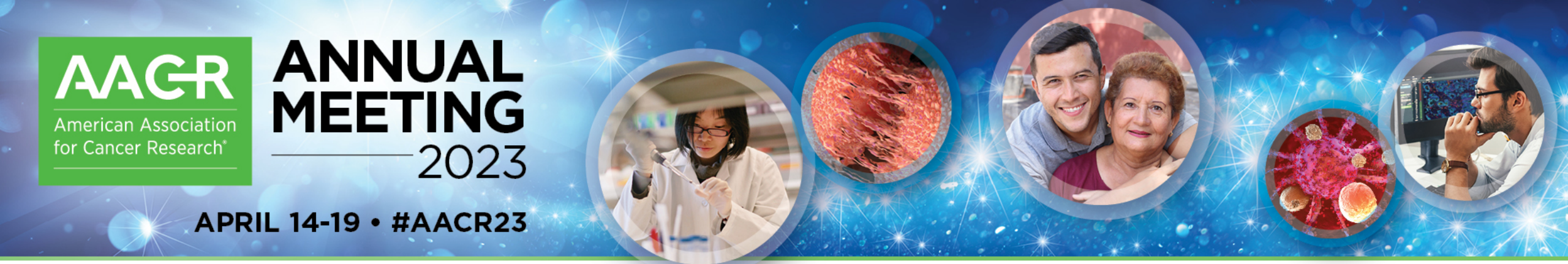


Development of MRT-2359, an orally bioavailable GSPT1 molecular glue degrader, for the treatment of lung cancers with MYC-induced translational addiction

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

Disclosure Information

AACR American Association for Cancer Research

ANNUAL MEETING 2023

APRIL 14-19 • #AACR23

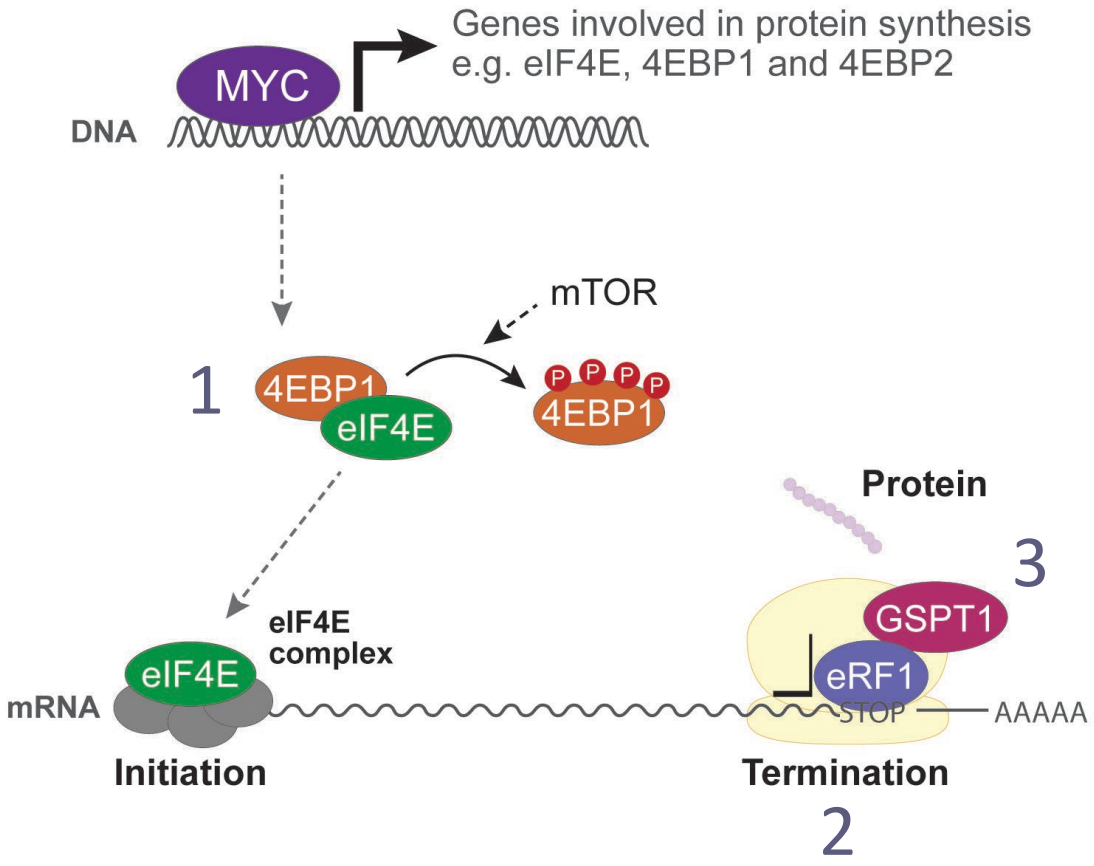
Gerald Gavory

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**

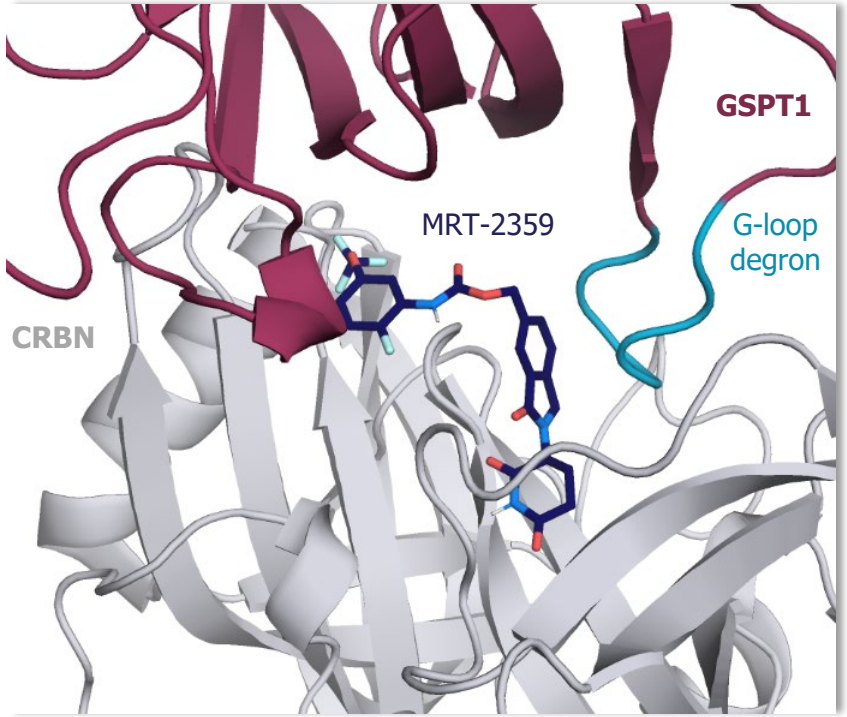
3

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

CRBN/MRT-2359/GSPT1 ternary complex

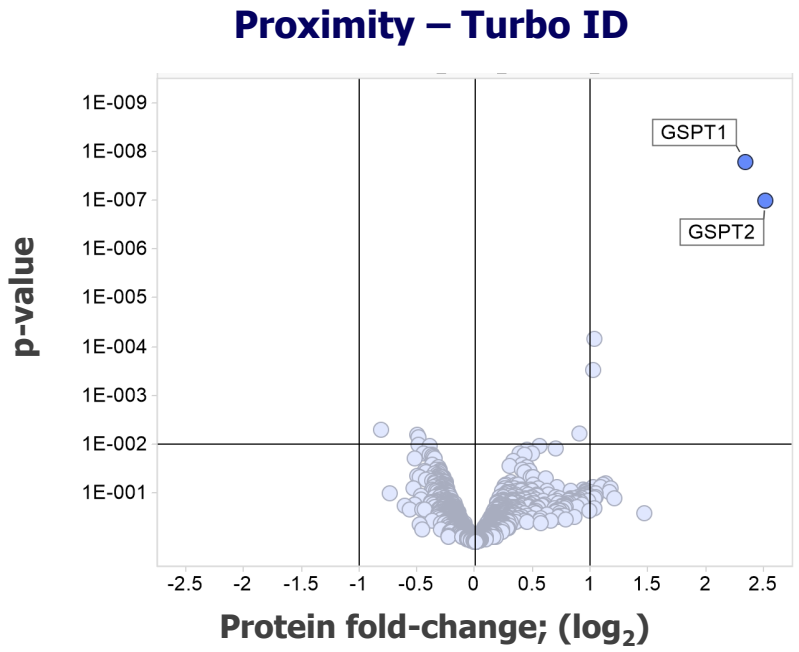


Biochemical and cellular data	
CRBN binding (HTRF; K_i)	113 nM
Ternary complex (HTRF; EC_{50})	7 nM
CRBN dependency (KO, multiple lines)	Yes
G-loop dependency (G575N mut., multiple lines)	Yes
Selectivity (proteomics)	GSPT1 / GSPT2
Degradation DC_{50}/D_{max} (in disease relevant lines)	1-20 nM / 100%
Viability EC_{50} (in disease relevant MYC high lines)	2-80 nM

ADMET profile	
CYP DDIs (7 isoforms)	> 30 µM
CEREP (Safety panel 44)	None
hERG inhibition (patch clamp)	EC_{50} > 30 µM
Oral bioavailability (all species)	~50%

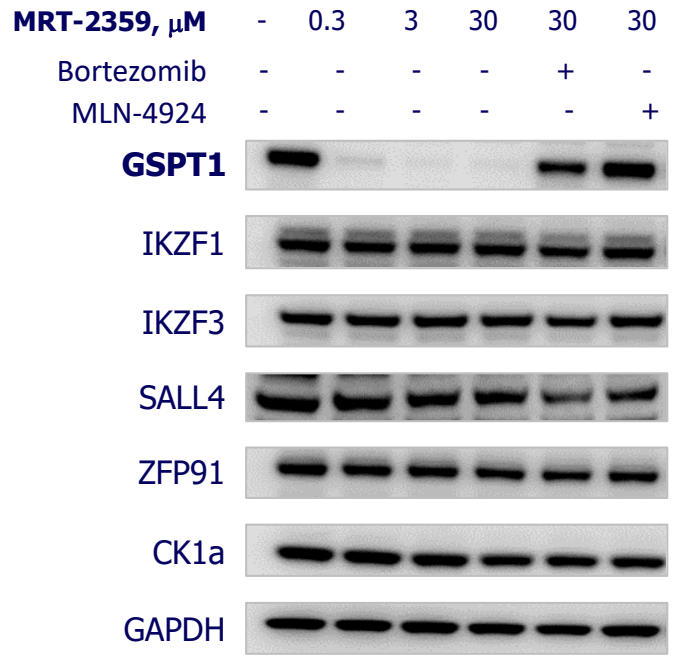
MRT-2359 is a Highly Selective Recruiter and Degrader of GSPT1

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



100 nM MRT-2359, 1hr post treatment

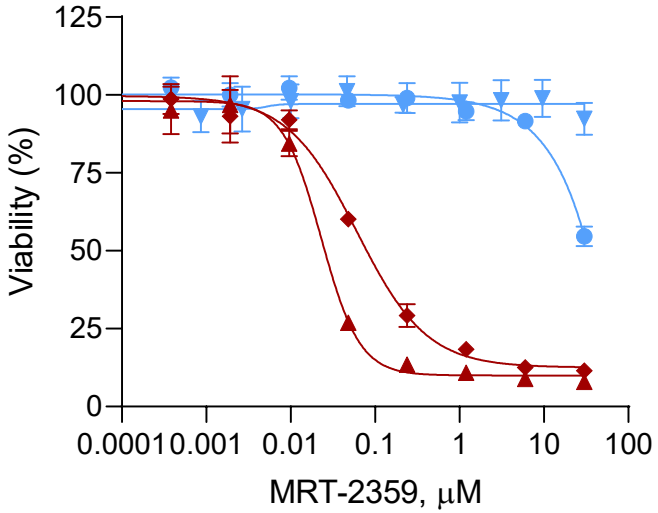
MRT-2359 is highly selective against common neosubstrates of CRBN



6hr post treatment in MM1S and Kelly (SALL4)

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

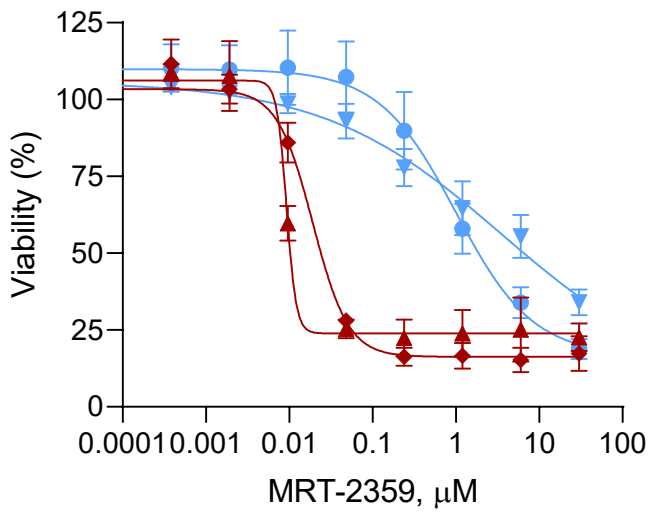
N-MYC - NSCLC lines



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

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

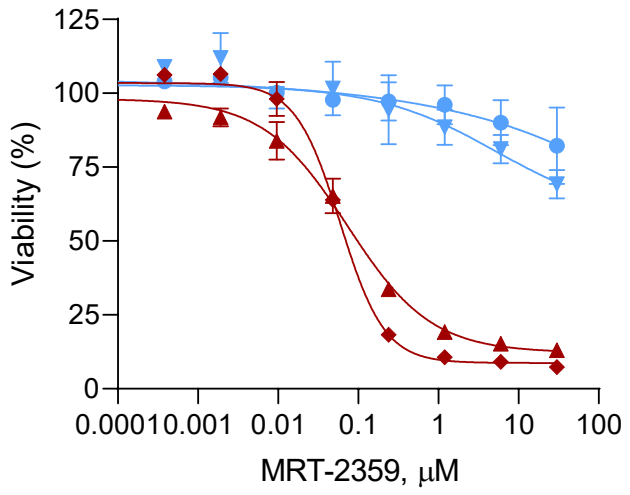
L-MYC - SCLC lines



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

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

NE positive lung lines



High NE
- NCI-H810
- NCI-H1770

Low NE
- NCI-H2405
- NCI-H1693

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

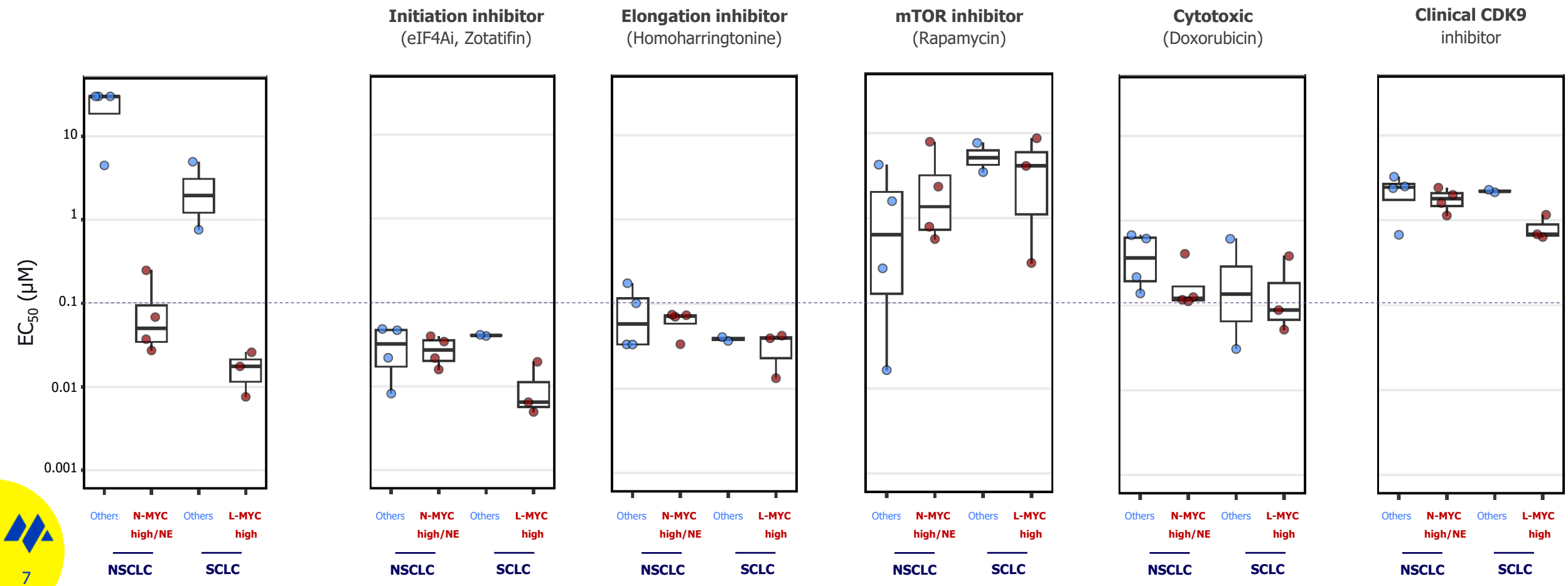
72 hr viability assay (CTG)

MRT-2359 Preferential Activity in MYC High Lung Cancer Lines is Unique

MRT-2359

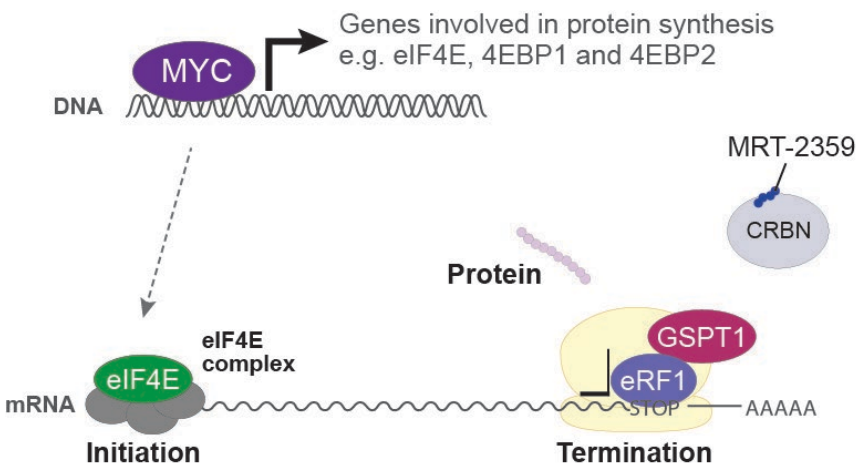
Other therapeutic agents targeting protein translation process or machinery lack preferential activity in the MYC high lung lines

Similarly for agent targeting Myc transcriptional reprogramming



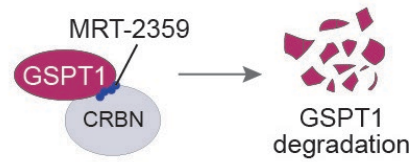
72 hr viability assay (CTG).

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

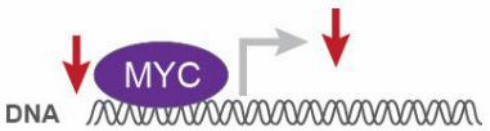


Preferential inhibition of translation

MRT-2359 preferentially impairs protein synthesis in tumor cells with high MYC expression

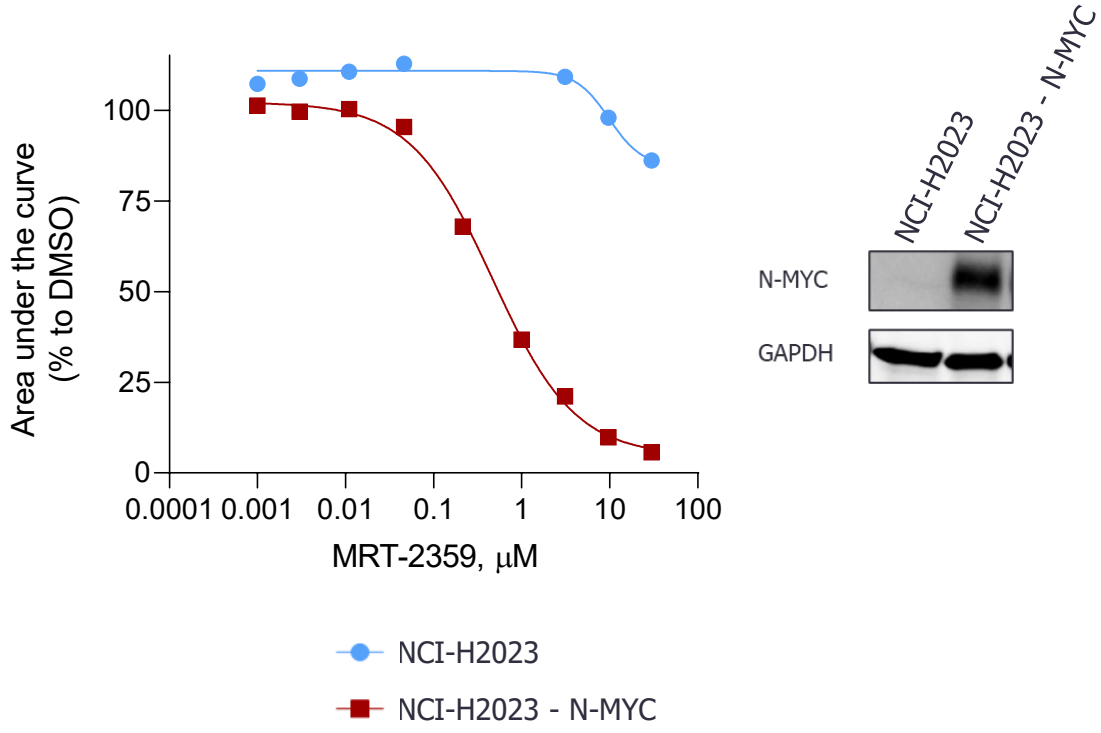
MYC down modulation

MRT-2359 indirectly affects MYC expression and transcriptional activity

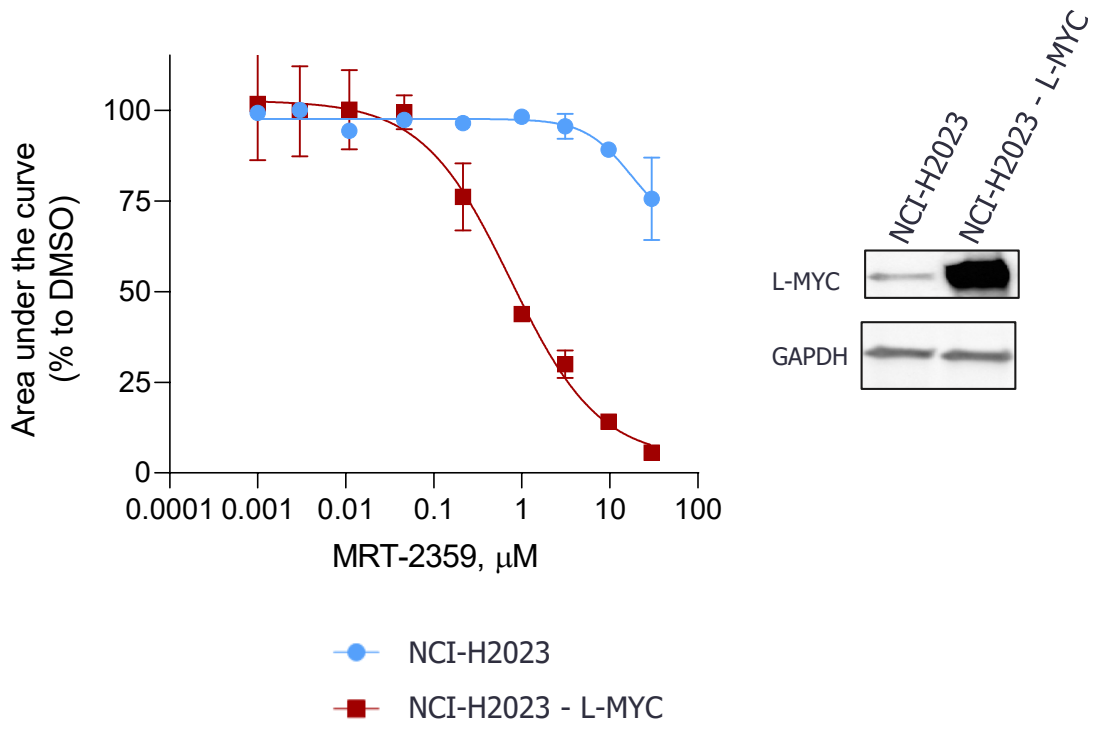


The Sole Overexpression of MYC Sensitizes Initially Resistant NSCLC Cells to MRT-2359

Consitutive N-MYC overexpression in NCI-H2023 cells

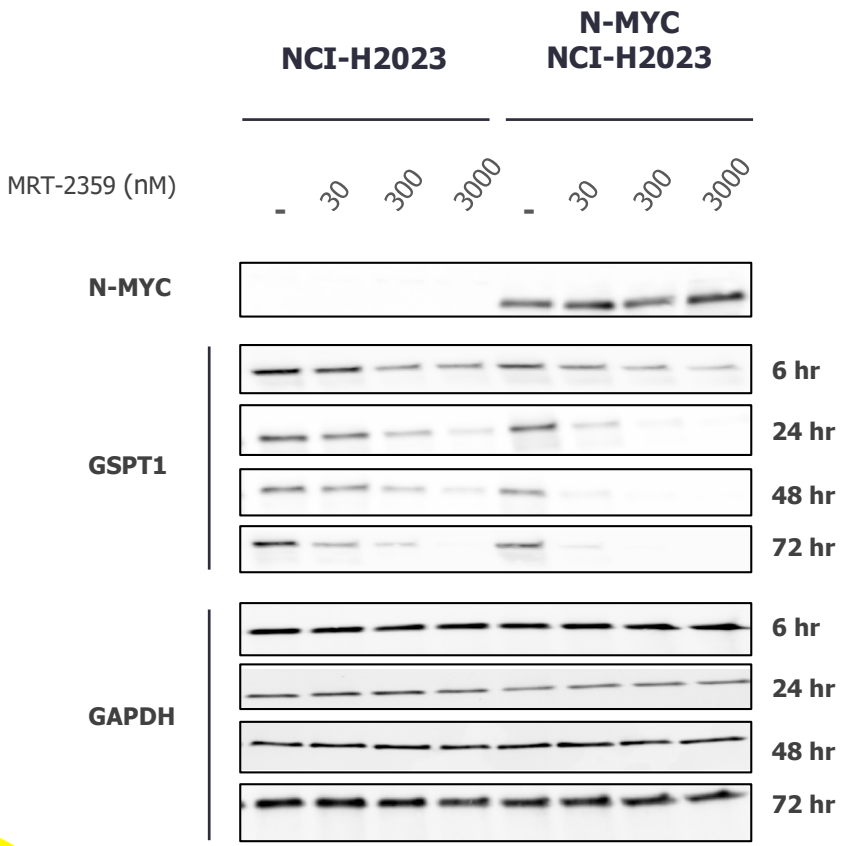


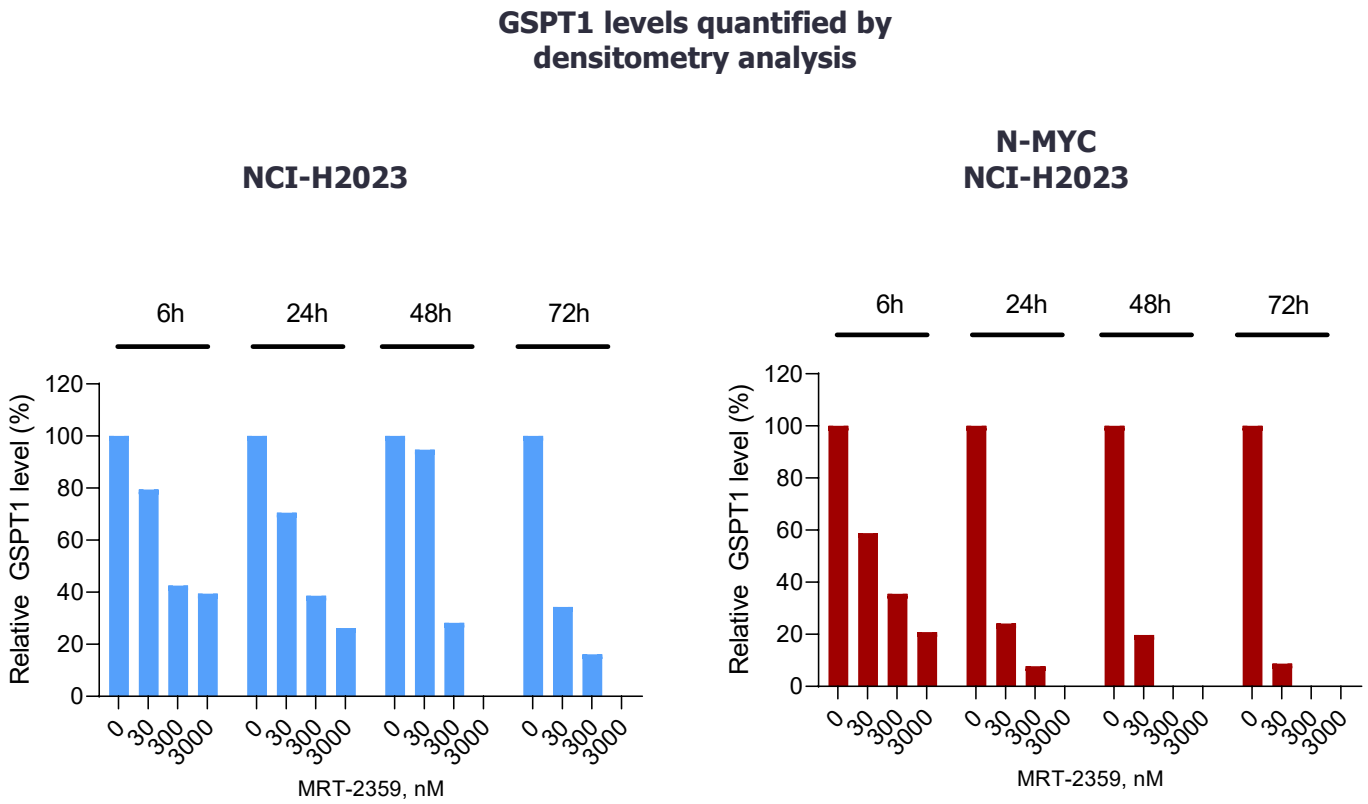
Consitutive L-MYC overexpression in NCI-H2023 cells



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

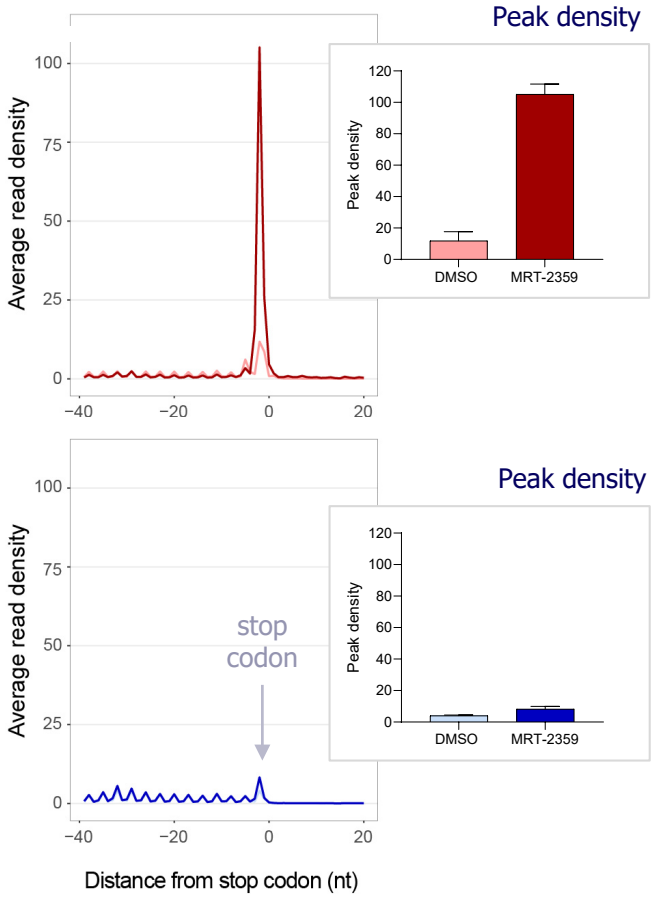
MRT-2359 induces ribosome stalling at stop codon only in N-MYC high cell line

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

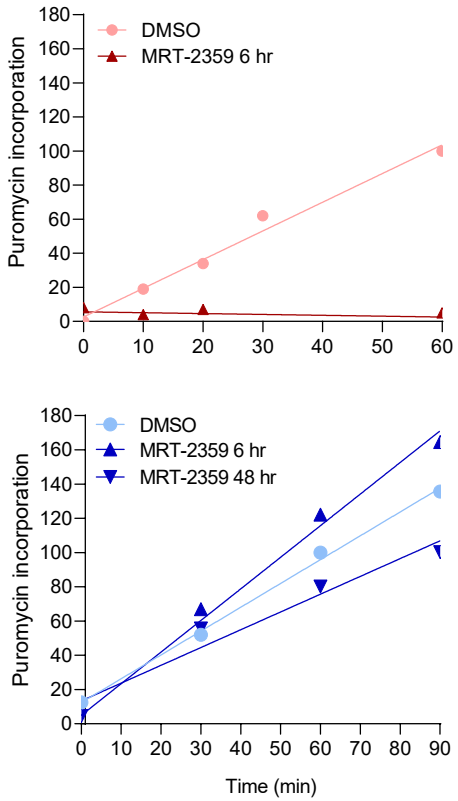
High N-MYC
NCI-H1155

Low N-MYC
NCI-H2023

Metagene plots



Puromycin incorporation

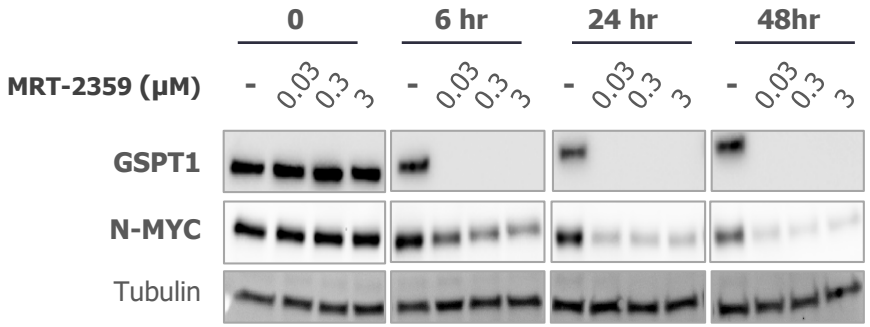


Ribo-Seq – 24 hr post-treatment

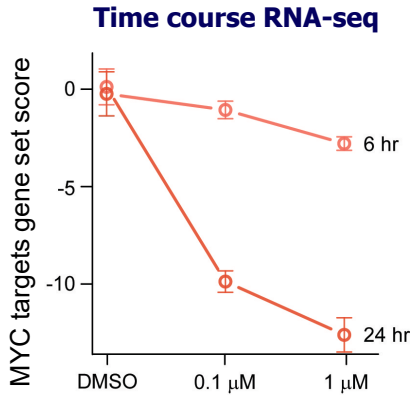
MRT-2359 Affects MYC and MYC Pathway in N-MYC High NSCLC Cell Lines

High N-MYC
NCI-H1155

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

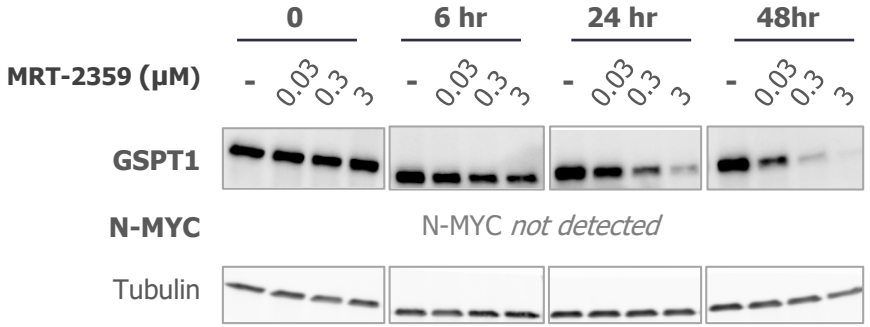


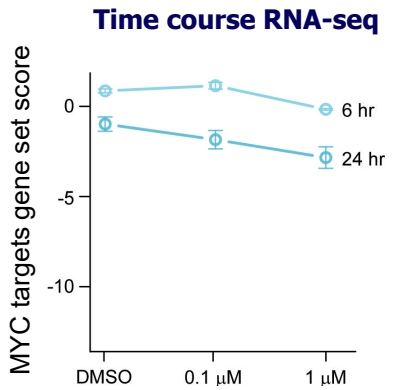
Degradation of GSPT1 leads to downregulation of N-MYC transcriptional output in NCI-H1155



Transcriptional modulation of >200 MYC target genes

Low N-MYC
NCI-H2023

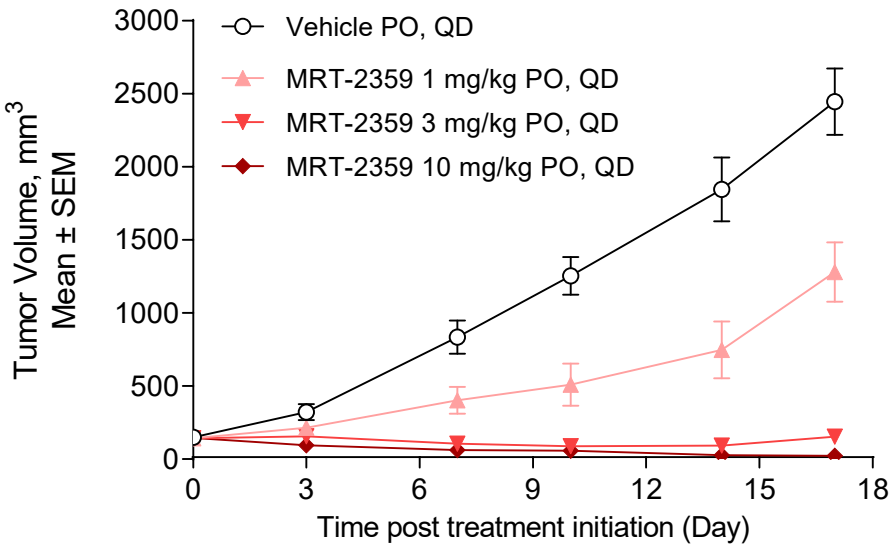




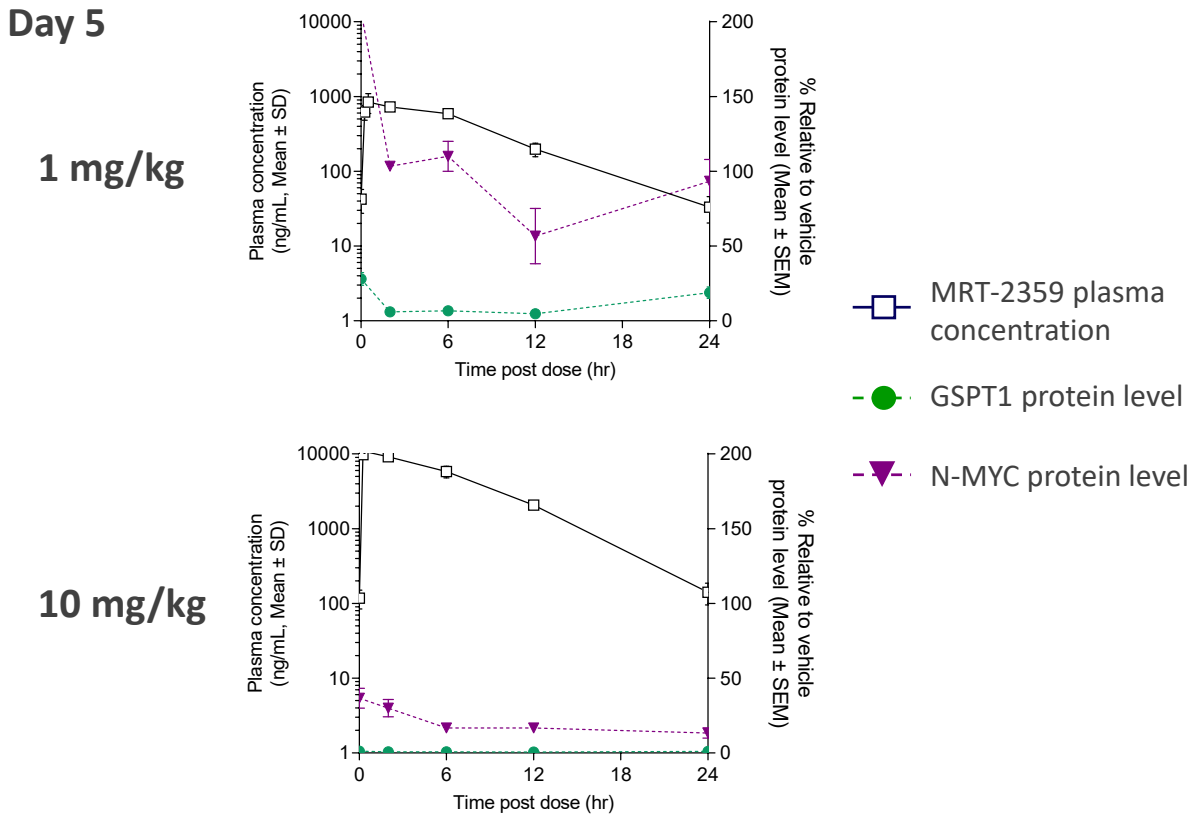
MRT-2359 Induces Tumor Regressions in N-MYC-driven Xenograft Models

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

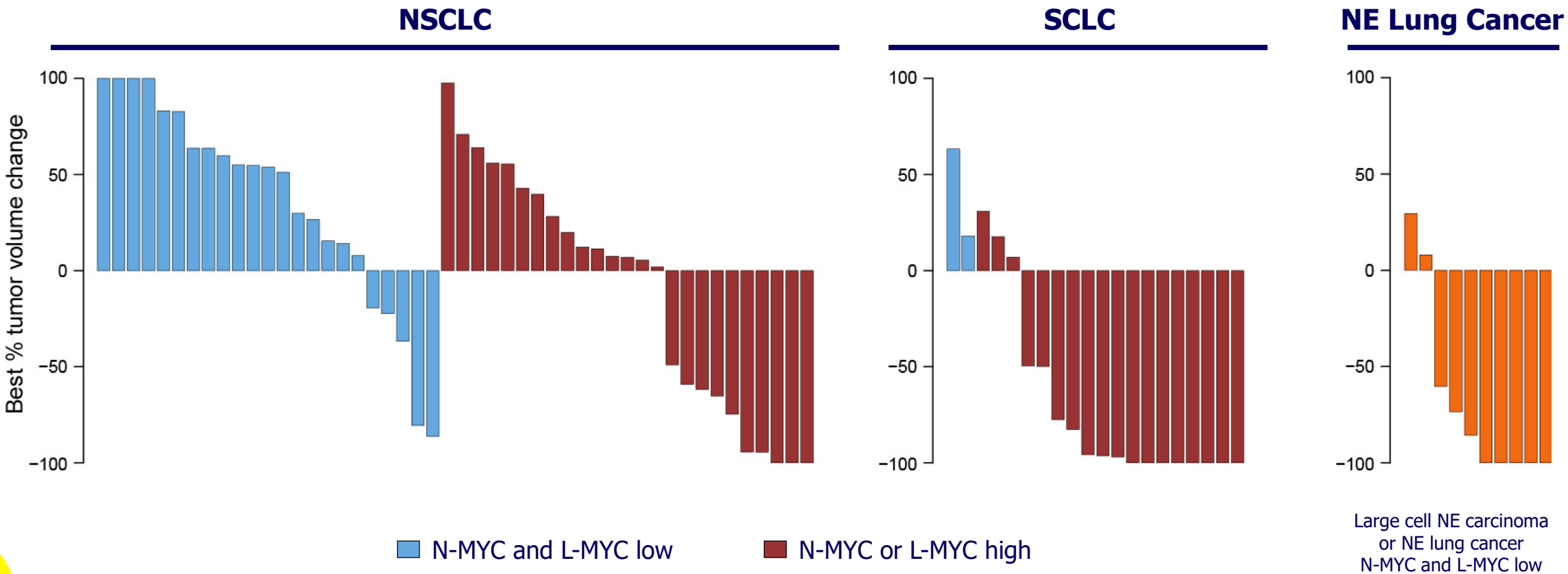
Similar observations in other high N-MYC expression models (ABC-1, NCI-H1770)



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

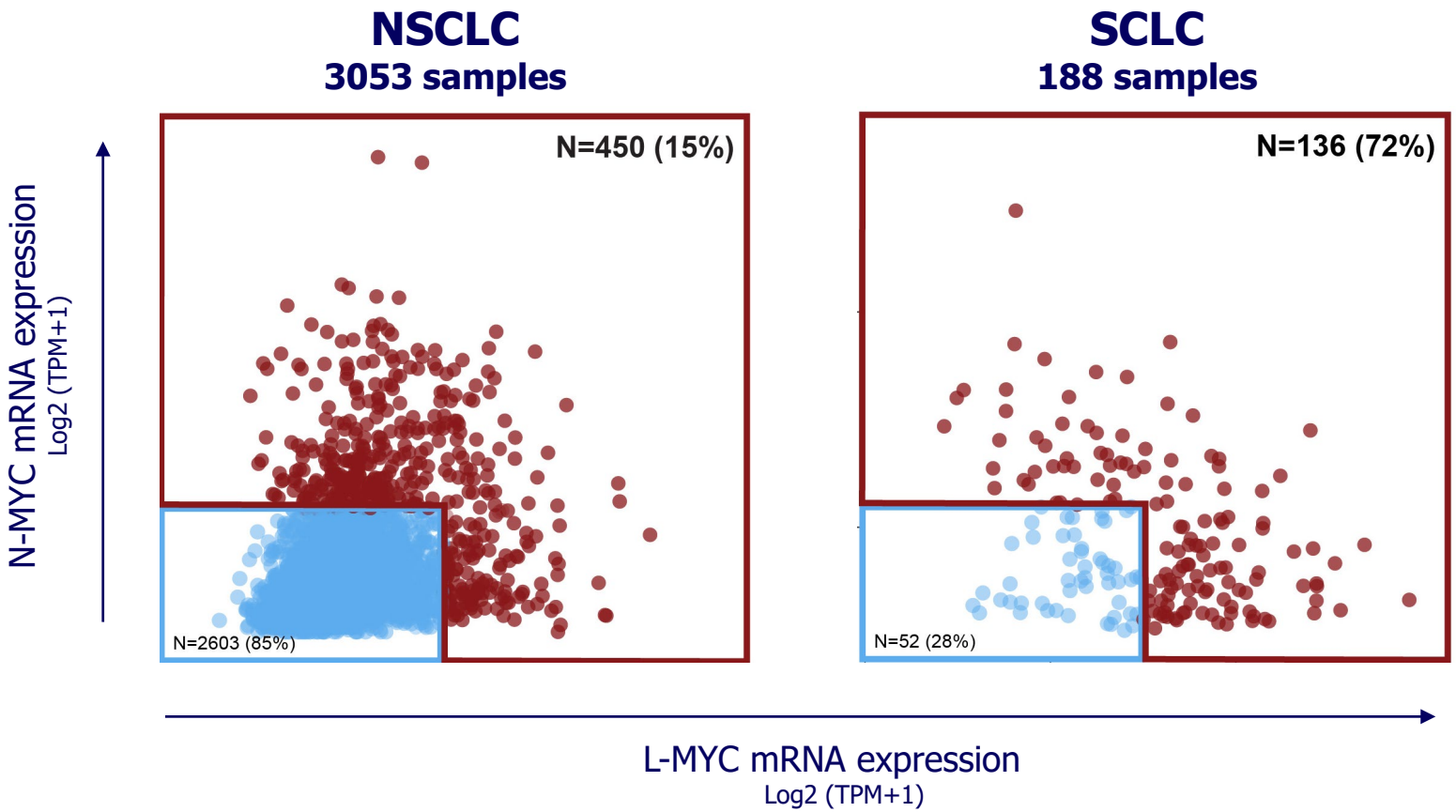


MRT-2359 Demonstrates Preferential Anti-tumor Activity in MYC High or Neuroendocrine (NE) Lung Cancer PDXs



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

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 QuEEN™ 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

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