI-H2023
  - NCI-H441

**L-MYC - SCLC lines**

![Graph showing viability vs MRT-2359 concentration for L-MYC high and low lines.](image)

- **High L-MYC**
  - NCI-H1836
  - NCI-H1876
- **Low L-MYC**
  - NCI-H2286
  - NCI-H196

**NE positive lung lines**

![Graph showing viability vs MRT-2359 concentration for NE positive lines.](image)

- **High NE**
  - NCI-H810
  - NCI-H1770
- **Low NE**
  - NCI-H2405
  - NCI-H1693

All cell lines are L-MYC and N-MYC low

*72 hr viability assay (CTG)*
MRT-2359 Preferential Activity in MYC High Lung Cancer Lines is Unique

Other therapeutic agents targeting protein translation process or machinery lack preferential activity in the MYC high lung lines

MRT-2359

initiation inhibitor (eIF4Ai, Zotatifin)

elongation inhibitor (Homoharringtonine)

mTOR inhibitor (Rapamycin)

Cytotoxic (Doxorubicin)

Similarly for agent targeting Myc transcriptional reprogramming

Clinical CDK9 inhibitor

EC50 (µM)

72 hr viability assay (CTG).

Monte Rosa Therapeutics – DO NOT POST - AACR Orlando, 17th April 2023
Three Mechanisms Driving Preferential Activity in MYC High Cancer Lines

**Preferential GSPT1 degradation**
MRT-2359 leads to rapid and deeper degradation of GSPT1 in cancer cells with high MYC expression

**Preferential inhibition of translation**
MRT-2359 preferentially impairs protein synthesis in tumor cells with high MYC expression

**MYC down modulation**
MRT-2359 indirectly affects MYC expression and transcriptional activity
The Sole Overexpression of MYC Sensitizes Initially Resistant NSCLC Cells to MRT-2359

**Consitutive N-MYC overexpression in NCI-H2023 cells**

**Consitutive L-MYC overexpression in NCI-H2023 cells**

Incucyte, 120 hr post treatment
MRT-2359 Induces a Faster and Deeper GSPT1 Degradation in the NCI-H2023 Line Overexpressing N-MYC

Doxycycline-inducible N-MYC NCI-H2023 cell line (4 days induction)
MRT-2359 Preferentially Impairs Protein Synthesis in Tumor Cells with High MYC Expression

MRT-2359 induces ribosome stalling at stop codon only in N-MYC high cell line

MRT-2359 completely abrogates protein synthesis only in N-MYC high cell line

High N-MYC
NCI-H1155

Low N-MYC
NCI-H2023

Puromycin incorporation
MRT-2359 Affects MYC and MYC Pathway in N-MYC High NSCLC Cell Lines

MRT-2359 induce GSPT1 degradation leading to N-MYC protein downregulation in NCI-H1155

Degradation of GSPT1 leads to downregulation of N-MYC transcriptional output in NCI-H1155

High N-MYC NCI-H1155

Low N-MYC NCI-H2023

Time course RNA-seq

Transcriptional modulation of >200 MYC target genes

Monte Rosa Therapeutics – DO NOT POST - AACR Orlando, 17th April 2023
MRT-2359 Induces Tumor Regressions in N-MYC-driven Xenograft Models

Oral dosing of MRT-2359 shows anti-tumor activity and regressions in NCI-H1155

Similar observations in other high N-MYC expression models (ABC-1, NCI-H1770)

Dose- and time-dependent degradation of GSPT1 is associated with N-MYC downregulation

Day 5

1 mg/kg

10 mg/kg
MRT-2359 Demonstrates Preferential Anti-tumor Activity in MYC High or Neuroendocrine (NE) Lung Cancer PDXs

**NSCLC**

- N-MYC and L-MYC low
- N-MYC or L-MYC high

**SCLC**

- N-MYC and L-MYC low

**NE Lung Cancer**

- Large cell NE carcinoma or NE lung cancer
- N-MYC and L-MYC low

MRT-2359 10 mg/kg, PO, QD
High Frequency of L-MYC and N-MYC Expression in NSCLC and SCLC from Real-world Data

NSCLC 3053 samples
- N=450 (15%)
- N=2603 (85%)

SCLC 188 samples
- N=136 (72%)
- N=52 (28%)

Demographic and Diseases Characteristic
- There is no notable difference in the proportion of MYC high expressors across disease staging, gender or racial groups

Treatment Outcomes
- No statistically significant associations between MYC high status and treatment outcomes
MRT-2359 is a Best-in-Class GSPT1-directed MGD for MYC-driven Tumors
Orally available and highly optimized towards MYC-driven solid tumor setting

- MRT-2359 is a **highly selective, orally bioavailable GSPT1 MGD** designed through our QuEENTM platform
- Has **optimal degradation kinetics** to achieve preferential activity in MYC-driven cancer cells
- Shows **preferential activity in MYC-driven cancer cells** of various solid tumor lineages, including **NSCLC and SCLC**
- Displays **preferential activity** across >70 primary human xenograft (PDX) models stratified for **MYC expression levels** as well as in **NE lung cancer PDX models**
- **IND cleared** for Phase 1/2 trial Sept. 2022 (NCT05546268)
- Patient **dosing initiated** Oct. 2022
Acknowledgments

MRT team

Project team

- Debora Bonenfant
- Silvia Buonamici
- Maciej Cabanski
- Lisa Cantagallo
- Qian Chen
- Agustin Chicas
- Cecile D’Alessandro
- Anna Diesslin
- Herve Farine
- Bernhard Fasching
- Gerald Gavory
- Mahmoud Ghandi
- Filip Janku
- Chris King
- Yimao Liu
- David Lyon
- Vittoria Massafra
- Rajiv Narayan
- Arnaud Osmont
- Asli Oztan Matos
- Vladas Oleinikovas
- Carolina Perdomo Ortiz
- Dave Peck
- Thomas Ryckmans
- Martin Schillo
- Ambika Singh
- Ralph Tiedt
- Simone Tortooli
- Peter Trenh
- Owen Wallace
- Markus Warmuth
- Lars Wiedmer