Preclinical and Mechanism of Action Studies of MRT-2359, a Potent and Selective GSPT1 Molecular Glue Degrader for the Treatment of MYC-driven Cancer

Silvia Buonamici | 5th Annual Targeted Protein Degradation Summit | October 27th, 2022

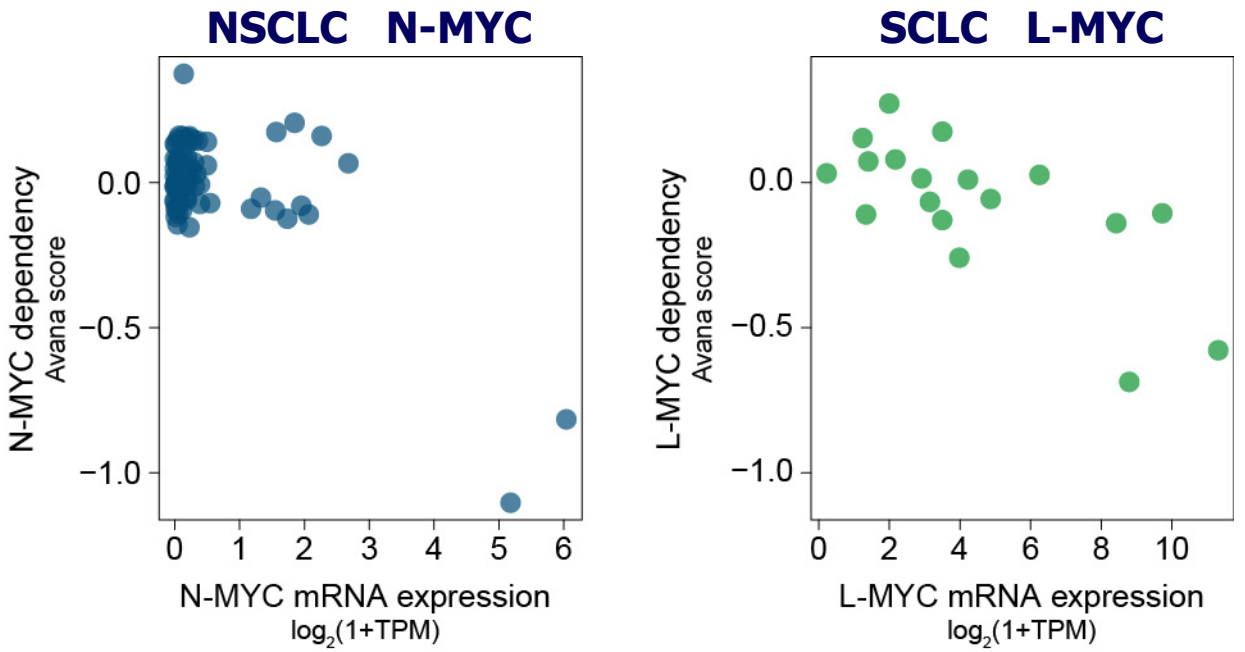
Monte Rosa Therapeutics

MYC Transcription Factors are Undruggable Oncogenes

MYC family members are amongst the most dysregulated oncogenes in human cancer

- MYC family: c-MYC, N-MYC, and L-MYC
- **MYC up-regulation** dysregulates key cellular processes (e.g. ribosome biogenesis and **protein synthesis**)
- **MYC dependency** is observed in **many cancer types**
- **MYC dysregulation** is frequently associated with **poor prognosis** and **unfavorable patient survival**

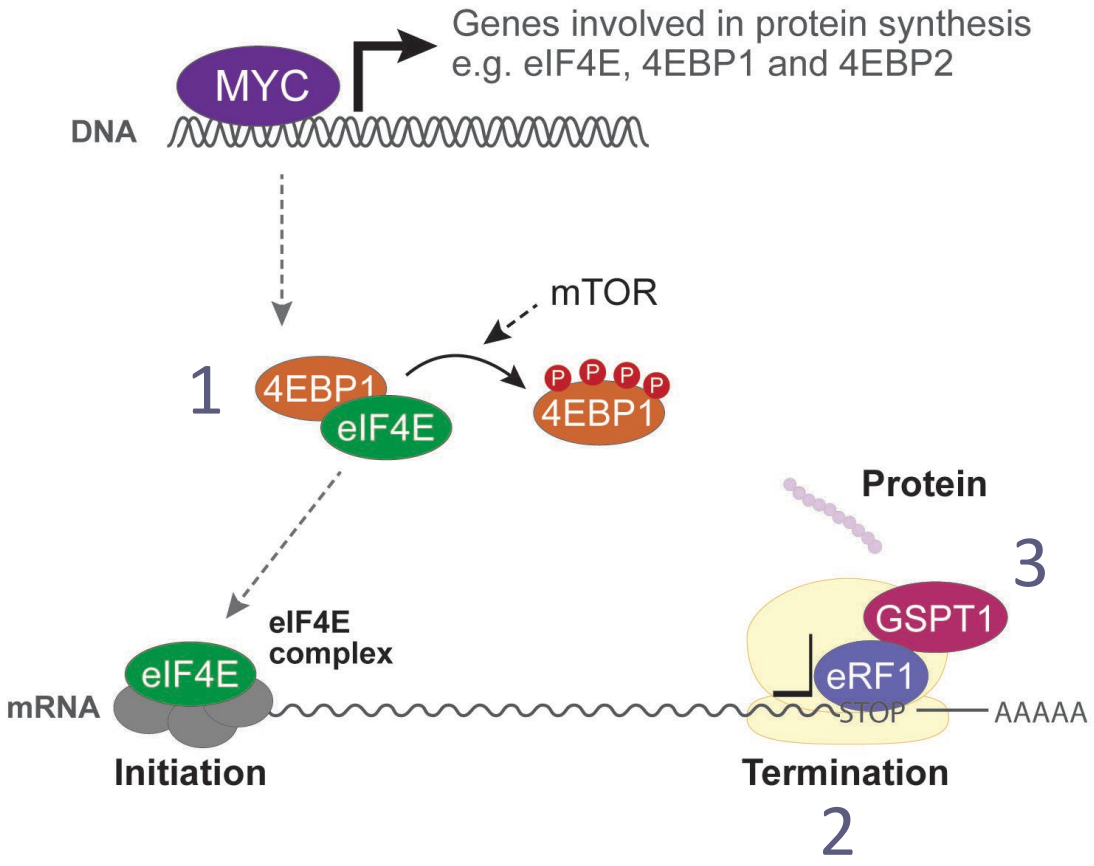
Cells expressing high MYC are sensitive to MYC CRISPR KO



DepMap data, each dot represents a cell line

Targeting enhanced translation induced by MYC represents an attractive alternative to direct targeting

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

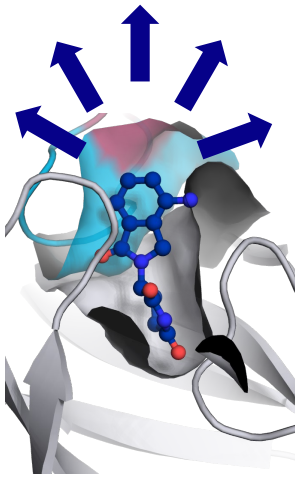
Therapeutic vulnerability

GSPT1 is a therapeutic vulnerability of MYC-driven tumors which can be targeted using MGD

QuEEN™ Discovery Engine Facilitates the Discovery of MRT-2359

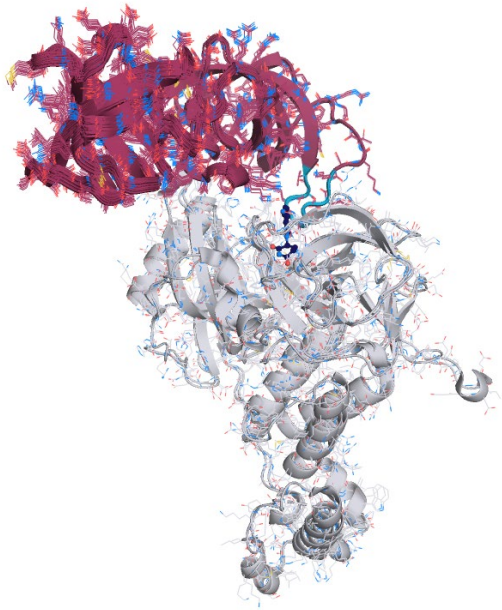
Proprietary MGD library

Diverse library, rationally designed, using structural insights to engage a variety of degrons

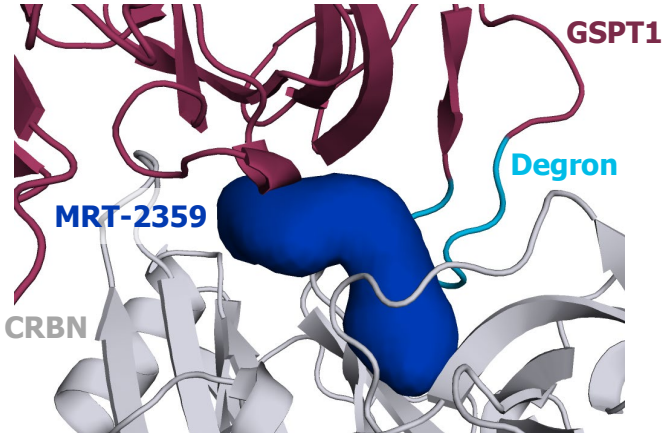


Rhapsody™

In silico ternary complex modelling using proprietary AI-powered algorithms



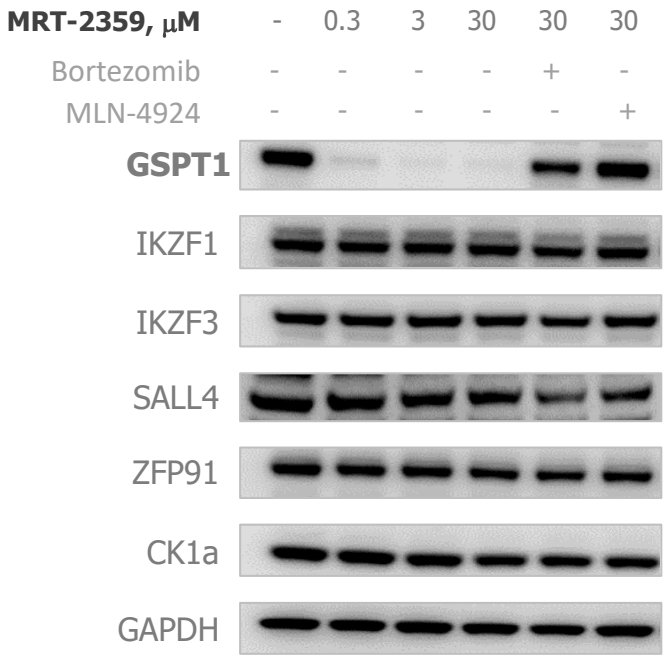
MRT-2359 is a potent GSPT1 degrader



in vitro **data**	
CRBN binding, K_i	113 nM
Ternary complex, EC_{50}	< 7 nM
Degradation, DC_{50}	80 nM

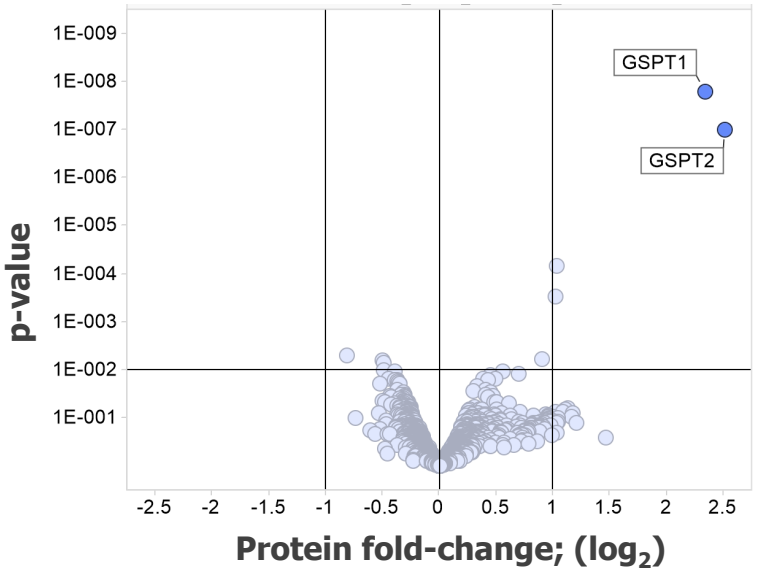
MRT-2359 is a GSPT1-directed MGD with Favorable Drug-like Properties

MRT-2359 is a selective GSPT1-directed MGD



6hr post treatment in MM1S and Kelly (SALL4)

Proximity – Turbo ID



1hr post treatment (CAL51)

MRT-2359 is orally bioavailable and has favorable ADMET profile

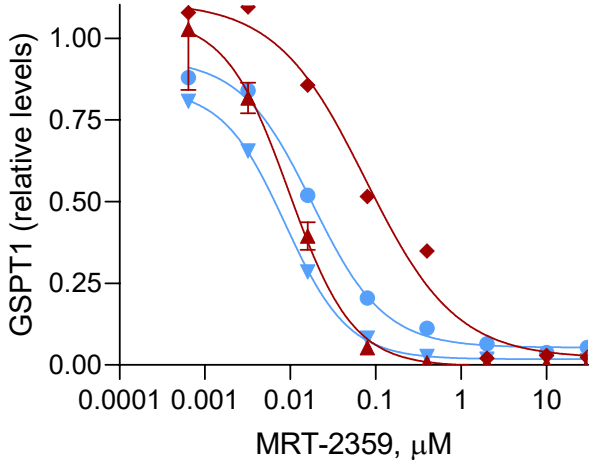
ADMET profile	
CYP DDIs	> 30 µM
hERG inhibition patch clamp	EC_{50} > 30 µM
Oral bioavailability all species	~50%

- MRT-2359 does not inhibit or induce major CYPs
- MRT-2359 does not inhibit hERG
- MRT-2359 is orally bioavailable

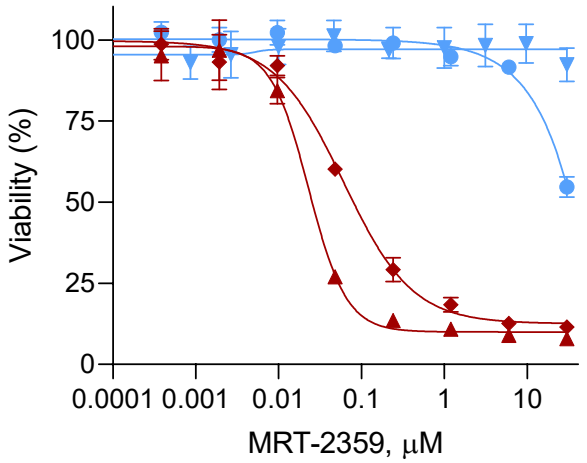
Preferential Activity of MRT-2359 in MYC-driven NSCLC Lines

MRT-2359 induces GSPT1 degradation in all cell models, but shows preferential antiproliferative activity in high N-MYC cell lines

GSPT1 degradation



Viability



High N-MYC

- NCI-H1155
- ABC-1

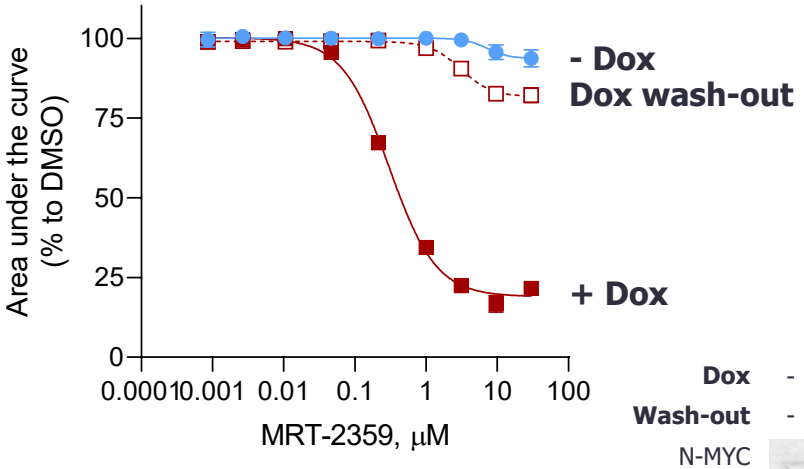
Low N-MYC

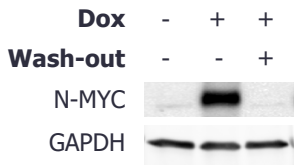
- NCI-H2023
- NCI-H441

GSPT1 western blot at 6 hr (N-MYC high) and 24 hr (low). 72 hr viability assay (CTG)

N-MYC overexpression sensitizes NCI-H2023 resistant cells to MRT-2359

Doxycycline-inducible N-MYC model



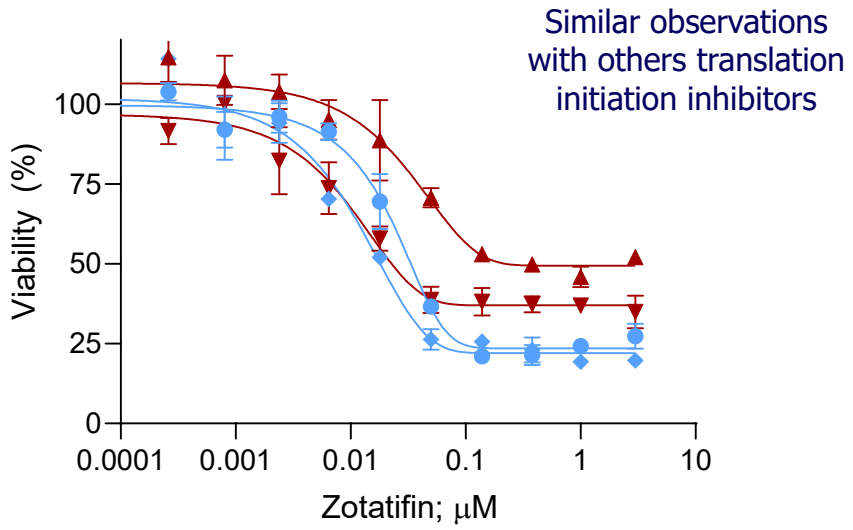


- NCI-H2023 Dox-inducible N-MYC **- Dox**
- NCI-H2023 Dox-inducible N-MYC **+ Dox**
- NCI-H2023 Dox-inducible N-MYC **Dox wash-out**

Incucyte, 96 hr post treatment

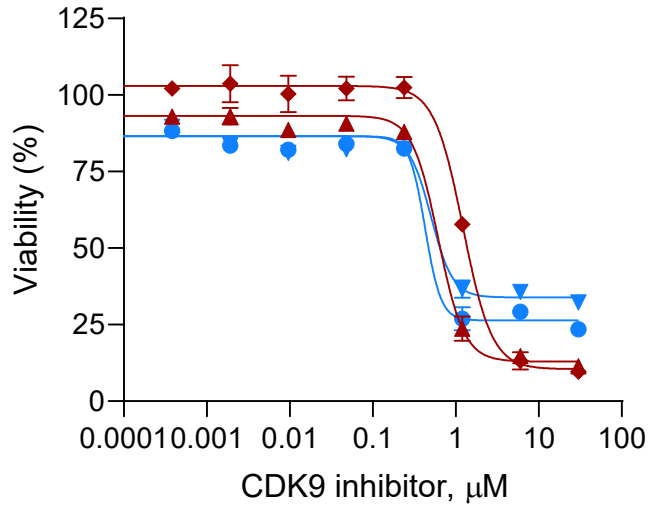
No Preferential Activity of Translation Initiation or CDK9 Inhibitors in NSCLC

No differential activity observed with translational initiation inhibitors



72 hr viability assay (CTG)

No differential activity observed with clinical CDK9 inhibitor



72 hr viability assay (CTG)

High N-MYC

- NCI-H1155
- ABC-1

Low N-MYC

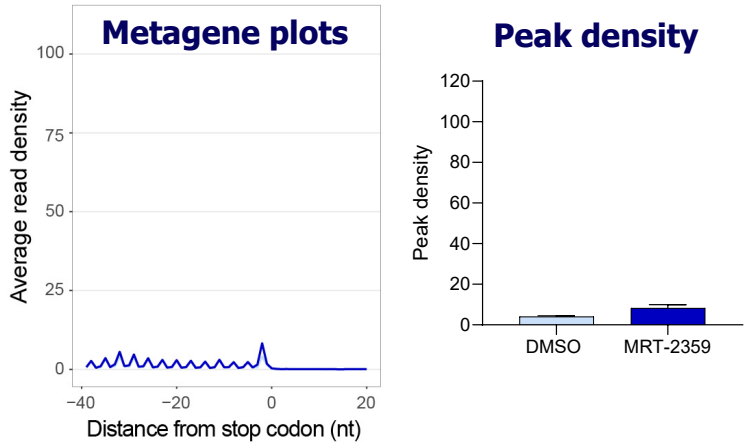
- NCI-H2023
- NCI-H441

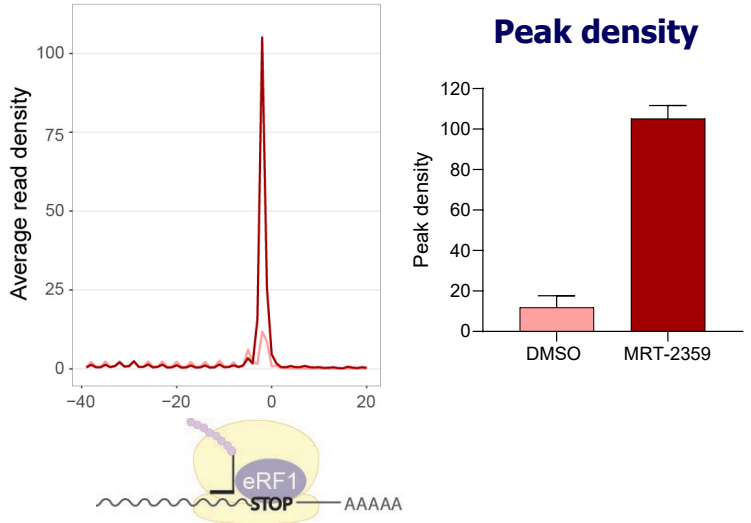
MRT-2359 Impairs Protein Synthesis in N-MYC High NSCLC Cell Lines

Low N-MYC
NCI-H2023

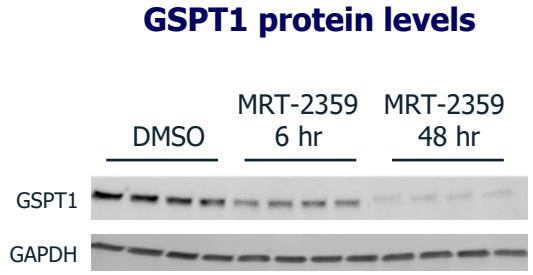
High N-MYC
NCI-H1155

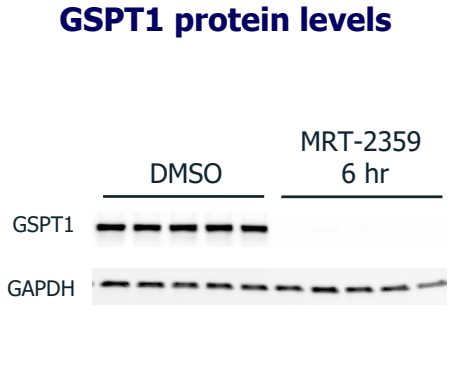
MRT-2359 induces ribosome stalling only in N-MYC high cell line





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

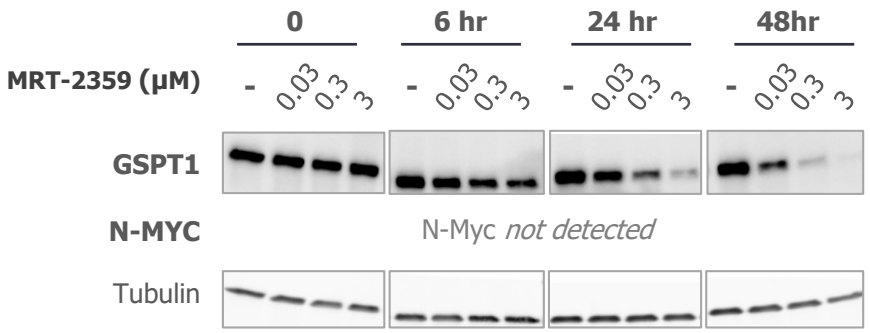




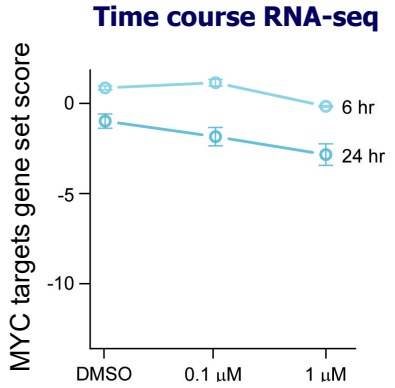
MRT-2359 Affects MYC and MYC Pathway in N-MYC High NSCLC Cell Lines

Low N-MYC
NCI-H2023

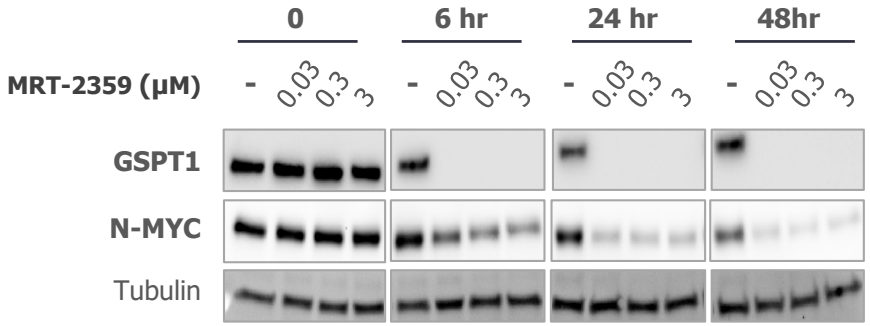
MRT-2359 induce GSPT1 degradation leading to N-MYC protein downregulation in NCI-H1155

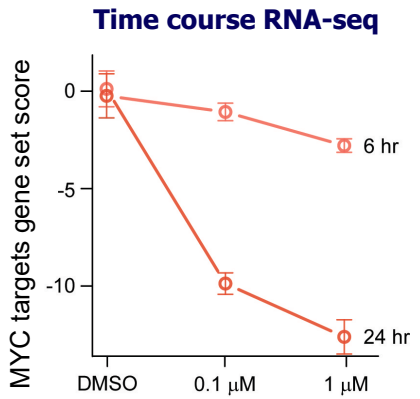


Degradation of GSPT1 leads to downregulation of N-MYC transcriptional output in NCI-H1155



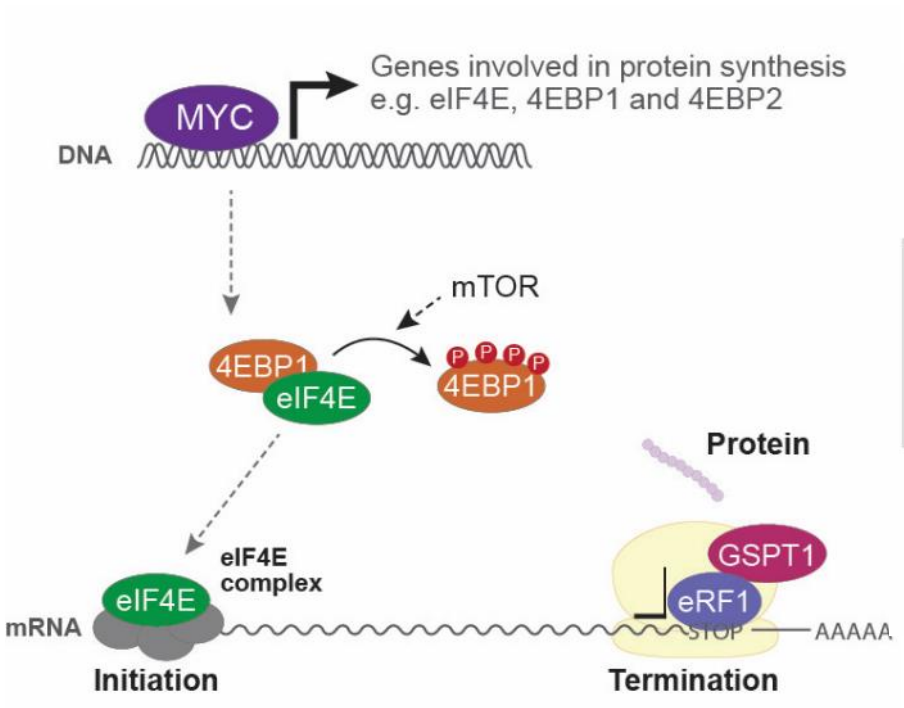
High N-MYC
NCI-H1155

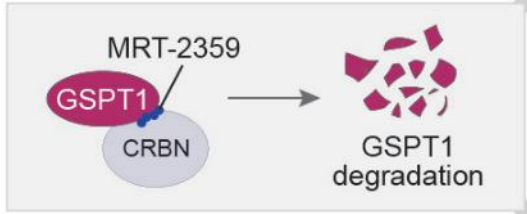




Transcriptional modulation of >200 MYC target genes

MRT-2359 Mechanism of Action in MYC-driven Tumors



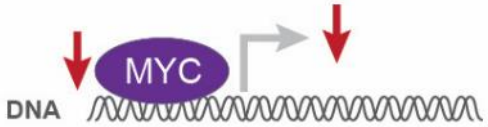


Synthetic lethality

MRT-2359 impairs protein synthesis in high MYC lines

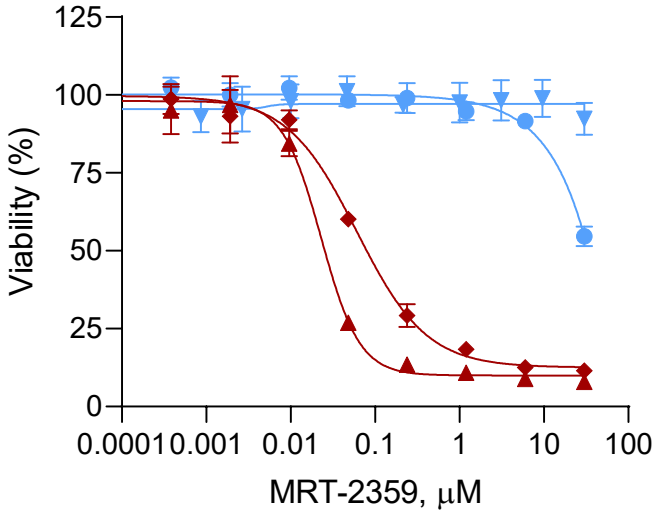
Oncogene addiction

MRT-2359 affects MYC and downstream in high MYC lines



MRT-2359 Shows Preferential Activity in MYC High or Neuroendocrine (NE) Positive Lung Cancer Lines

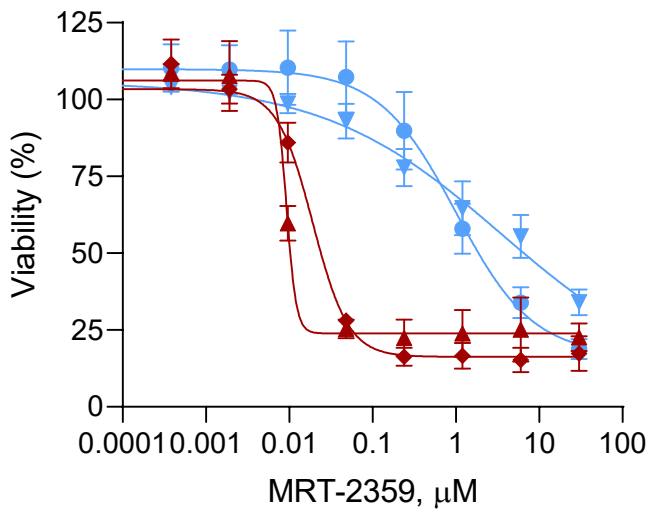
NSCLC cell lines (N-MYC)



High N-MYC
- NCI-H1155
- ABC-1

Low N-MYC
- NCI-H2023
- NCI-H441

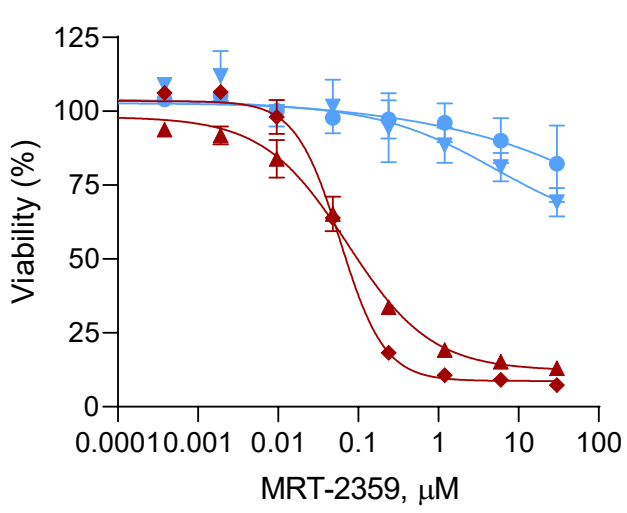
SCLC cell lines (L-MYC)



High L-MYC
- NCI-H1836
- NCI-H1876

Low L-MYC
- NCI-H2286
- NCI-H196

Lung cancer cell lines (NE)



High NE
- NCI-H810
- NCI-H1770

Low NE
- NCI-H2405
- NCI-H1693

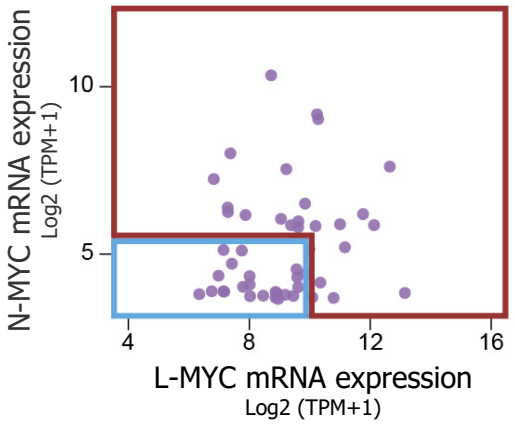
72 hr viability assay (CTG)

MRT-2359 Mouse-trial in NSCLC, SCLC and Lung NE Patient-derived Xenografts

Collection of PDX models

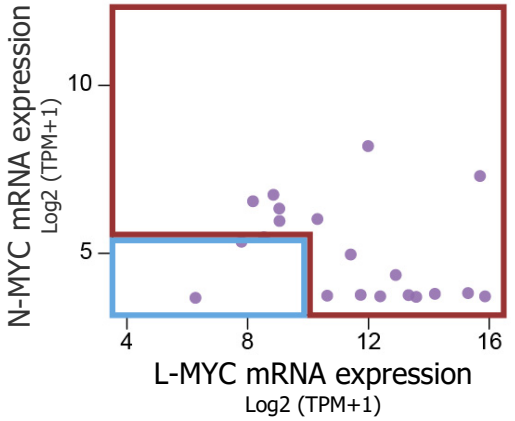
All models have been characterized by DNA and RNA-seq

NSCLC



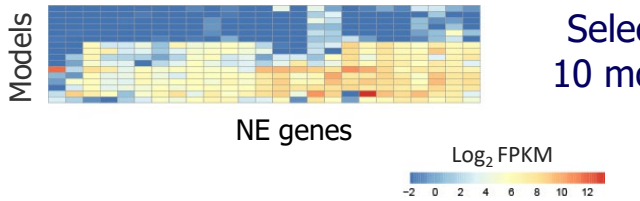
Selected 48 models

SCLC



Selected 20 models

Large cell NE carcinoma or NE lung cancer



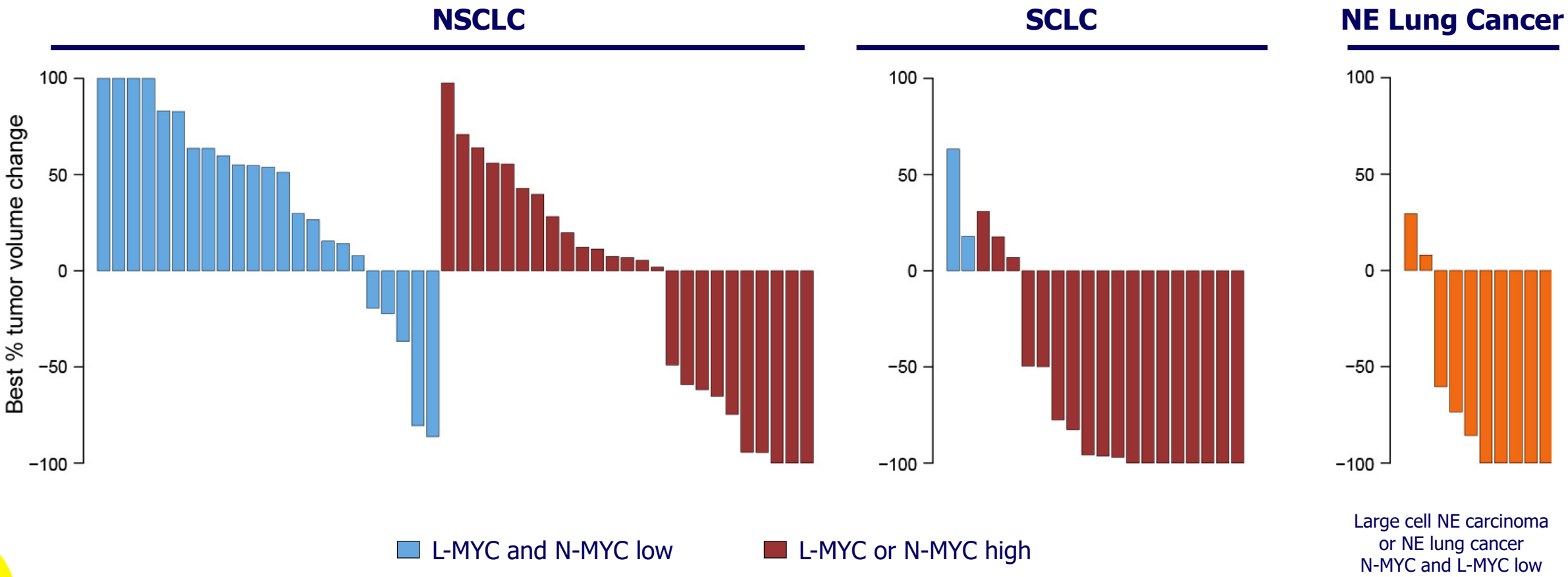
Selected 10 models

Models selected across a range of N-MYC and L-MYC mRNA expression levels or NE status were treated with

- Vehicle
- MRT-2359 10 mg/kg PO QD

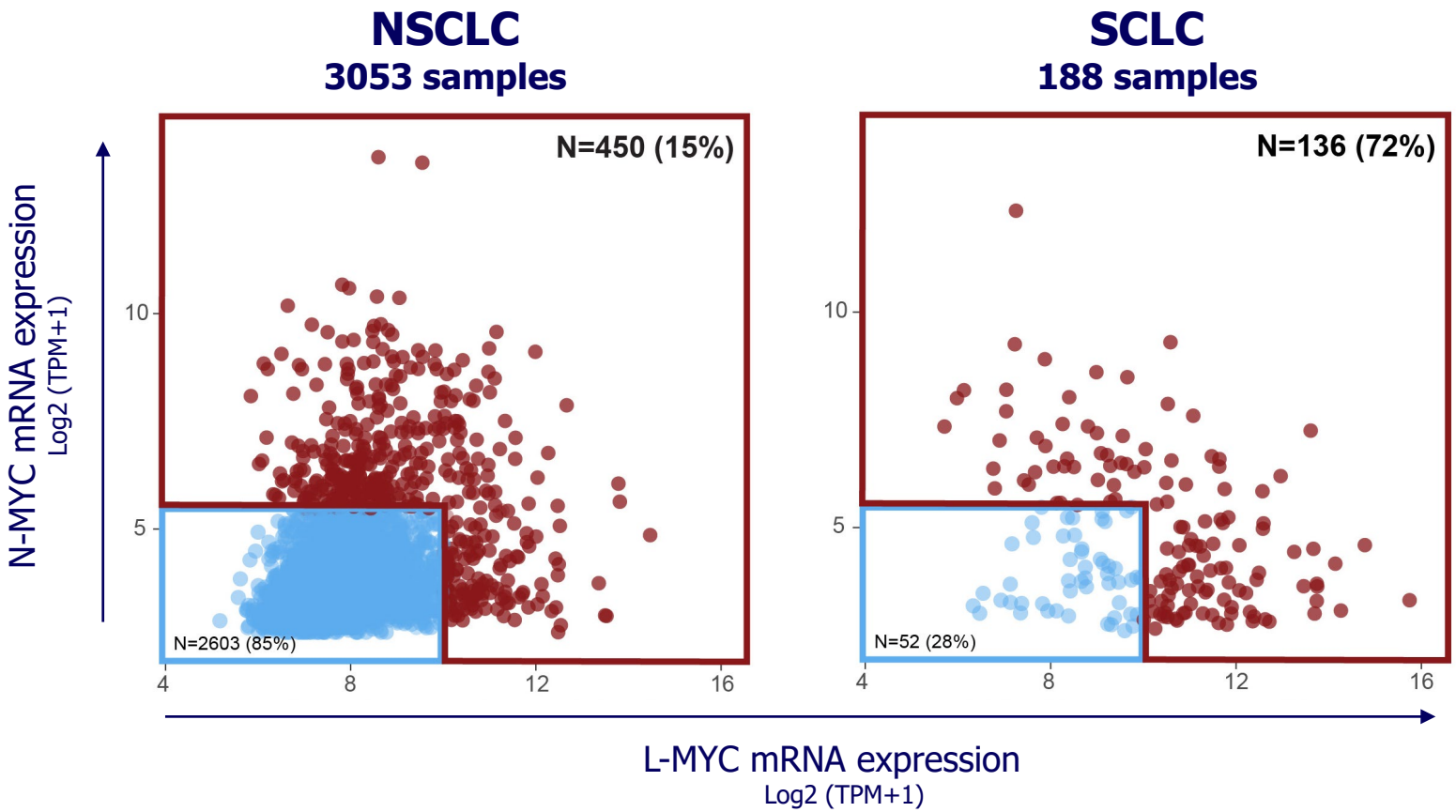
3 mice for each treatment group

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



MRT-2359 10 mg/kg, PO, QD

High Frequency of L-MYC and N-MYC Expression in NSCLC and SCLC from Real-world Data



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

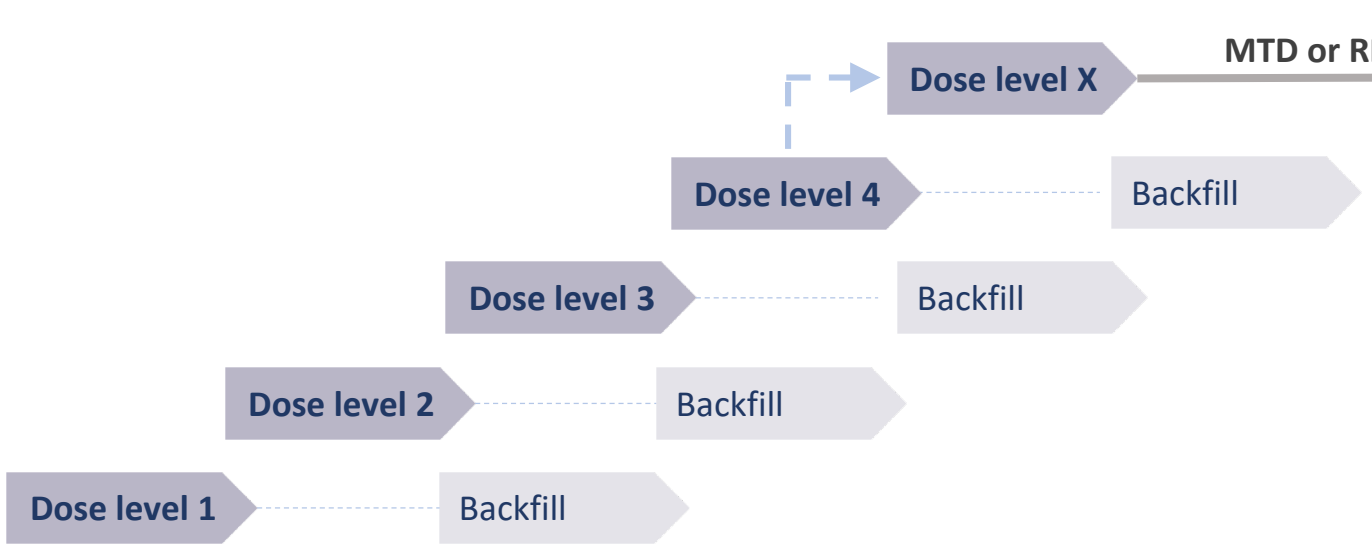
- No statistically significant associations between MYC high status and treatment outcomes

TEMPUS

MRT-2359-001 Clinical Study Design

Phase 1: Dose Escalation

Lung cancer (NSCLC & SCLC), DLBCL, high-grade neuroendocrine tumors, and N-/L-MYC amplified solid tumors



Backfill slots for additional patients for each dose level

Phase 2: Expansion Cohorts

NSCLC* – high N- or L-MYC expression
– low N- and L-MYC expression

SCLC* – high N- or L-MYC expression
– low N- and L-MYC expression

Solid tumors – N- or L-MYC amplification

* Efficacy guided stratification per N-/L-MYC expression

ClinicalTrials.gov - NCT05546268

Conclusions

- MRT-2359 is a rationally designed, potent, selective, and **orally bioavailable** GSPT1-directed MGD
- MRT-2359 **impairs protein synthesis** and **affects MYC and its downstream targets** in high MYC cell lines
- MRT-2359 demonstrates robust **anti-tumor activity** preferentially in **MYC-driven lung cancer models**
- **Dose escalation** phase of MRT-2359 first-in-man clinical study **is enrolling**

Acknowledgments


Thank You
Monte Rosa
Therapeutics