MRT-2359 KOL Webinar hosted by Cowen

October 24, 2022

Guest Speakers

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Monte Rosa Therapeutics

Forward-Looking Statements

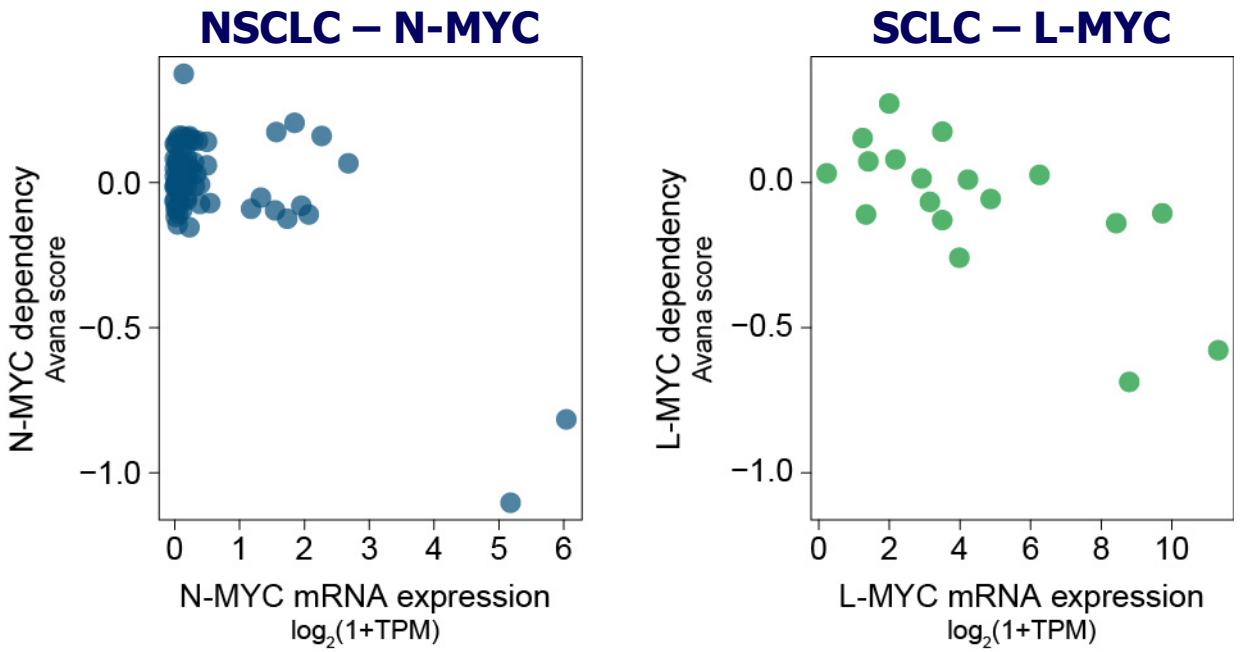
These materials include express and implied "forward-looking statements," including forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Forward looking statements include all statements that are not historical facts, and in some cases, can be identified by terms such as "may," "might," "will," "could," "would," "should," "expect," "intend," "plan," "objective," "anticipate," "believe," "estimate," "predict," "potential," "continue," "ongoing," or the negative of these terms, or other comparable terminology intended to identify statements about the future. Forward-looking statements contained in herein include, but are not limited to, statements about our product development activities, including our expectations around MRT-2359 and the ongoing development of our QuEEN™ platform, and the advancement of our pipeline and the various products therein, our expectations of timing for initiation of our clinical trial for MRT-2359, our expectations of timing for dosing patients in our clinical trial for MRT-2359, our ability to initiate and the timing of initiation of additional lead optimization programs, and our expectations regarding our ability to nominate and the timing of our nominations of additional development candidates. By their nature, these statements are subject to numerous risks and uncertainties, including the impact that the current COVID-19 pandemic will have on our development activities and operations, as well as those risks and uncertainties set forth in our Annual Report on Form 10-K for the fourth quarter and full year ended December 31, 2021 filed, with the US Securities and Exchange Commission on March 29, 2022, and any subsequent filings, including our Quarterly Report on Form 10-Q for the second quarter of 2022 ending on June 30, filed on August 11, 2022, that could cause actual results, performance or achievement to differ materially and adversely from those anticipated or implied in the statements. You should not rely upon forward looking statements as predictions of future events. Although our management believes that the expectations reflected in our statements are reasonable, we cannot guarantee that the future results, performance or events and circumstances described in the forward-looking statements will be achieved or occur. Recipients are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date such statements are made and should not be construed as statements of fact. We undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, any future presentations or otherwise, except as required by applicable law. Certain information contained in these materials and any statements made orally during any presentation of these materials that relate to the materials or are based on studies, publications, surveys and other data obtained from third-party sources and our own internal estimates and research. While we believe these third-party studies, publications, surveys and other data to be reliable as of the date of these materials, we have not independently verified, and make no representations as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. In addition, no independent source has evaluated the reasonableness or accuracy of our internal estimates or research and no reliance should be made on any information or statements made in these materials relating to or based on such internal estimates and research.

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

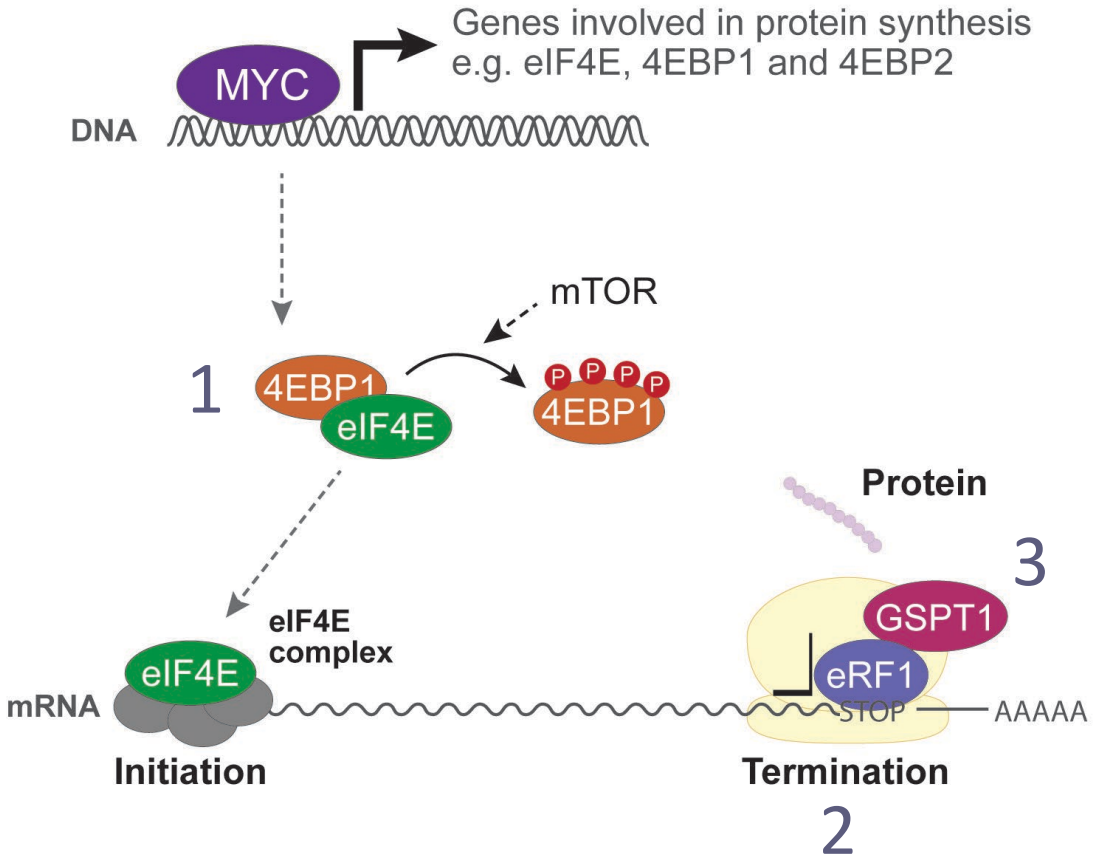
Cells expressing high MYC are sensitive to MYC CRISPR KO



DepMap data, each dot represents a cell line

Targeting enhanced translation induced by MYC represents an attractive alternative

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

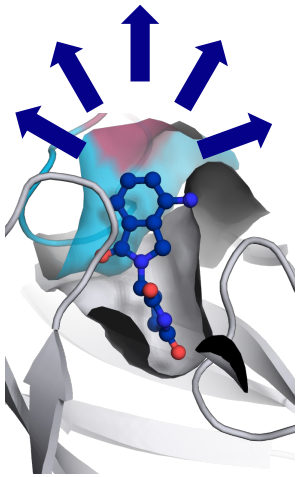
Therapeutic vulnerability

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

QuEEN™ Discovery Engine Facilitates the Discovery of MRT-2359

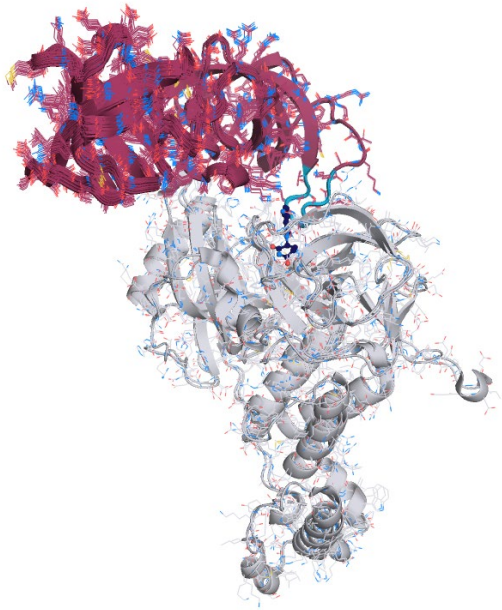
Proprietary MGD library

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

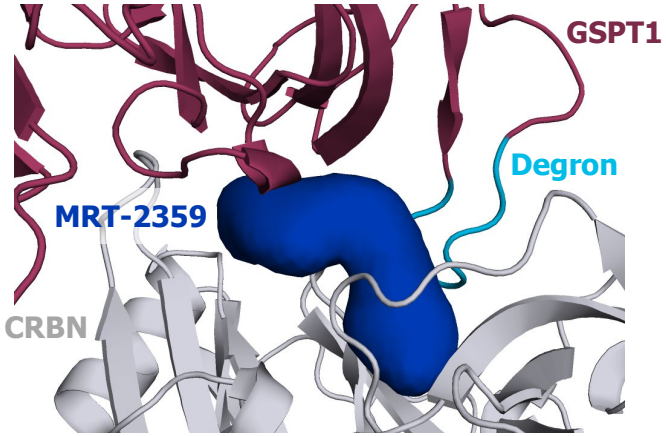


Rhapsody™

In silico ternary complex modelling using proprietary AI-powered algorithms



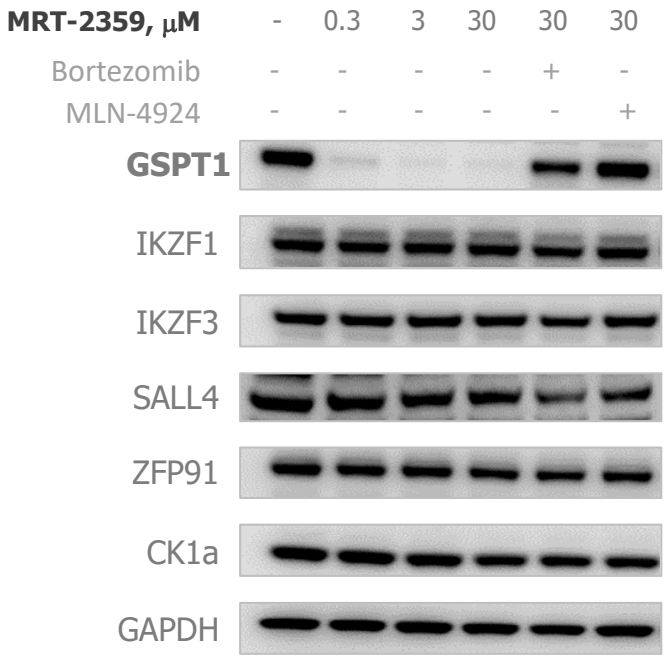
MRT-2359 is a potent GSPT1 degrader



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

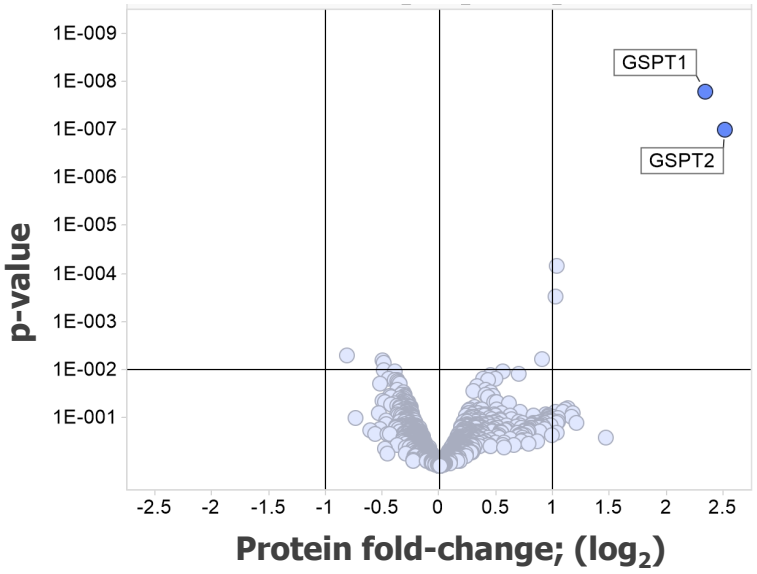
MRT-2359 is a GSPT1-directed MGD with Favorable Drug-like Properties

MRT-2359 is a selective GSPT1-directed MGD



6hr post treatment in MM1S and Kelly (SALL4)

Proximity – Turbo ID



1hr post treatment

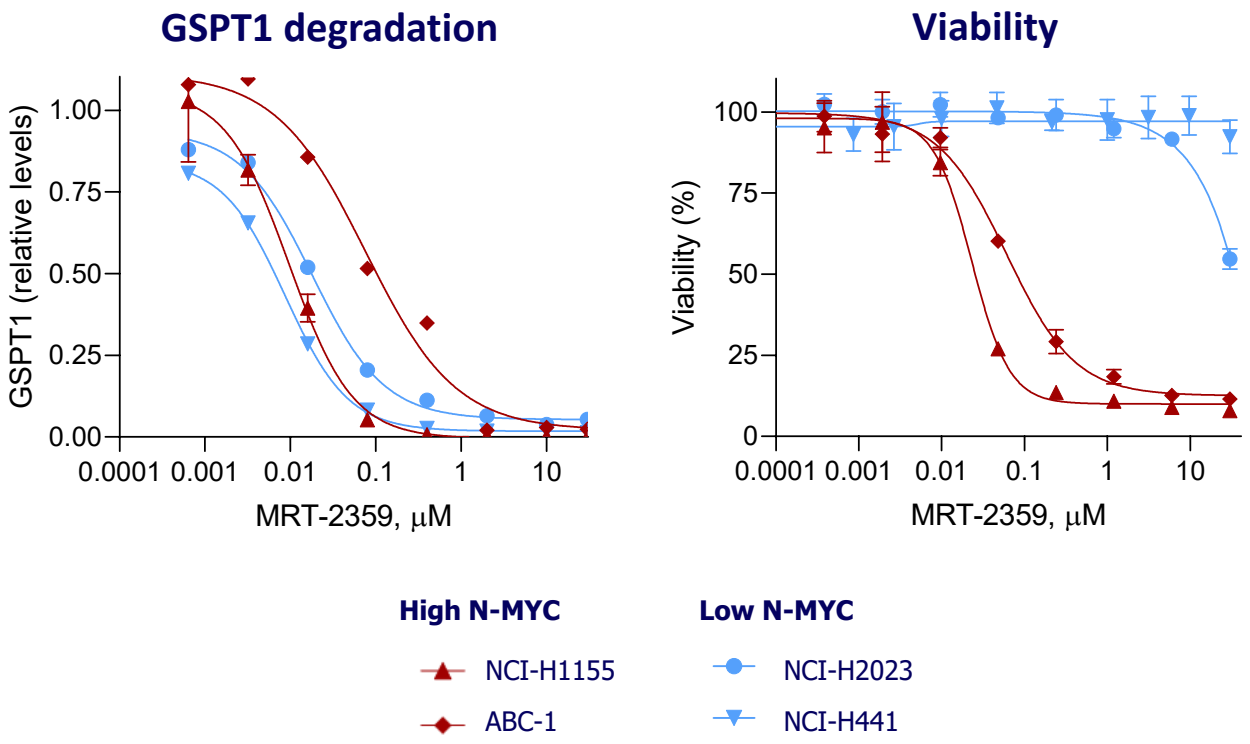
MRT-2359 is orally bioavailable and has favorable ADMET profile

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

- MRT-2359 is neither an inhibitor, nor an inducer of major CYPs
- MRT-2359 doesn't inhibit hERG
- MRT-2359 is orally bioavailable

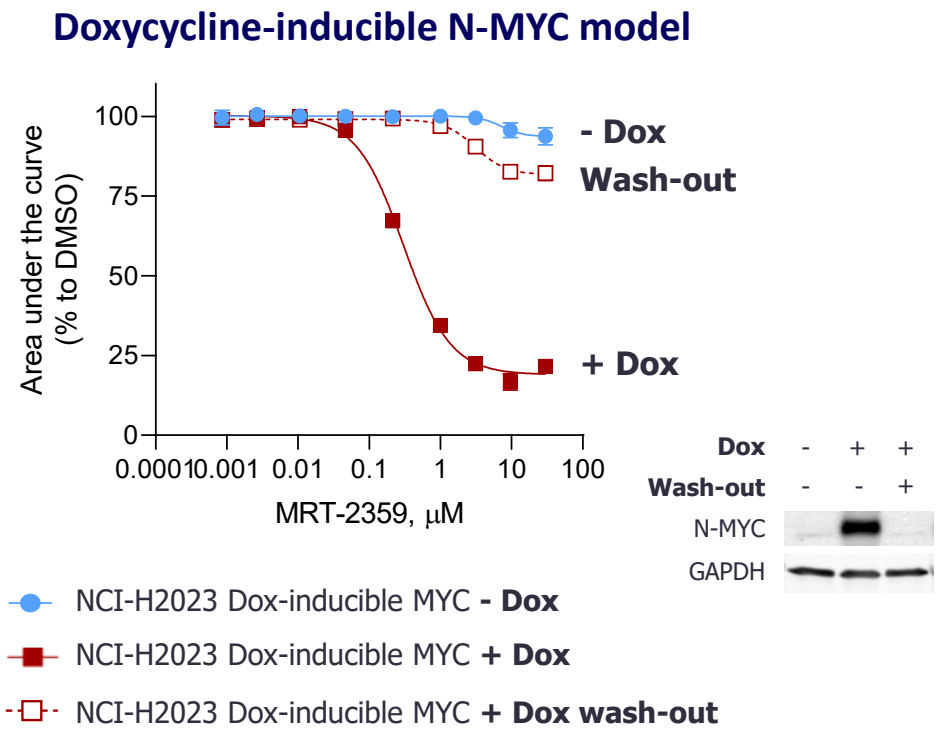
Preferential activity of MRT-2359 in MYC-Driven NSCLC Lines

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



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

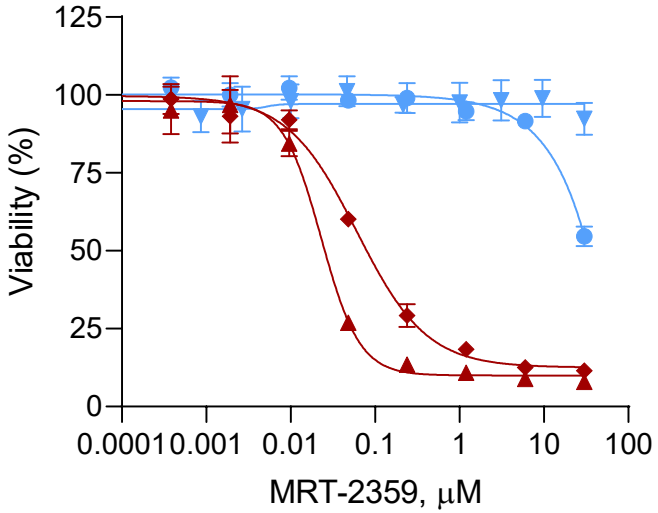
N-MYC overexpression sensitizes NCI-H2023 resistant cells to MRT-2359



Incucyte, 96 hr post treatment

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

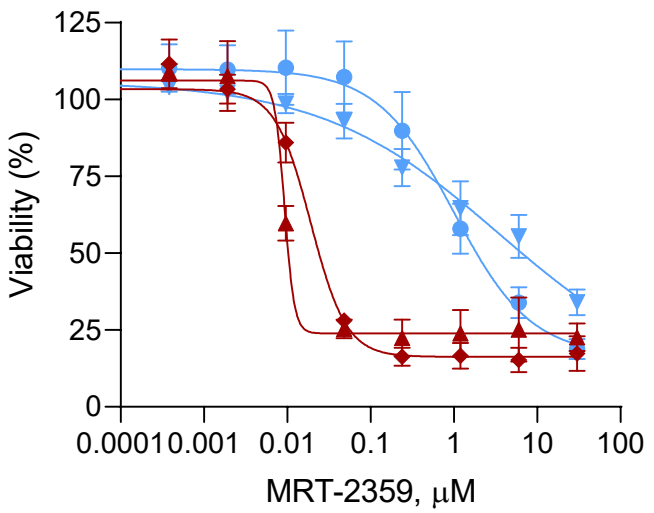
N-MYC - NSCLC lines



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

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

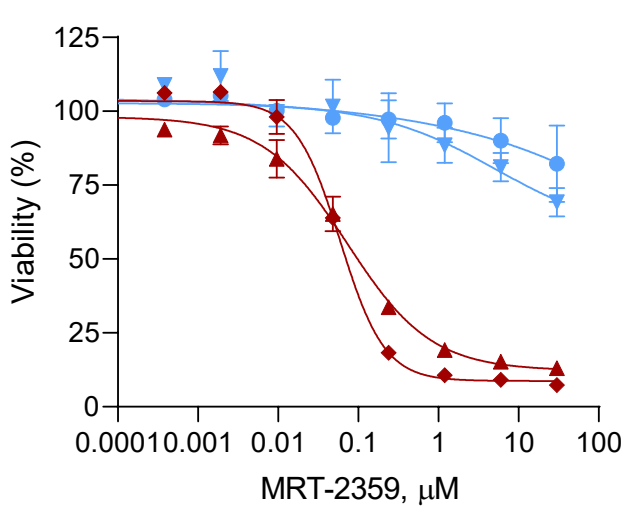
L-MYC - SCLC lines



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

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

NE positive lung lines



High NE
- NCI-H810
- NCI-H1770

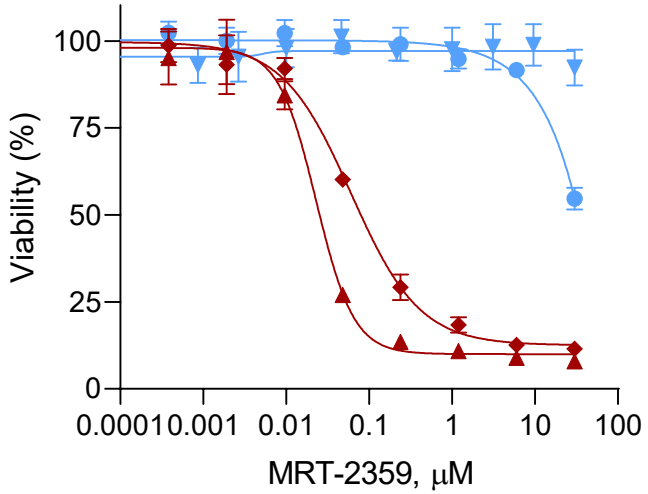
Low NE
- NCI-H2405
- NCI-H1693

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

72 hr viability assay (CTG)

MRT-2359 Shows Preferential Activity Compared to "Rapid" GSPT1 Degraders

MRT-2359



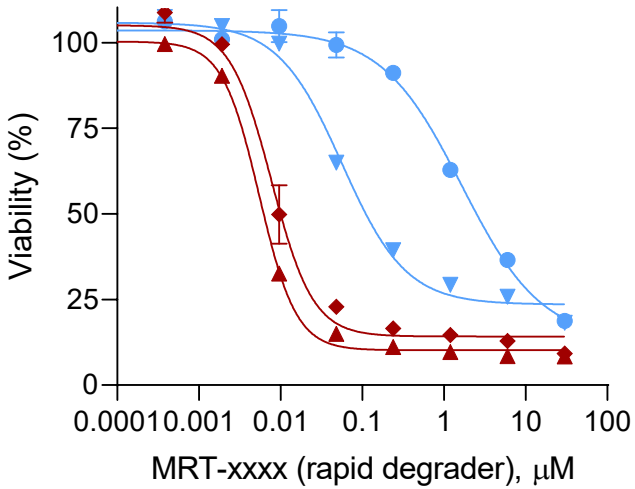
High N-MYC

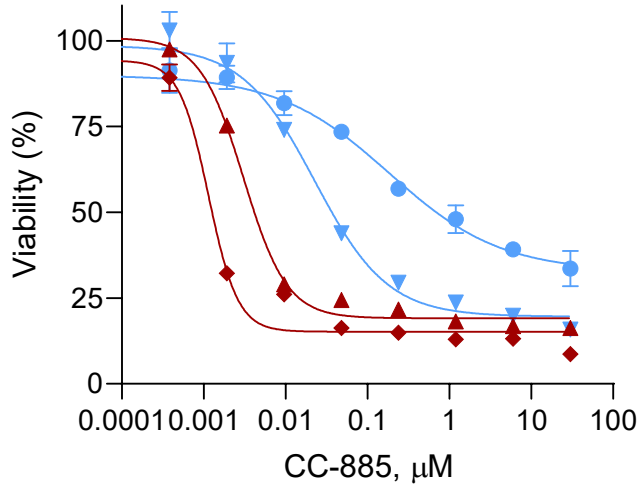
- NCI-H1155
- ABC-1

Low N-MYC

- NCI-H2023
- NCI-H441

¨Rapid¨ GSPT1 degraders lack preferantial actvity in N-MYC high cell lines





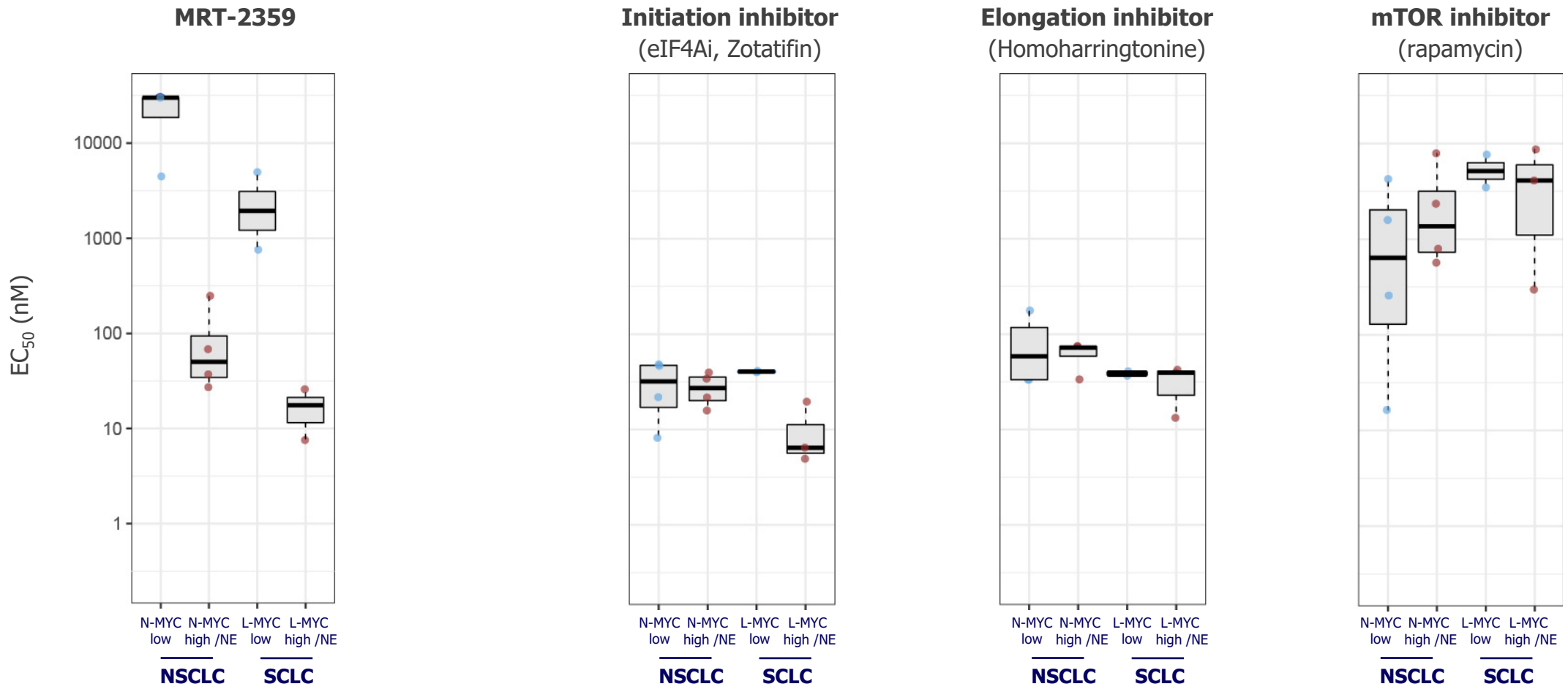
- Differential activity can be optimized and is a funtion of selectivity and degradation dynamics
- High selectivity and intermediate fast degradation (6h – vs 1-2h to maximum degradation) lead to greater differential activity

72 hr viability assay (CTG)

Translation Initiation/Elongation Inhibitors Do Not Show Preferential Activity in MYC High NSCLC and SCLC Cell Lines

MRT-2359 shows preferentially activity in MYC high lung lines

Translation initiation and elongation inhibitors lack differential activity



72 hr viability assay (CTG).

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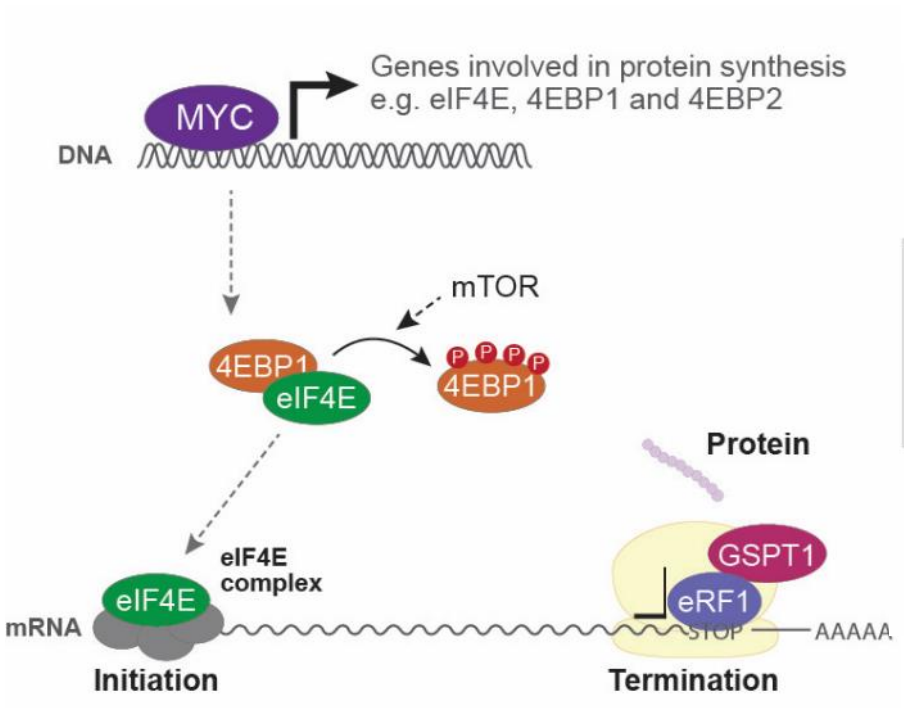
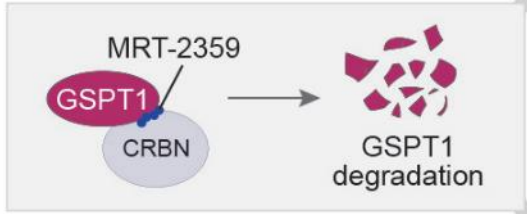
MRT-2359 Mechanism of Action

MRT-2359 Mechanism of Action in MYC-driven Tumors



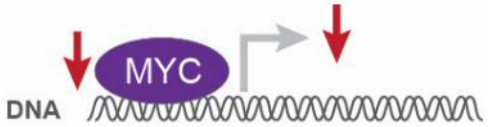


Synthetic lethality

MRT-2359 impairs protein synthesis in MYC high lines

Oncogene addiction

MRT-2359 affects MYC and downstream in MYC high lines

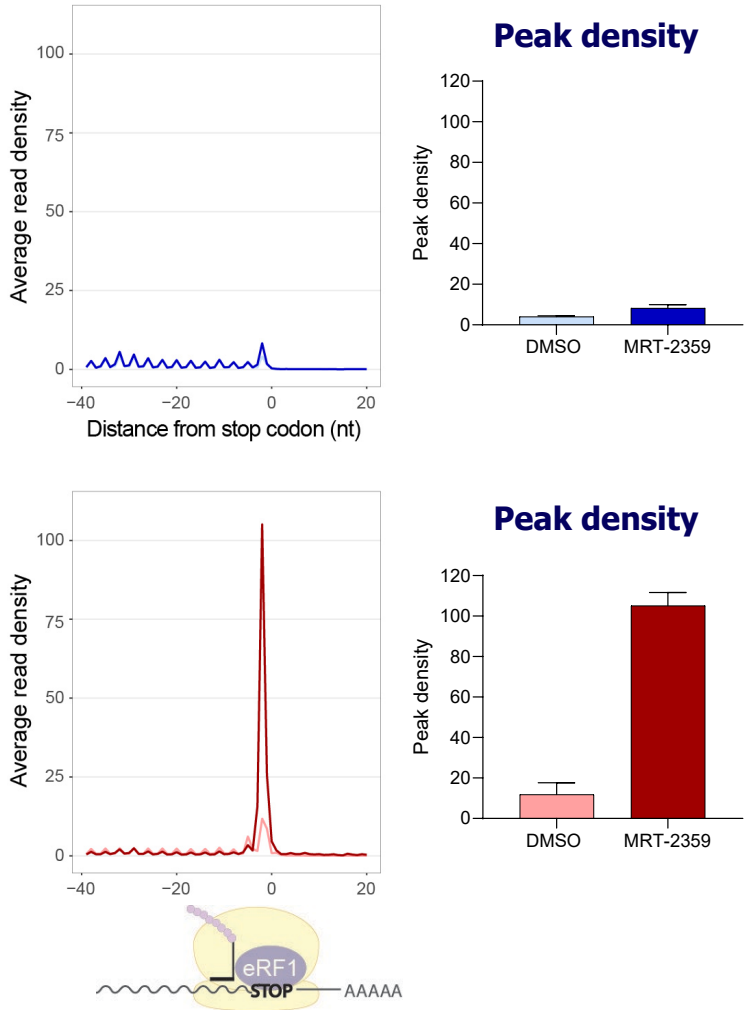


MRT-2359 Impairs Protein Synthesis in N-MYC High NSCLC Cell Lines

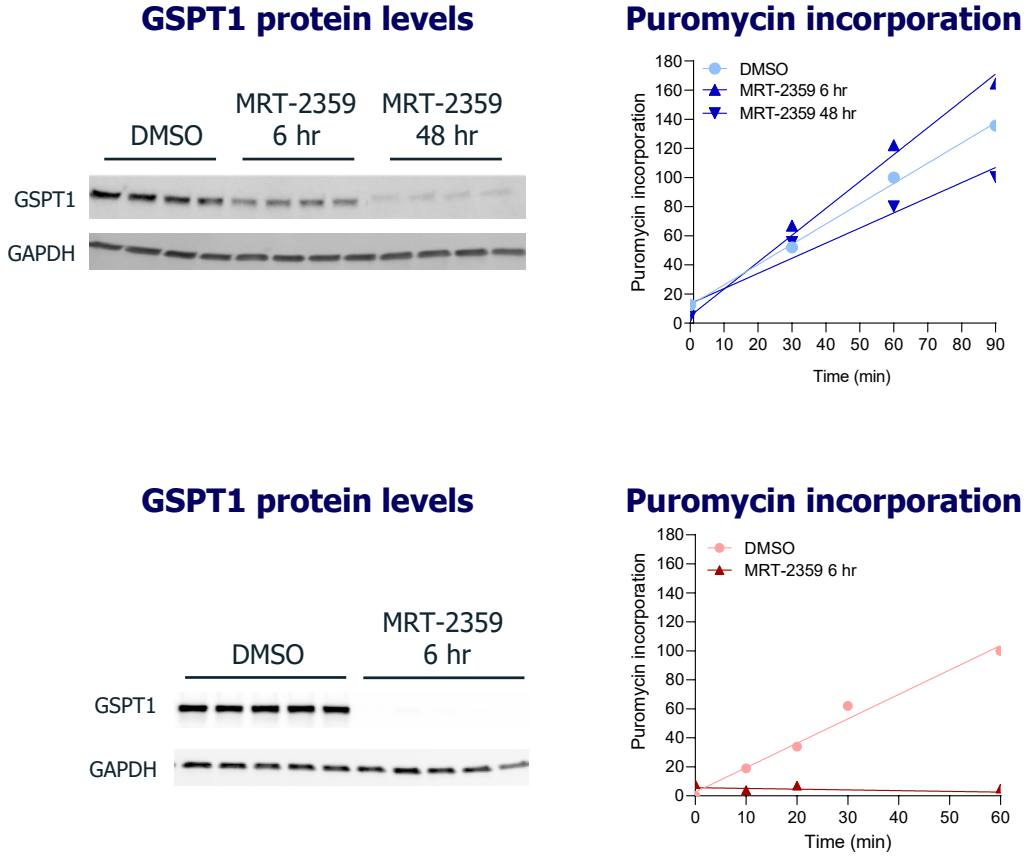
Low N-MYC
NCI-H2023

High N-MYC
NCI-H1155

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



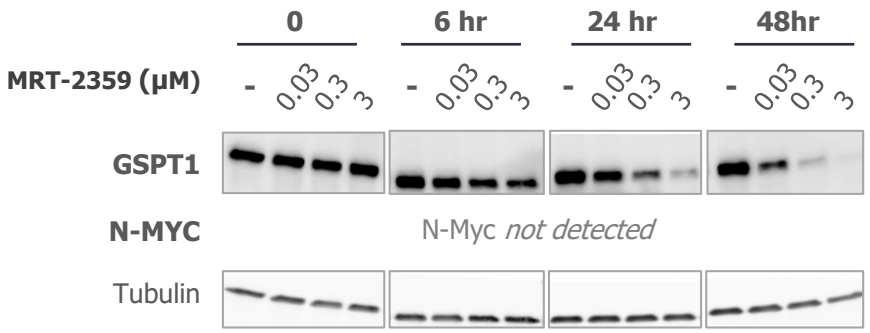
MRT-2359 rapidly and completely abrogates protein synthesis only in N-MYC high cell line



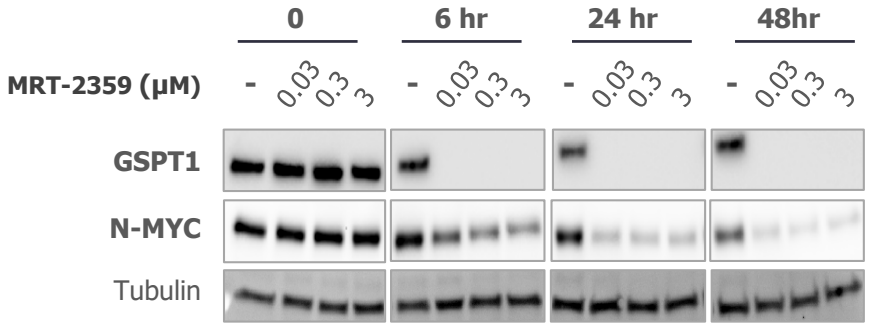
MRT-2359 Affects MYC and MYC Pathway in N-MYC High NSCLC Cell Lines

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

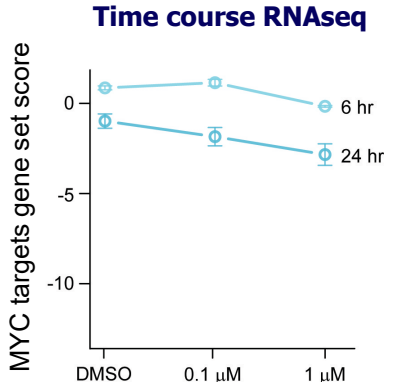
Low N-MYC
NCI-H2023

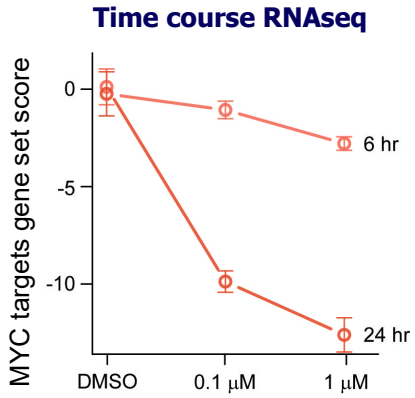


High N-MYC
NCI-H1155



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





Transcriptional modulation of >200 MYC targets genes

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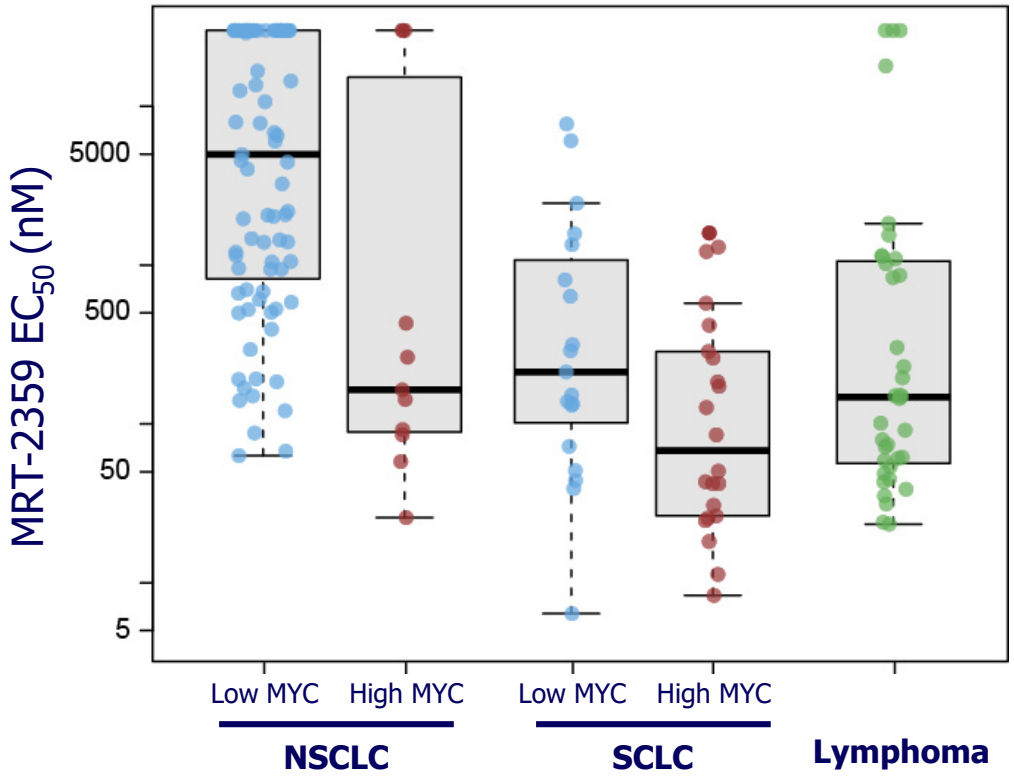
MRT-2359 and Other Clinical Stage GSPT1 Degrader

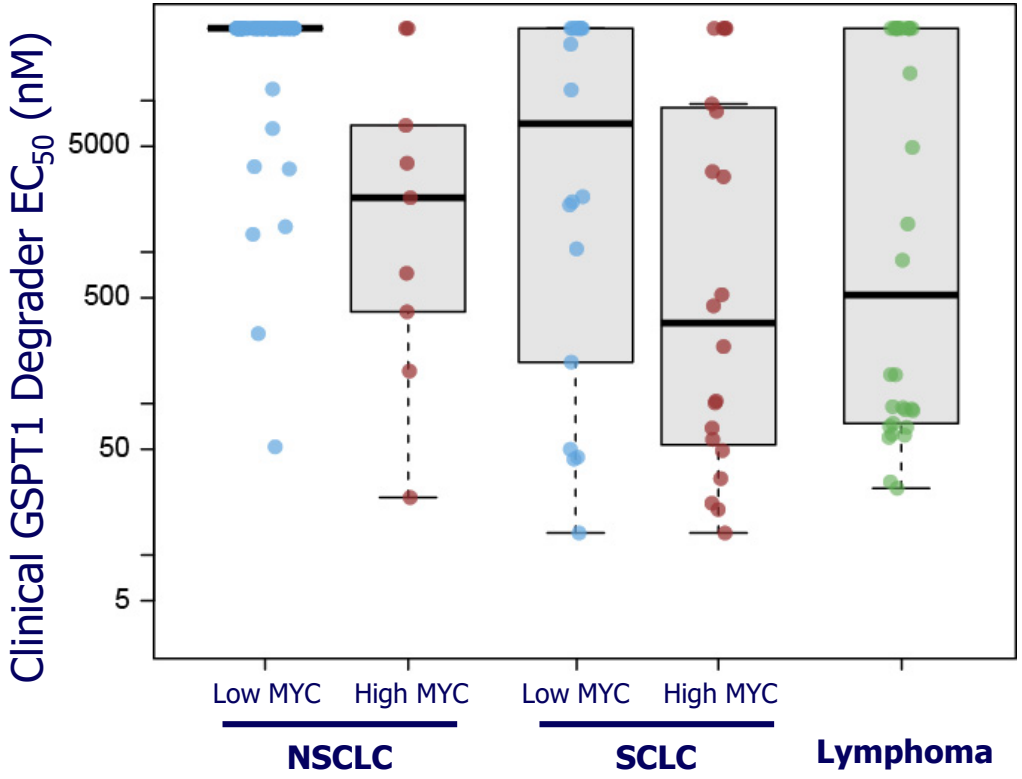
MRT-2359 Shows Superior Characteristics Compared to Clinical GSPT1 Degrader

	Assay	MRT-2359	Clinical GSPT1 Degrader
in vitro			
	Selectivity (TMT Px, WB)	GSPT1, GSPT2	GSPT1, GSPT2, SALL4, FIZ1, RNF166, ODC1
	CYP DDI (2B6, 1A2, 2D6,3A4, 2C8,2C9, 2C19)	> 30 uM	CYP2C19 @ 1.5 uM
	hERG (patch clamp)	> 30 uM	5.3 uM
	CEREP	a1A > 50% @ 10 uM	M1/M2 > 50% @ 10 uM
	Caco2 (Efflux Ratio)	9	>100
in vivo	Route of Administration	PO	IV
Clinical	Development status	Ph I	Phase I/Ib
	Stratification	Myc high	None reported

* Comparison based on internal profiling. Selectivity based on internal data as well as data from DFCI Proteomic data base https://proteomics.fischerlab.org

Superior Activity of MRT-2359 in MYC-driven Cancer Cell Lines





* Comparison based on internal profiling

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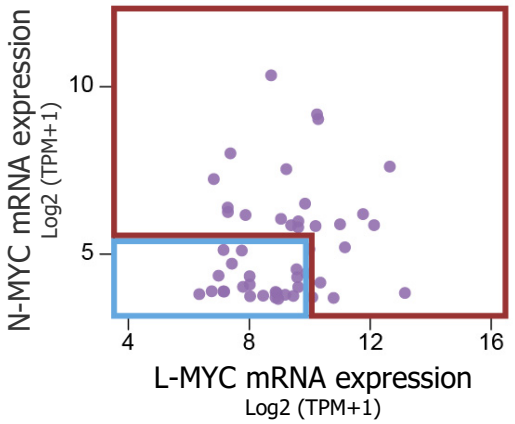
Preclinical Anti-tumor Activity of MRT-2359 in MYC-driven Animal Models

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

Collection of PDX models

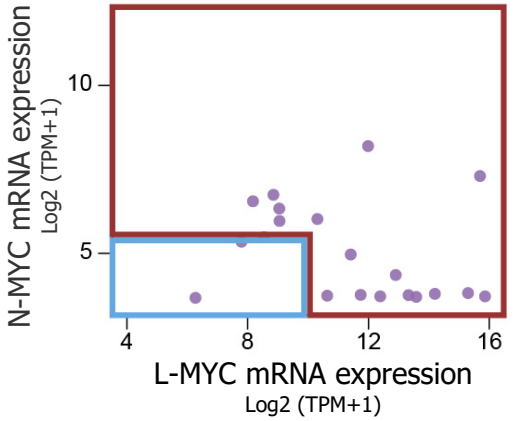
All models have been characterized by DNA and RNAseq

NSCLC



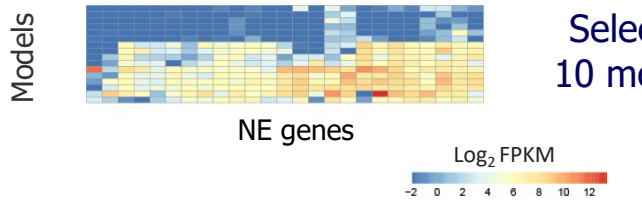
Selected 48 models

SCLC



Selected 20 models

Large cell NE carcinoma or NE lung cancer



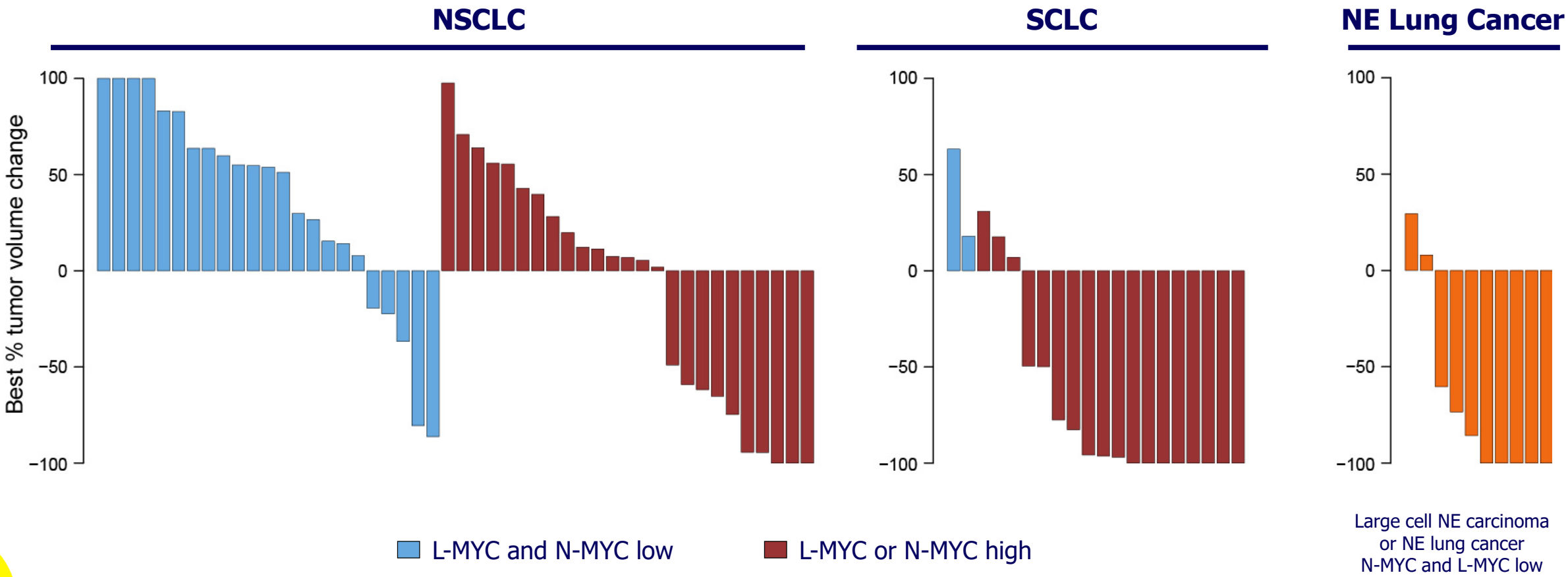
Selected 10 models

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

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

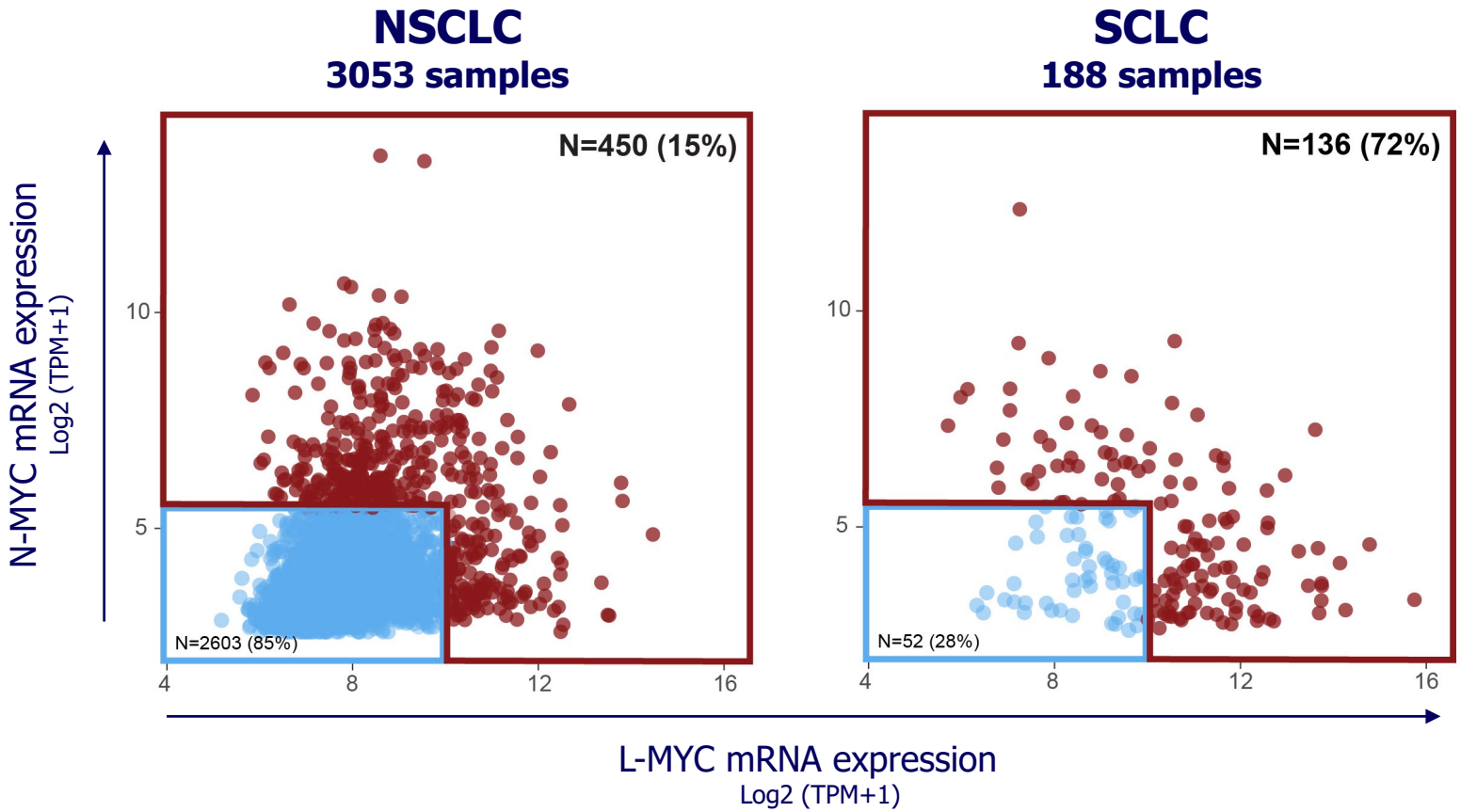
3 mice for each treatment group

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

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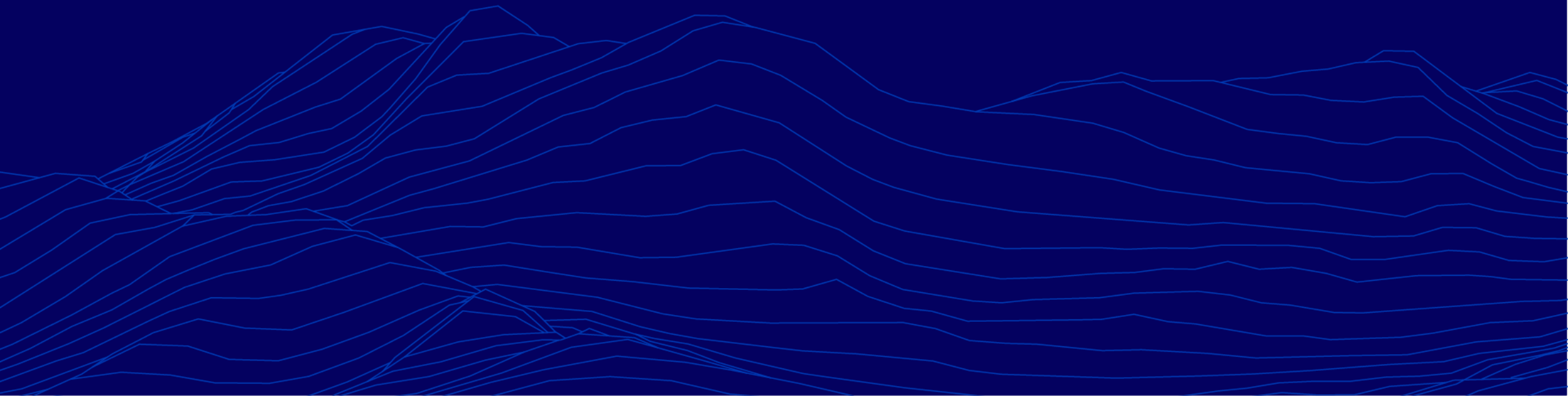
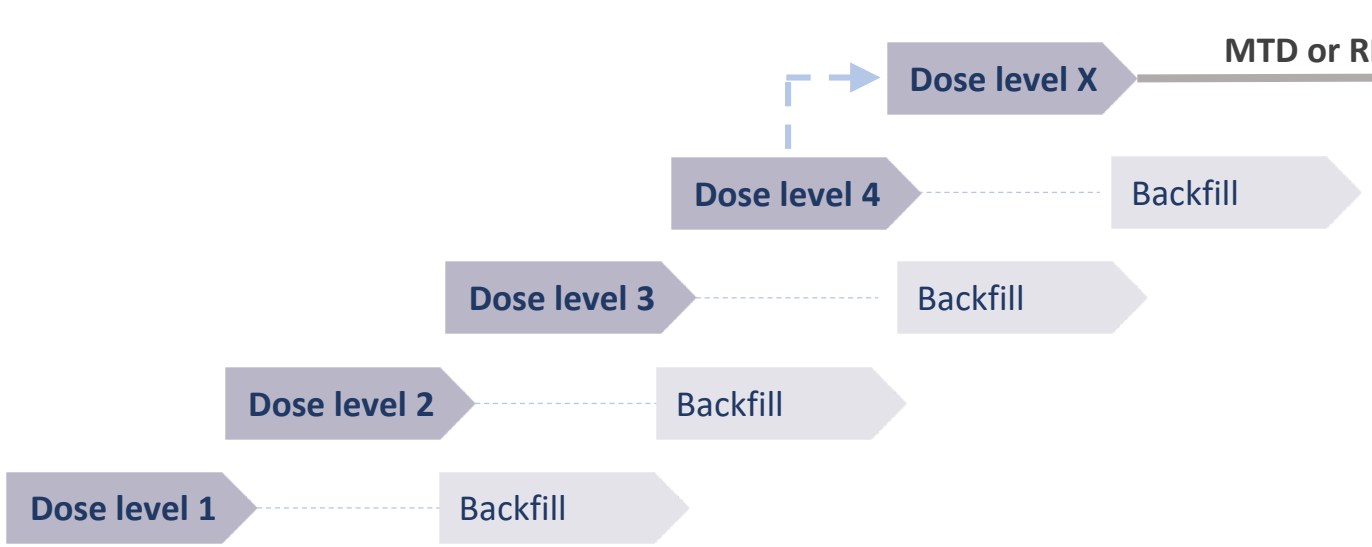
Phase 1/2 Clinical Study



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

Clinical Sites

Clinical Site	PI	Expertise
MDACC	Dr. Rodon	Phase I/Lung
SCRI	Dr. Spigel	Lung
MSKCC	Dr. Choudhury	Phase I/Lung
DFCI	Dr. Janne	Lung
Mary Crowley CR	Dr. Barve	Phase I
START TX	Dr. Papadopoulos	Phase I
Honor Health	Dr. Tsai	Phase I
Indiana University	Dr. Opyrchal	Phase I

ClinicalTrials.gov Identifier: NCT05546268


Thank You
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