Discovery of MRT-2359, an orally bioavailable GSPT1 molecular glue degrader, for MYC-driven cancers

Owen B. Wallace, Ph.D.

Monte Rosa Therapeutics, Boston MA & Basel Switzerland

Disclosure Information

AACR American Association for Cancer Research
ANNUAL MEETING 2023
APRIL 14-19 • #AACR23

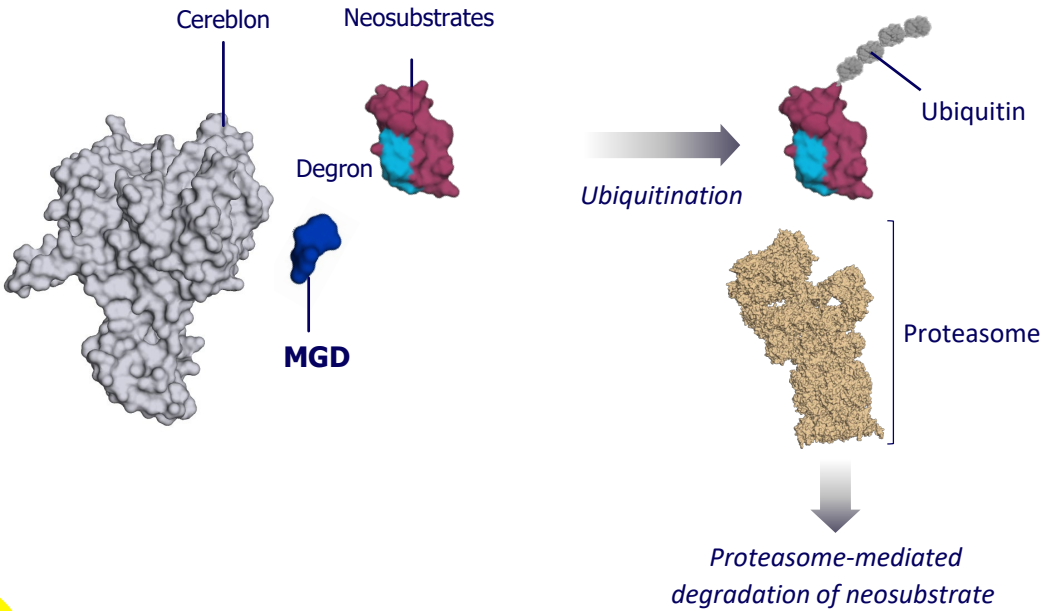
Owen B. Wallace

I have the following relevant financial relationships to disclose:

Employee of Monte Rosa Therapeutics

Stockholder in Monte Rosa Therapeutics

Molecular Glue Degraders are a Clinically Validated Modality



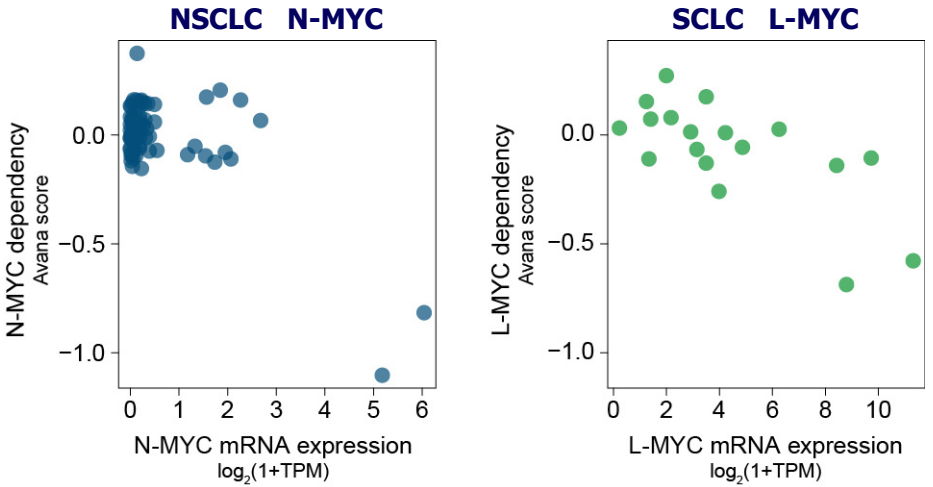
- **MGD** binds to **E3 ligase**
- Protein **surface is reshaped**
- **PPI** induced with **neosubstrate**
- **Neosubstrate** is **ubiquitinated**
- Ubiquitinated **protein** shuttled to **proteasome**
- **Protein is degraded**

MYC Family Transcription Factors are Key Cancer Dependence Genes

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

- **MYC up-regulation** dysregulates key cellular processes (e.g. ribosome biogenesis and **protein synthesis**)
- **MYC dysregulation** is frequently associated with **poor prognosis** and **unfavorable patient survival**
- **MYC family**: c-MYC, N-MYC, and L-MYC
- MYCs are **considered undruggable** by classic methods

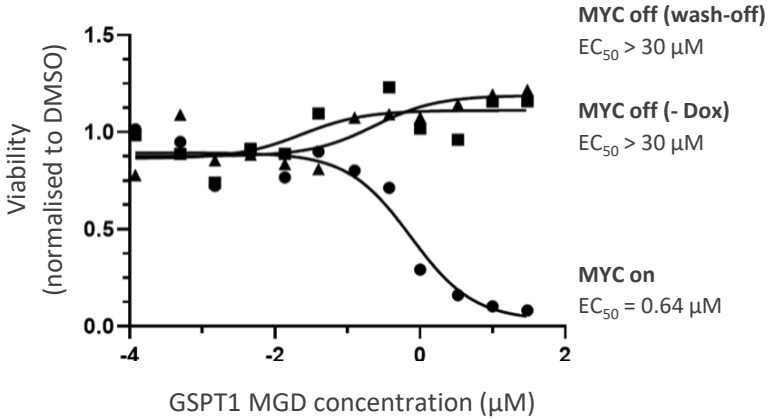
Cells expressing high MYC are sensitive to MYC CRISPR KO



DepMap data, each dot represents a cell line

Identification of GSPT1 Degraders Active in MYC-driven Solid Tumors

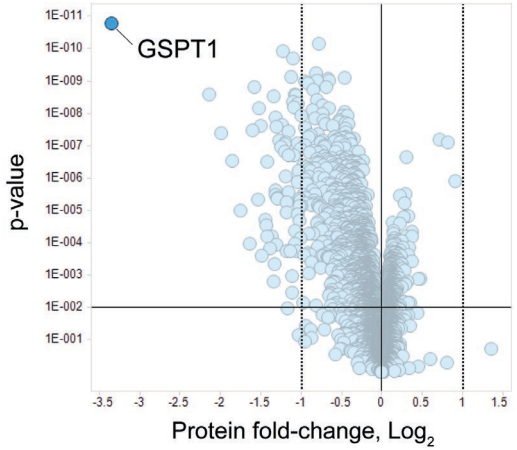
GSPT1 MGDs selectively affect MYC-addicted cells



Viability effects are cereblon-dependent

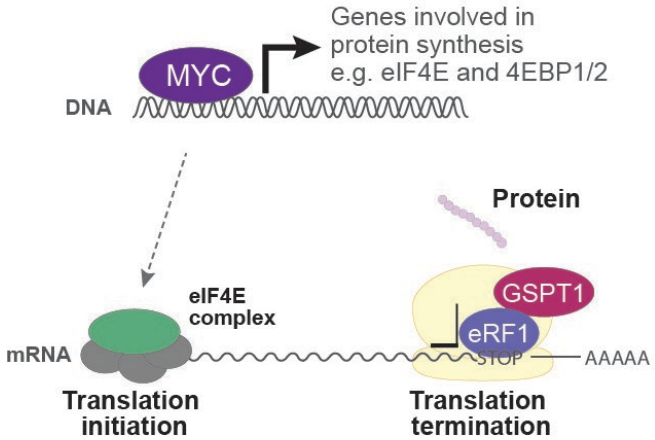
MYC expression status governs cell sensitivity to primary hit

Proteomics reveals selective degradation of GSPT1



Representative hit from MGD library inducing the degradation of GSPT1

GSPT1 Target and Desired MGD Profile

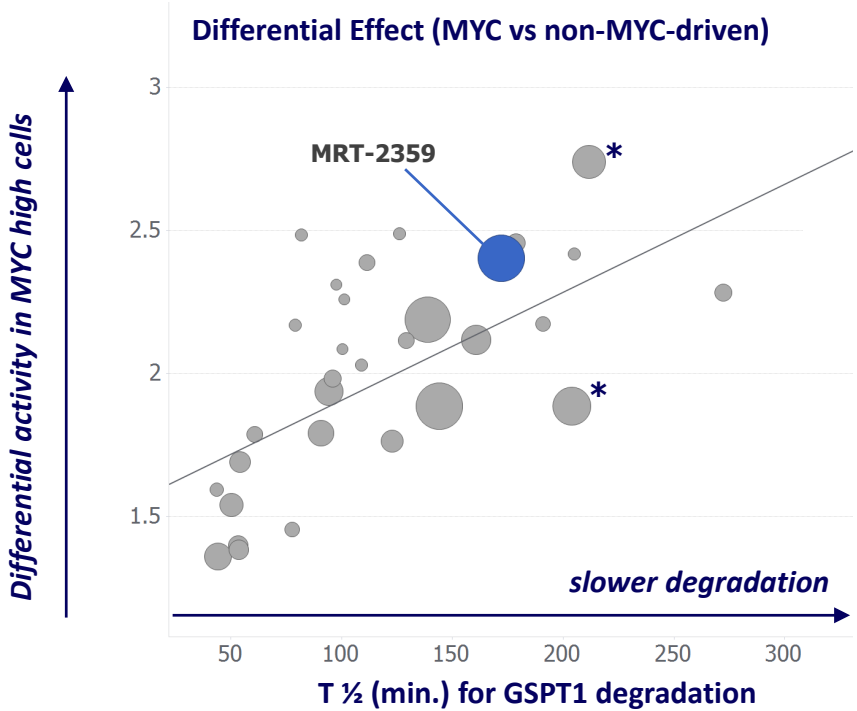


- To sustain growth, MYC-driven tumors are **addicted to protein translation**
- This addiction creates a **dependency on** the translation termination factor **GSPT1**

Desired MGD Profile:

- Oral
- Optimal selectivity for GSPT1 vs other neosubstrates
- Maximal preferential effect (MYC-driven vs non MYC-driven cancers)
- Differentiation over other pathway mechanisms/compounds

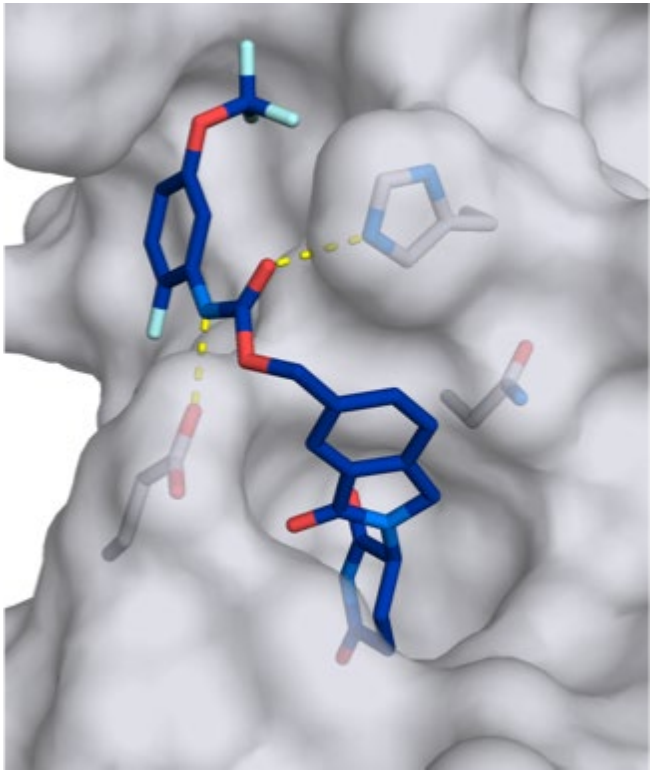
MedChem Design was Focused on Degradation Kinetics, Selectivity, Oral Bioavailability

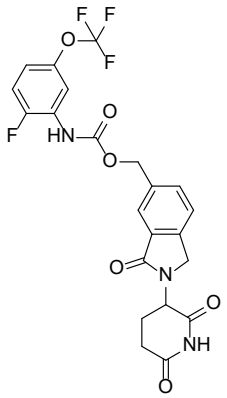


- Kinetic measurements of degradation reveal **novel parameter for optimization**
- GSPT1 degradation **kinetics are linked to its MoA**
- MRT-2359 achieves **a high selective effect** (2.4 U) in NSCLC
- MRT-2359 has been rationally designed to be in the ADMET sweet-spot
- Several compounds with good oral bioavailability discovered (large circles = >40%F po)

*** Compounds with reactive metabolite flag**

Carbonyl-Switch of MRT-2359 was Critical for Selectivity

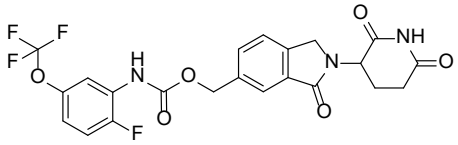




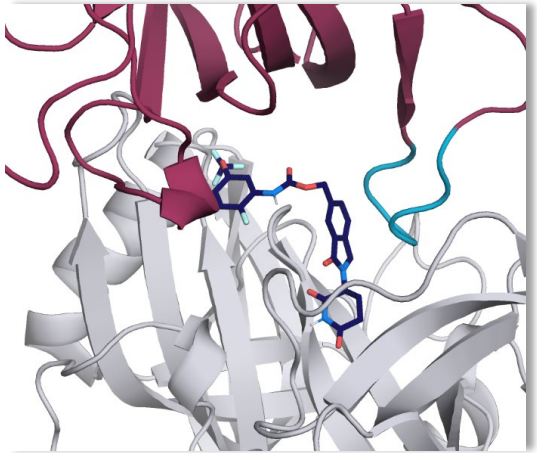
MRT-2359

- **Sidechain dictated binding-mode** forces isoindolinone carbonyl in new position
- GSPT1 degron is engaged through **extended sidechain interactions**
- Alternative ZnF neosubstrates are no longer recruited resulting in **high selectivity**

MRT-2359 is a Highly Optimized and Potent GSPT1 MGD



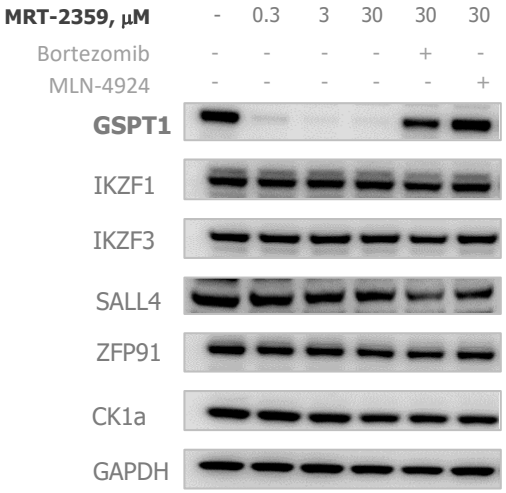
CRBN/MRT-2359/GSPT1 ternary complex



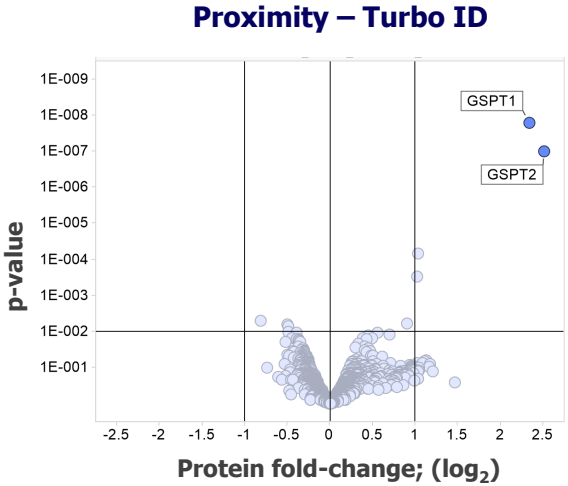
Biochemical and cellular data	
CRBN binding (HTRF; K_i)	113 nM
Ternary complex (HTRF; EC_{50})	7 nM
Selectivity (TMT proteomics)	GSPT1 / GSPT2
DC_{50}/Dmax (high Myc lung lines, 6 hr)	1-20 nM / 100%
High N-Myc NSCLC H1155 / ABC-1 (EC_{50})	25 / 74 nM
High L-Myc SCLC H82 / H1836 (EC_{50})	31 / 11 nM
MM/lymphoma panel	broad activity

MRT-2359 is a Highly Selective & Oral GSPT1-directed MGD

MRT-2359 is a selective GSPT1-directed MGD



6hr post treatment in MM1S and Kelly (SALL4)



1hr post treatment

MRT-2359 is orally bioavailable and has favorable ADMET profile

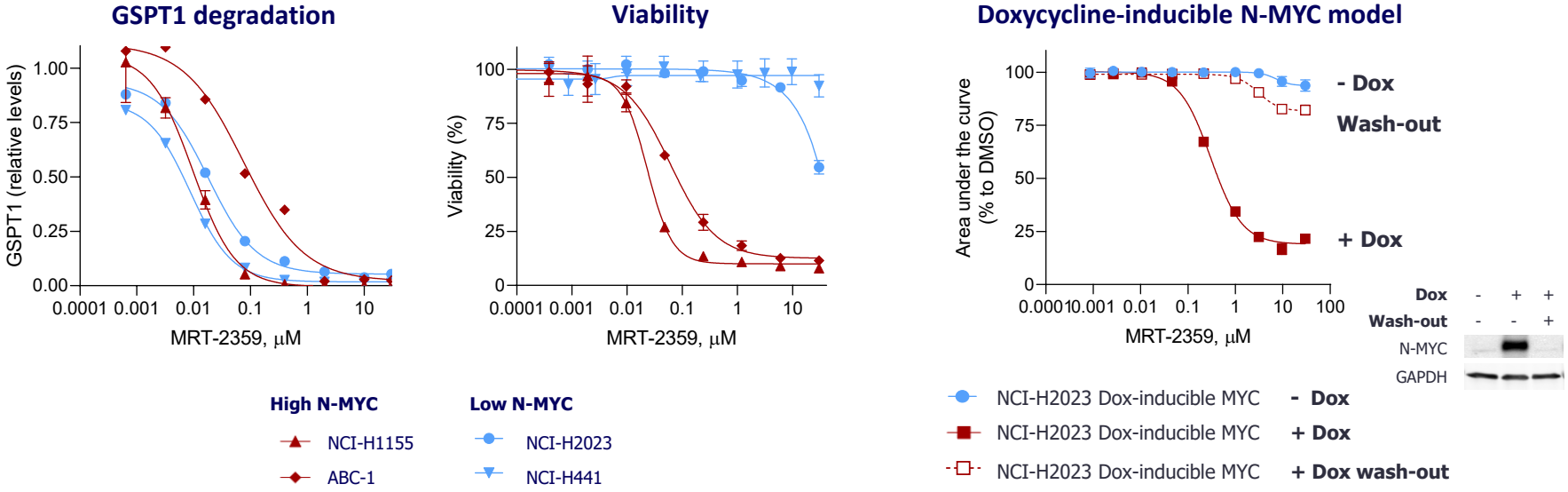
ADMET profile	
CYP DDIs	> 30 μM
hERG inhibition patch clamp	EC_{50} > 30 μM
Oral bioavailability all species	~50%

- No activity observed in an in vitro panel of 44 safety targets

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

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

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

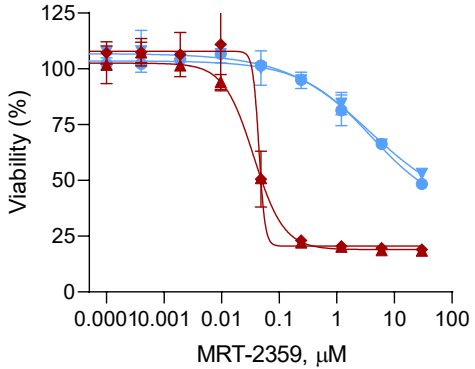


GSPT1 western blot at 6 hr (N-Myc high) and 24 hr (low). 72 hr viability assay (CTG)

Incucyte, 96 hr post treatment

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

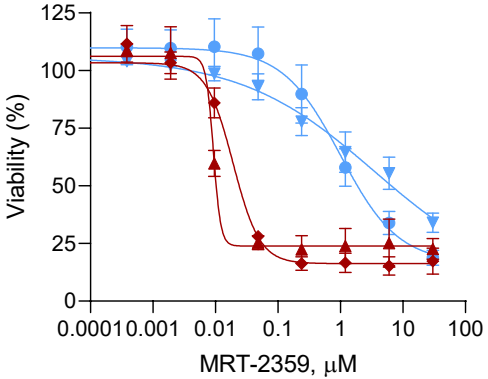
Prostate cell lines (c-MYC)



High c-MYC
- 22RV1
- VCaP

Low c-MYC
- PC3
- DU-145

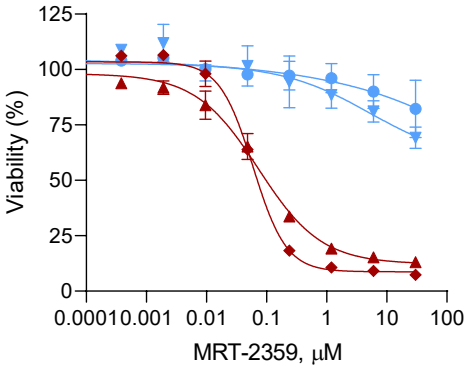
SCLC cell lines (L-MYC)



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 Preferentially Impairs Protein Synthesis in Tumor Cells with High MYC Expression

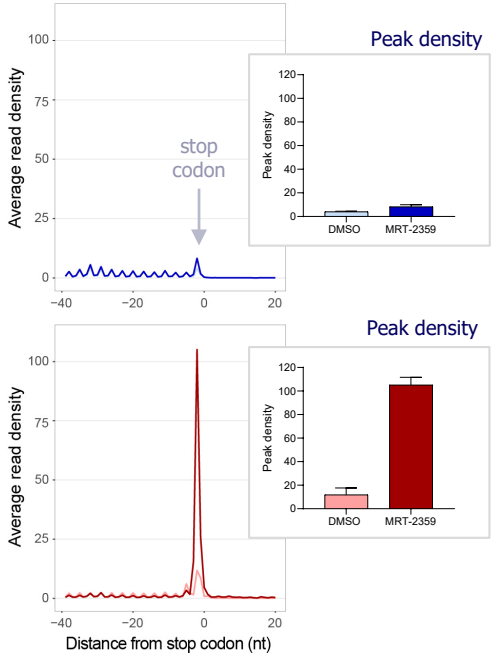
MRT-2359 induces ribosome stalling at stop codon only in N-MYC high cell line

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

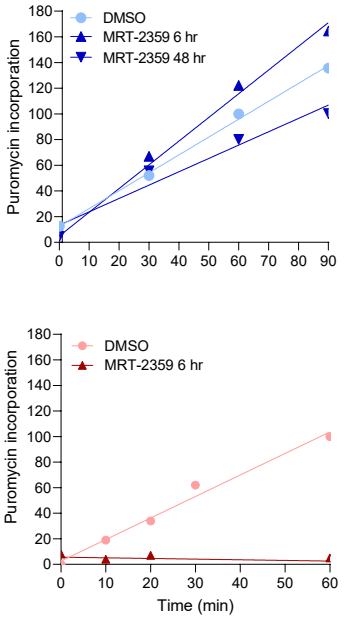
Low N-MYC
NCI-H2023

High N-MYC
NCI-H1155

Metagene plots



Puromycin incorporation



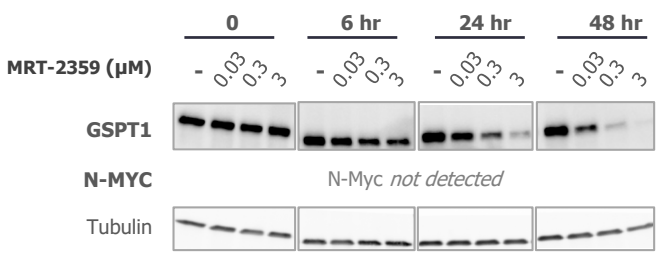
Ribo-Seq – 24 hr post-treatment

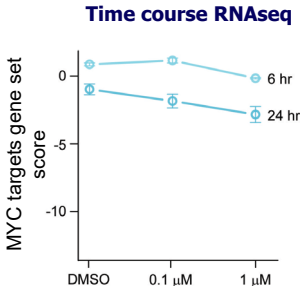
MRT-2359 Affects MYC and MYC Pathway in N-MYC High NSCLC Cell Lines

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

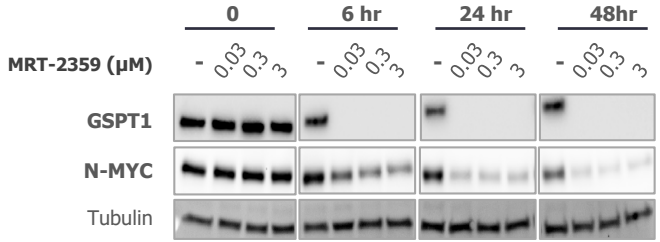
Degradation of GSPT1 leads to downregulation of N-MYC transcriptional output in NCI-H1155

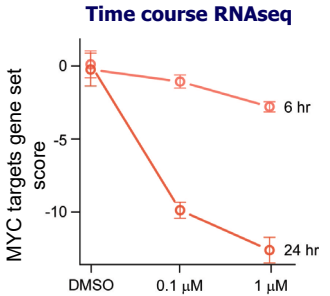
Low N-MYC
NCI-H2023





High N-MYC
NCI-H1155





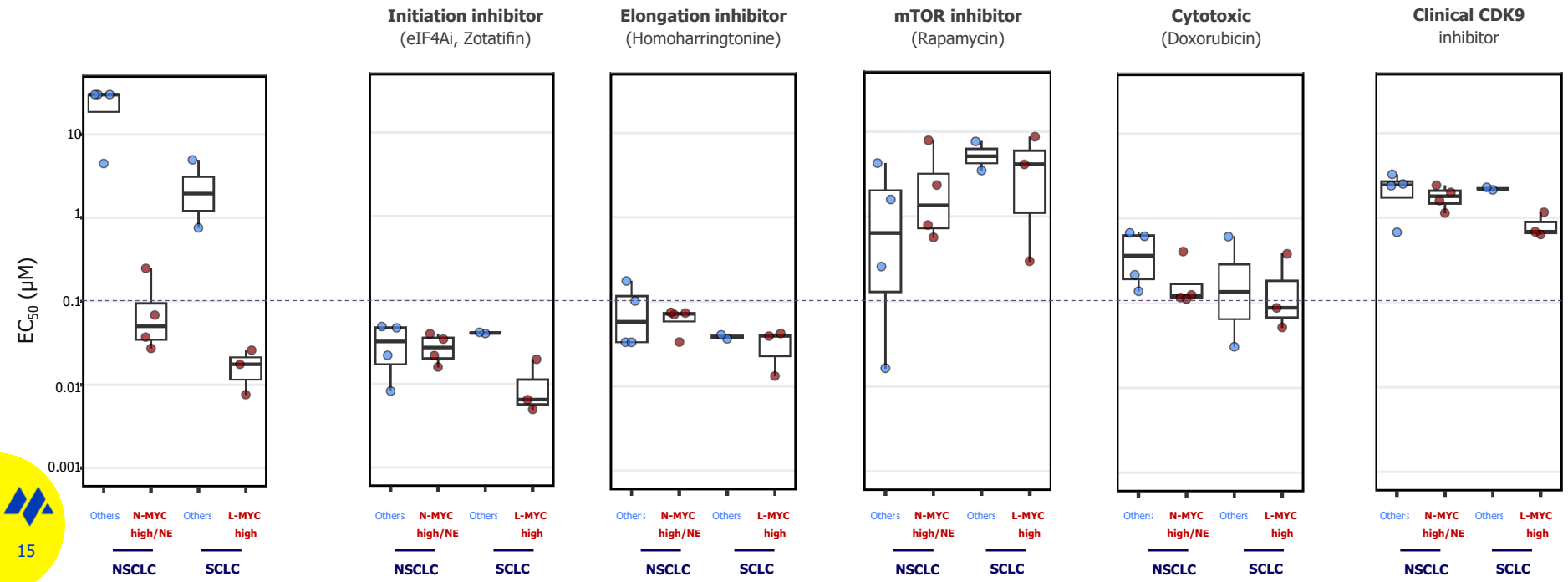
Transcriptional modulation of >200 MYC targets genes

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

MRT-2359

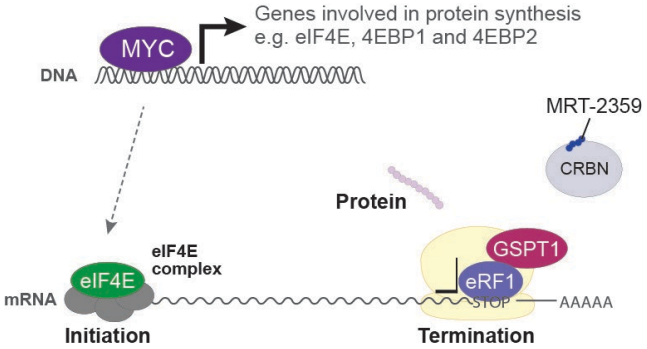
Other therapeutic agents targeting protein translation process or machinery lack preferential activity in the MYC high lung lines

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

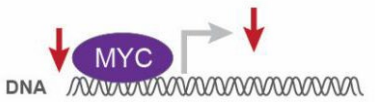
MRT-2359 leads to rapid and deeper degradation of GSPT1 in cancer cells with high MYC expression

Preferential inhibition of translation

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

MYC down modulation

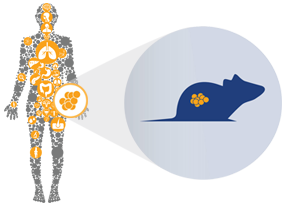
MRT-2359 indirectly affects MYC expression and transcriptional activity



Mechanism is applicable to c-MYC, N-MYC and L-MYC

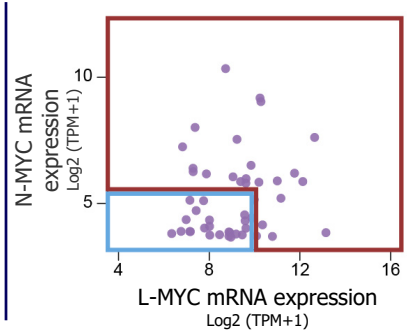
MRT-2359 Mouse-trial in NSCLC, SCLC and Lung NE Patient-derived Xenografts

Collection of PDX models



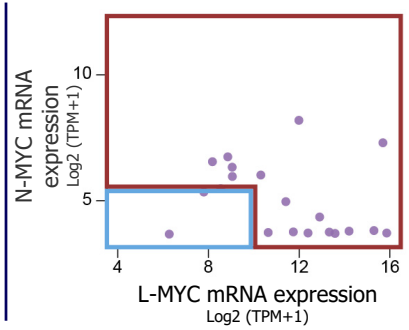
All models have been characterized by DNA and RNAseq

NSCLC



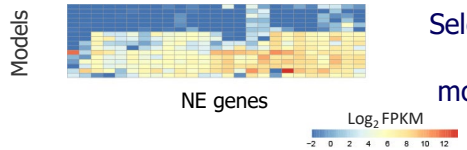
Selected 48 models

SCLC



Selected 20 models

Large cell NE carcinoma or NE lung cancer



Selected 10 models

L-MYC or N-MYC high

L-MYC and N-MYC low

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

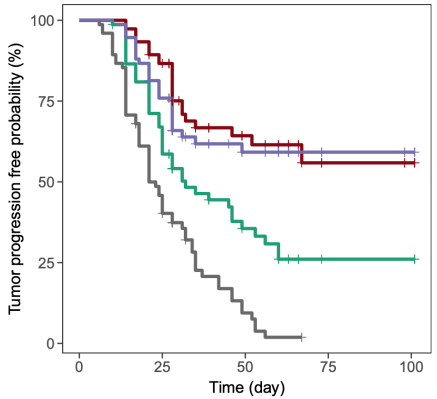
- Vehicle
- MRT-2359

3 mice for each treatment group

Dose-dependent Anti-tumor Activity Post Treatment with MRT-2359 and Using Different Schedules in PDX Models

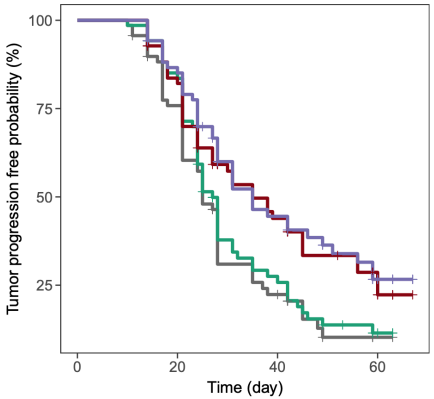
NSCLC N- or L-MYC high

25 PDXs



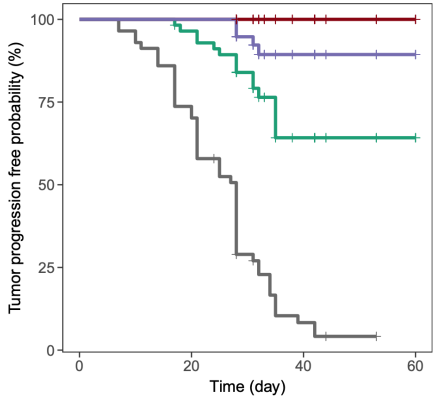
NSCLC N- and L-MYC low

23 PDXs



SCLC N- or L-MYC high

19 PDXs



Vehicle

MRT-2359 3 mg/kg PO QD

MRT-2359 10 mg/kg PO QD

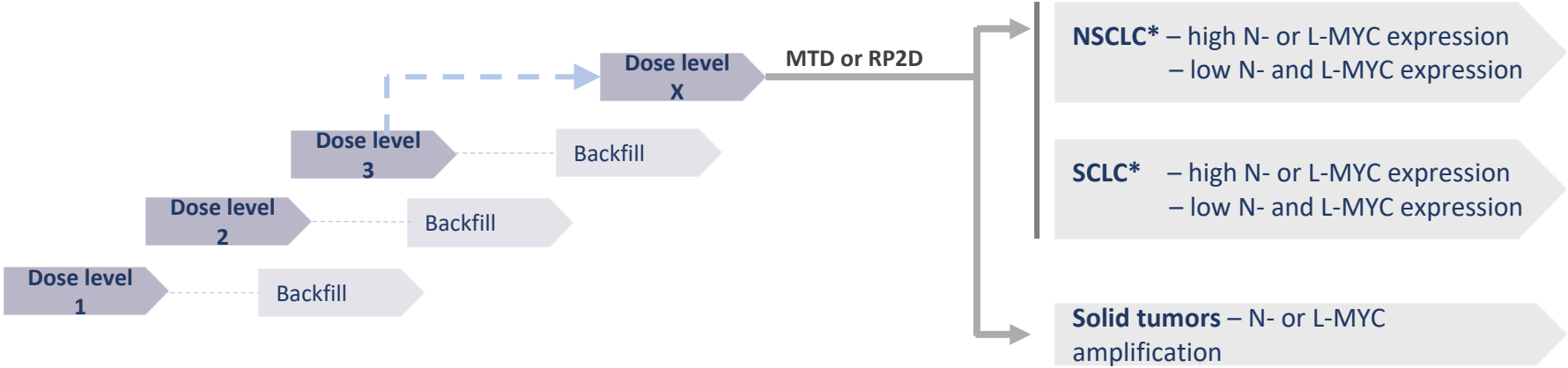
MRT-2359 30 mg/kg PO 5 ON/9 OFF

Study suggests dose dependent activity and similar efficacy of continuous vs on/off schedule

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

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

Patient dosing initiated in October 2022

Acknowledgments

MRT team

Project team

- Debora Bonenfant
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