Development of MRT-2359, a GSPT1 Molecular Glue Degrader, to Target MYC-driven Malignancies

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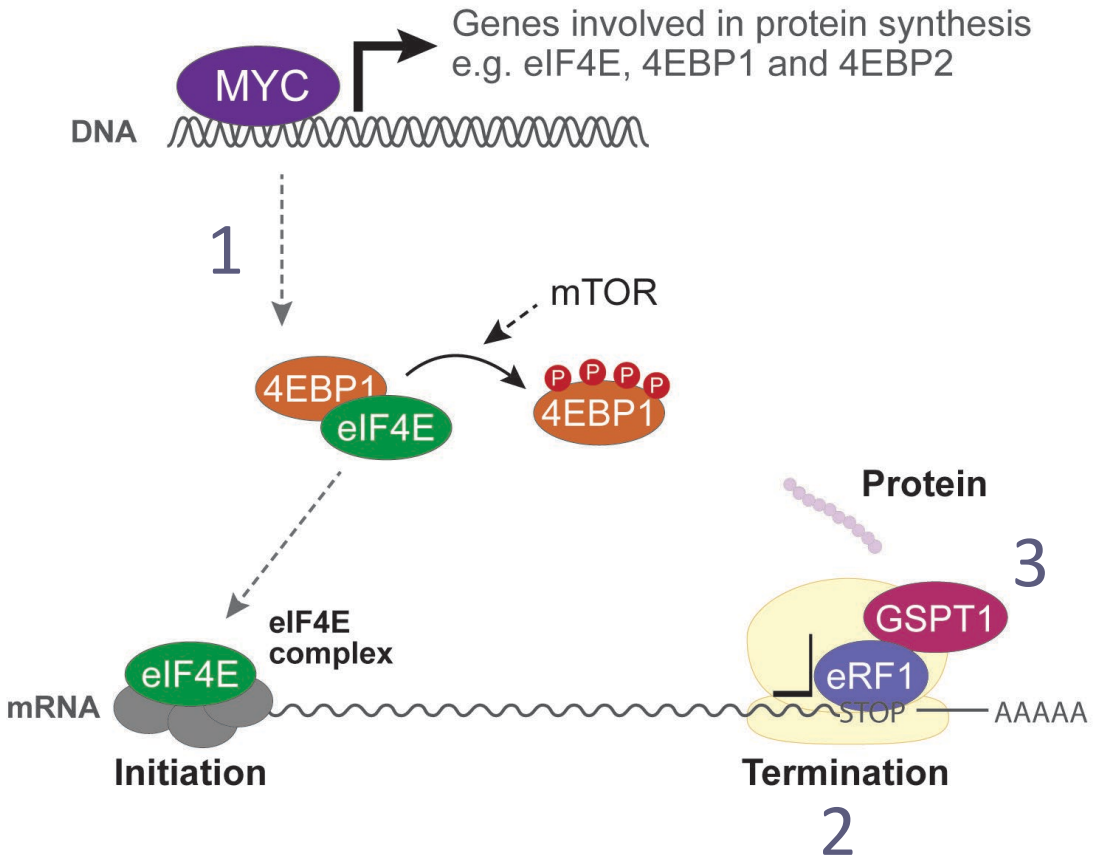
Monte Rosa Therapeutics

Disclosures

- Employment: Monte Rosa Therapeutics
- Stocks/Options: 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

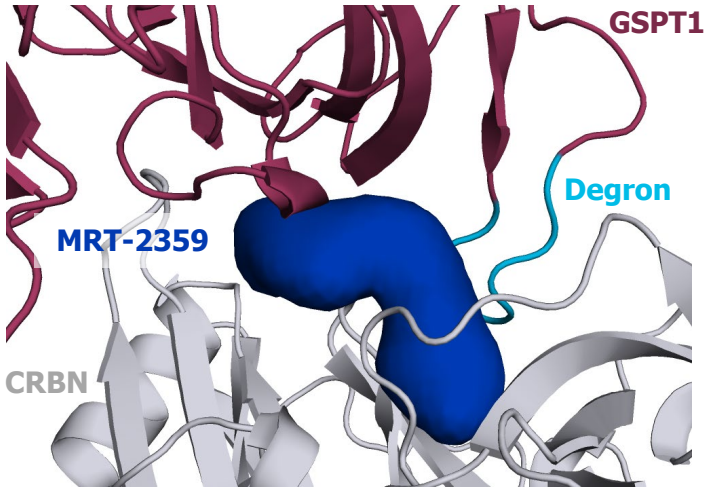
Therapeutic vulnerability

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

MRT-2359: a Potent, Selective and Orally Bioavailable GSPT1 MGD

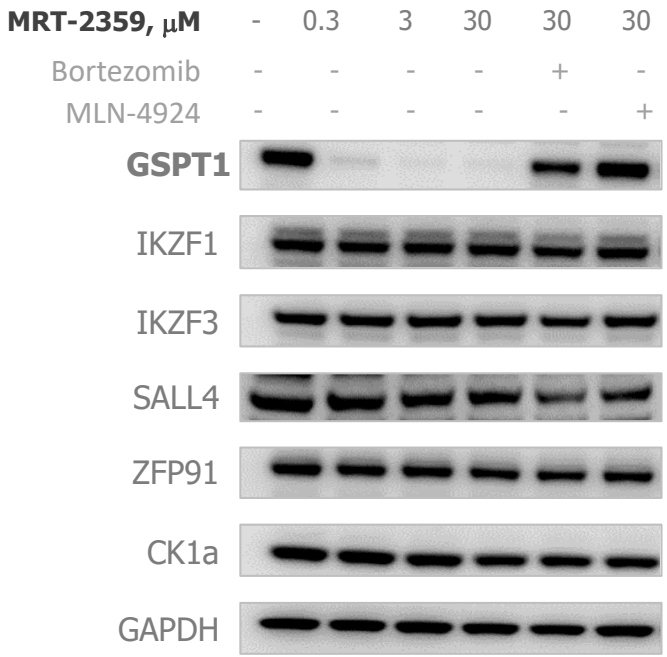
MRT-2359 is a potent inducer of GSPT1-cereblon proximity

Ternary complex model



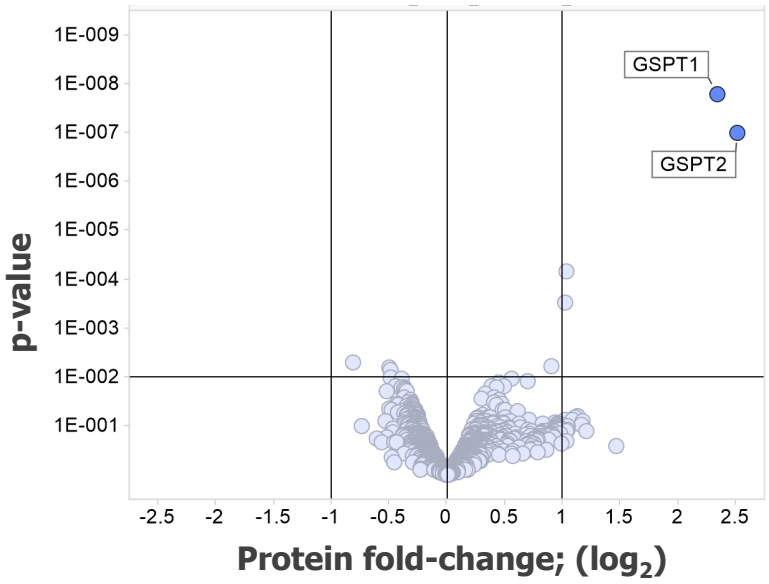
MRT-2359 profile overview	
Ternary complex, EC_{50}	< 7 nM
CYP DDIs	> 30 µM
hERG inhibition patch clamp	EC_{50} > 30 µM
Oral bioavailability all species	~50%

MRT-2359 is a selective GSPT1-directed MGD



6hr post treatment in MM1S and Kelly (SALL4)

Proximity – Turbo ID



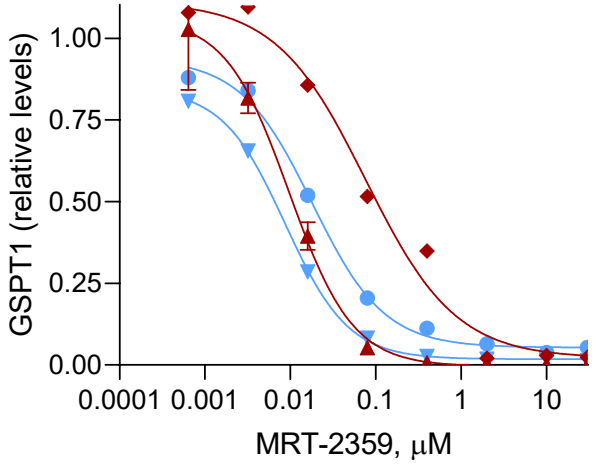
1hr post treatment

Preferential activity of MRT-2359 in MYC-Driven NSCLC Lines

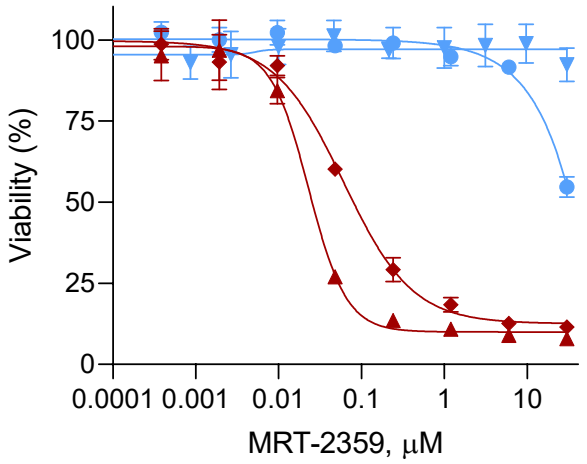
MRT-2359 induces GSPT1 degradation in all cell models, but show preferential antiproliferative activity in N-MYC high cell lines

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

GSPT1 degradation



Viability



High N-MYC

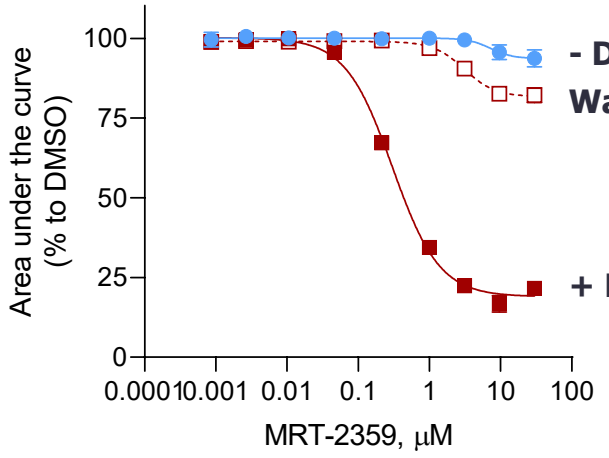
- NCI-H1155
- ABC-1

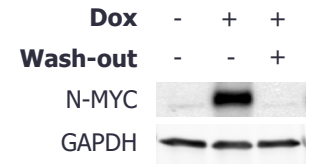
Low N-MYC

- NCI-H2023
- NCI-H441

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

Doxycycline-inducible N-MYC model



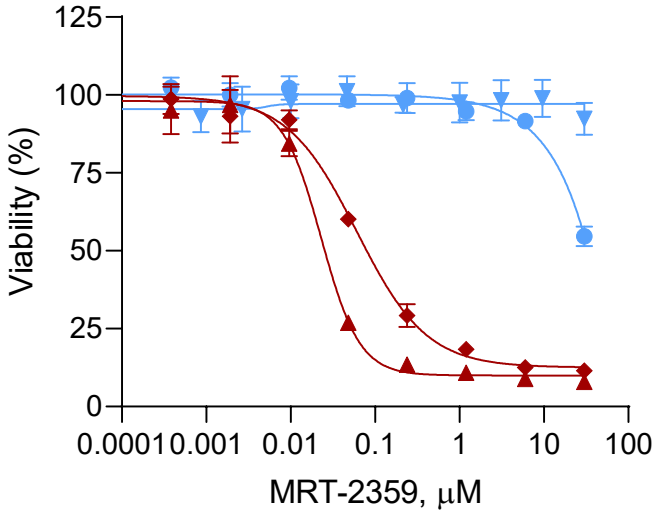


- NCI-H2023 Dox-inducible MYC **- Dox**
- NCI-H2023 Dox-inducible MYC **+ Dox**
- NCI-H2023 Dox-inducible MYC **+ Dox wash-out**

Incucyte, 96 hr post treatment

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

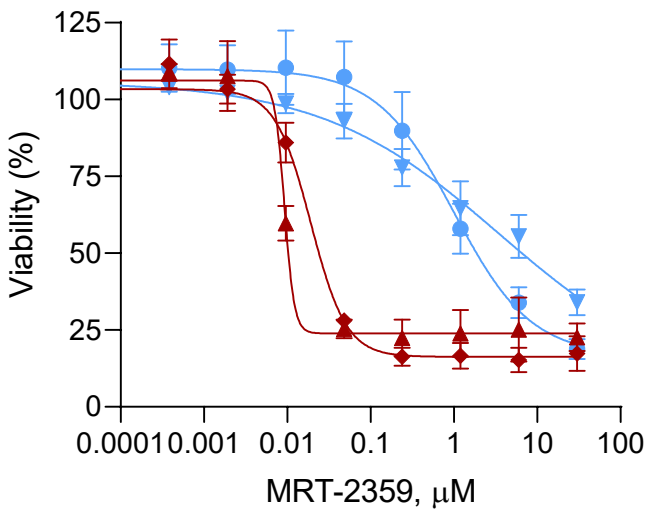
N-MYC - NSCLC lines



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

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

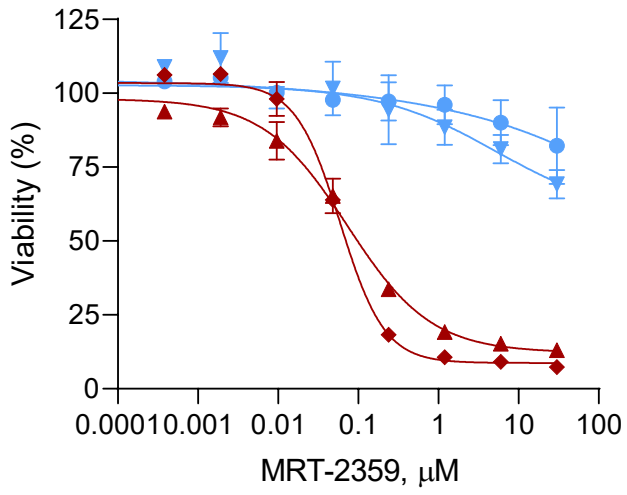
L-MYC - SCLC lines



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

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

NE positive lung lines



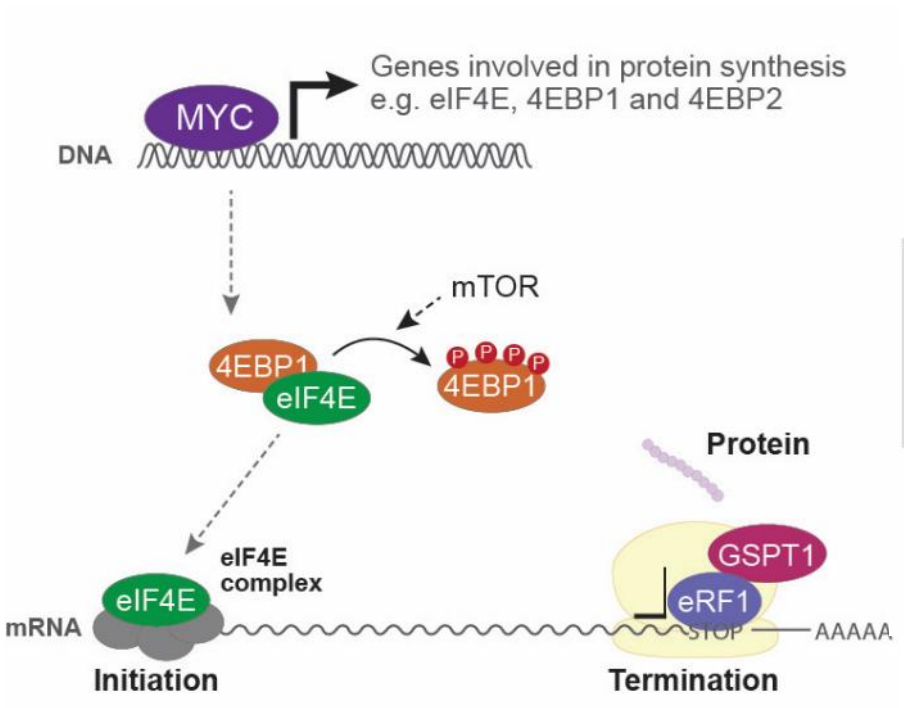
High NE
- NCI-H810
- NCI-H1770

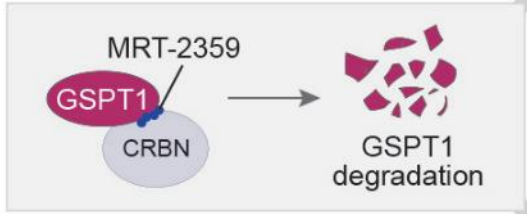
Low NE
- NCI-H2405
- NCI-H1693

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

72 hr viability assay (CTG)

MRT-2359 Mechanism of Action in MYC-driven Tumors



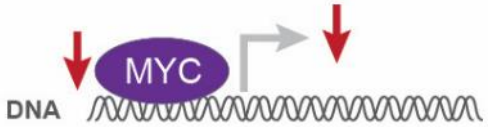


Synthetic lethality

MRT-2359 impairs protein synthesis in high MYC lines

Oncogene addiction

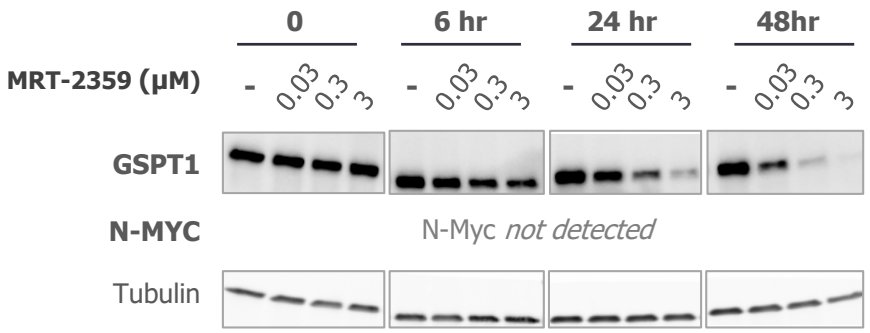
MRT-2359 affects MYC and downstream in high MYC lines



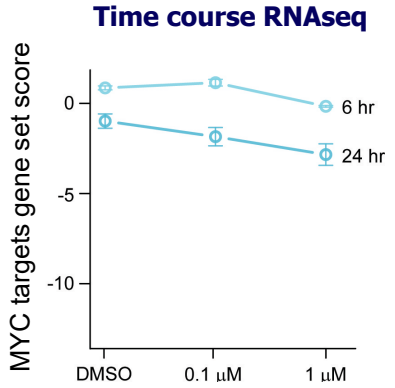
MRT-2359 Affects MYC and MYC Pathway in N-MYC High NSCLC Cell Lines

Low N-MYC
NCI-H2023

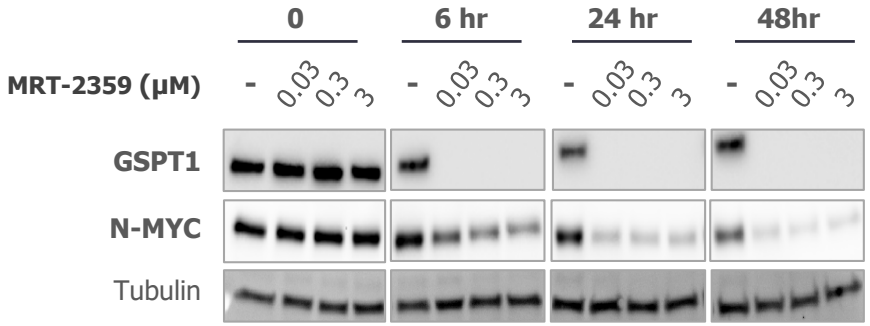
MRT-2359 induce GSPT1 degradation leading to N-MYC protein downregulation in NCI-H1155

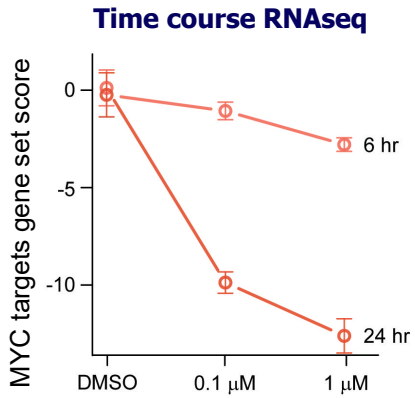


Degradation of GSPT1 leads to downregulation of N-MYC transcriptional output in NCI-H1155



High N-MYC
NCI-H1155





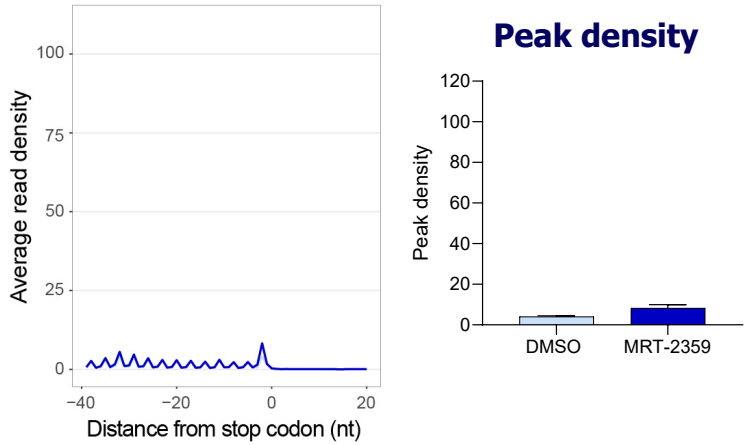
Transcriptional modulation of >200 MYC targets genes

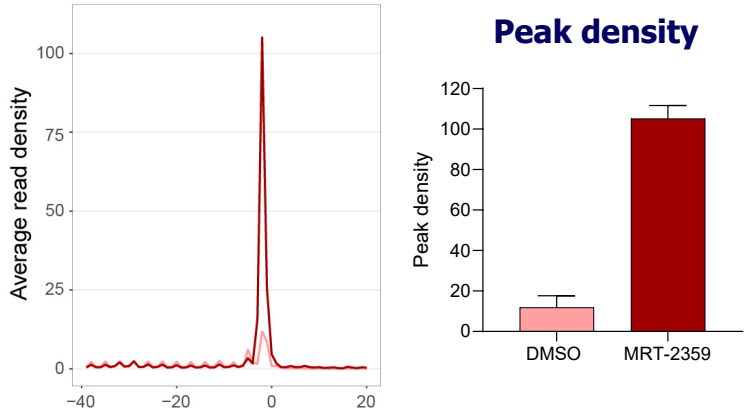
MRT-2359 Impairs Protein Synthesis in N-MYC High NSCLC Cell Lines

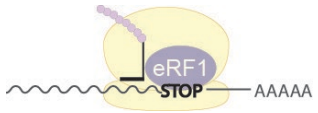
Low N-MYC
NCI-H2023

High N-MYC
NCI-H1155

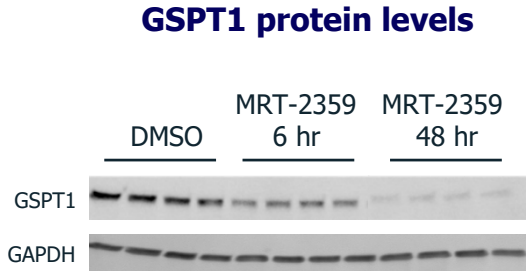
MRT-2359 induces ribosome stalling only in N-MYC high cell line

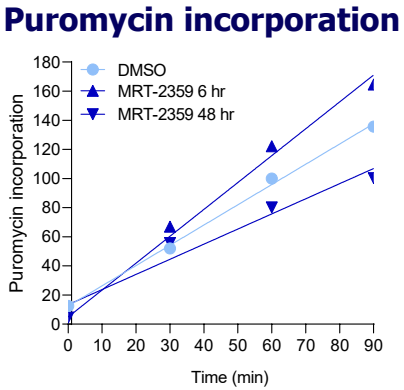


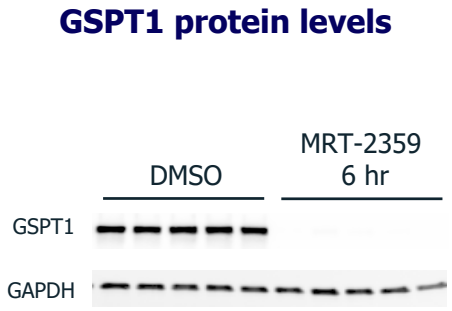


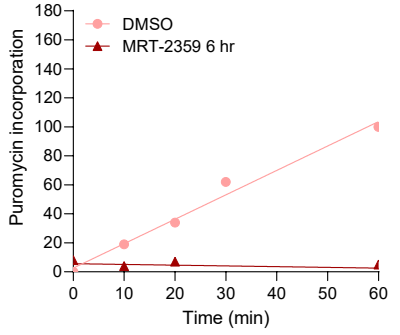


MRT-2359 rapidly and completely abrogates protein synthesis only in N-MYC high cell line

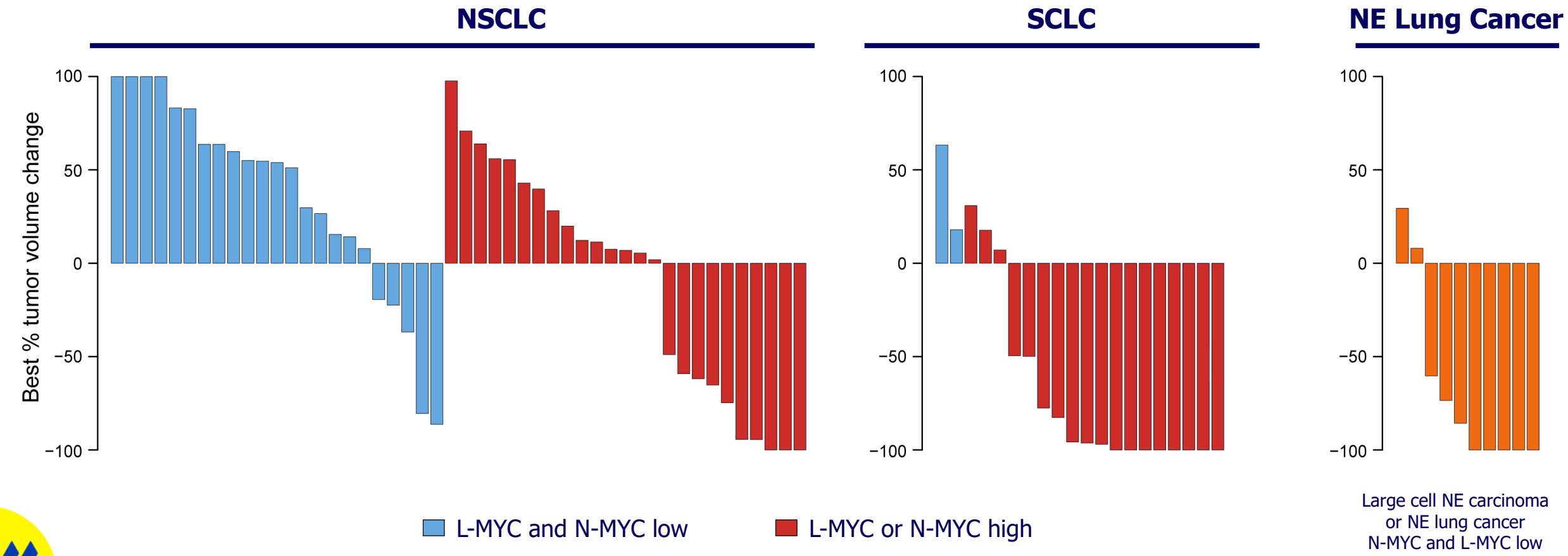






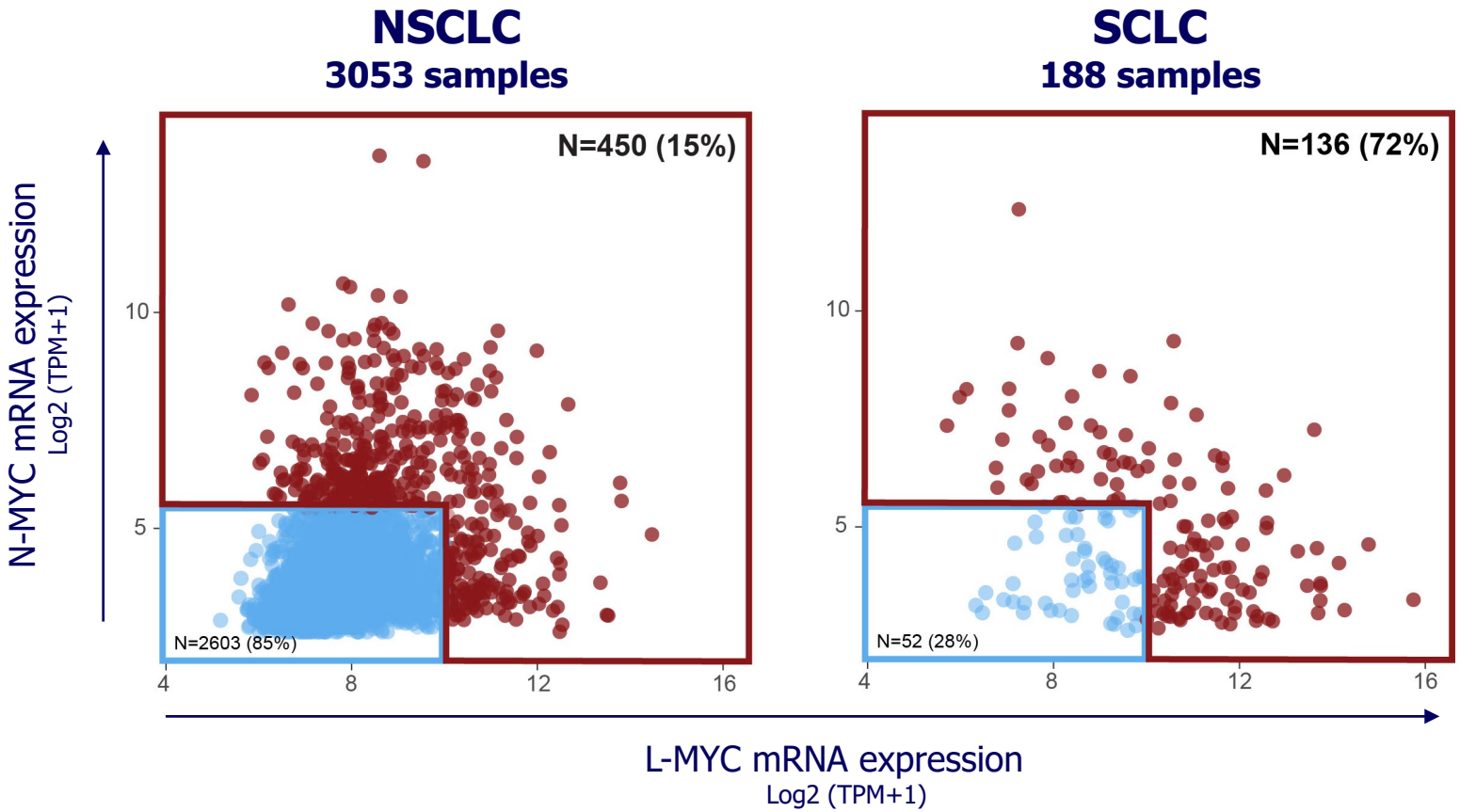


MRT-2359 Demonstrates Preferential Anti-tumor Activity in MYC high or Neuroendocrine (NE) Lung Cancer PDXs



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

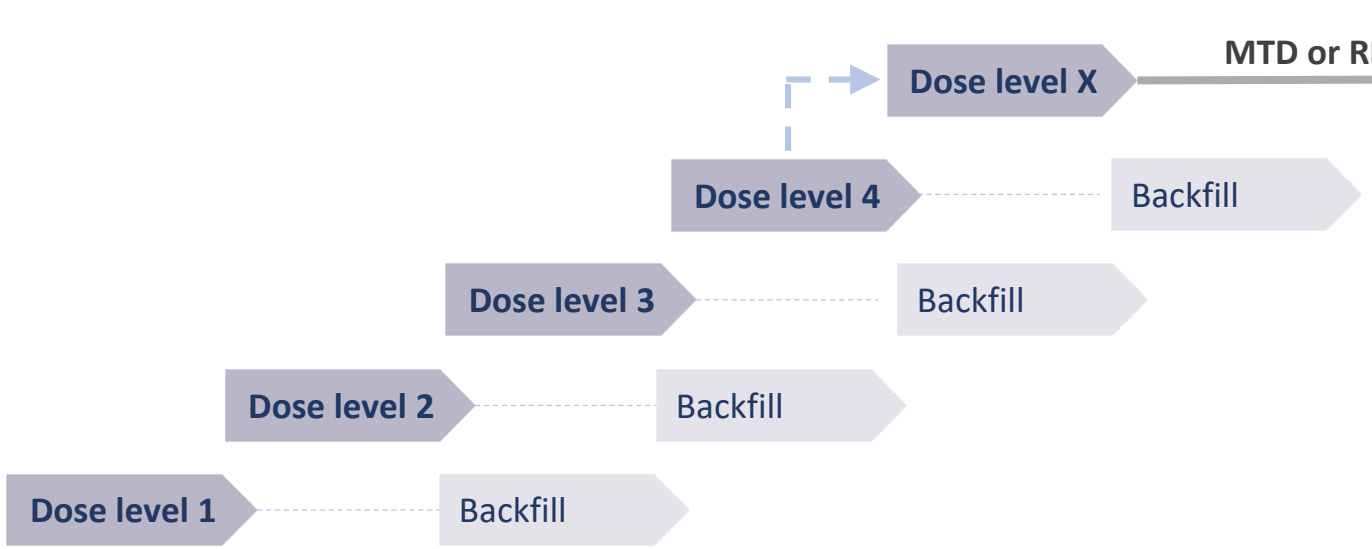
- No statistically significant associations between MYC high status and treatment outcomes

TEMPUS

MRT-2359-001 Clinical Study (NCT05546268)

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

MTD or RP2D

- **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

Conclusions

- MRT-2359 is rationally designed, potent, selective, and **orally bioavailable** GSPT1-directed MGD
- MRT-2359 demonstrated robust **antitumor activity** especially in **MYC-driven lung cancer models**
- **Dose escalation** phase of MRT-2359 first-in-man clinical study **is enrolling**

Acknowledgments

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    - Dr. Pasi Janne
  - Honor Health, Scottsdale, AZ
    - Dr. Frank Tsai
  - Indiana University, Indianapolis, IN
    - Dr. Mateusz Opyrchal
  - Mary Crowley Research Institute, Dallas, TX
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  - MD Anderson Cancer Center, Houston , TX
    - Dr. Jordi Rodon
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