Molecular Glue Degraders (MGDs) – From the Bench to the Clinic

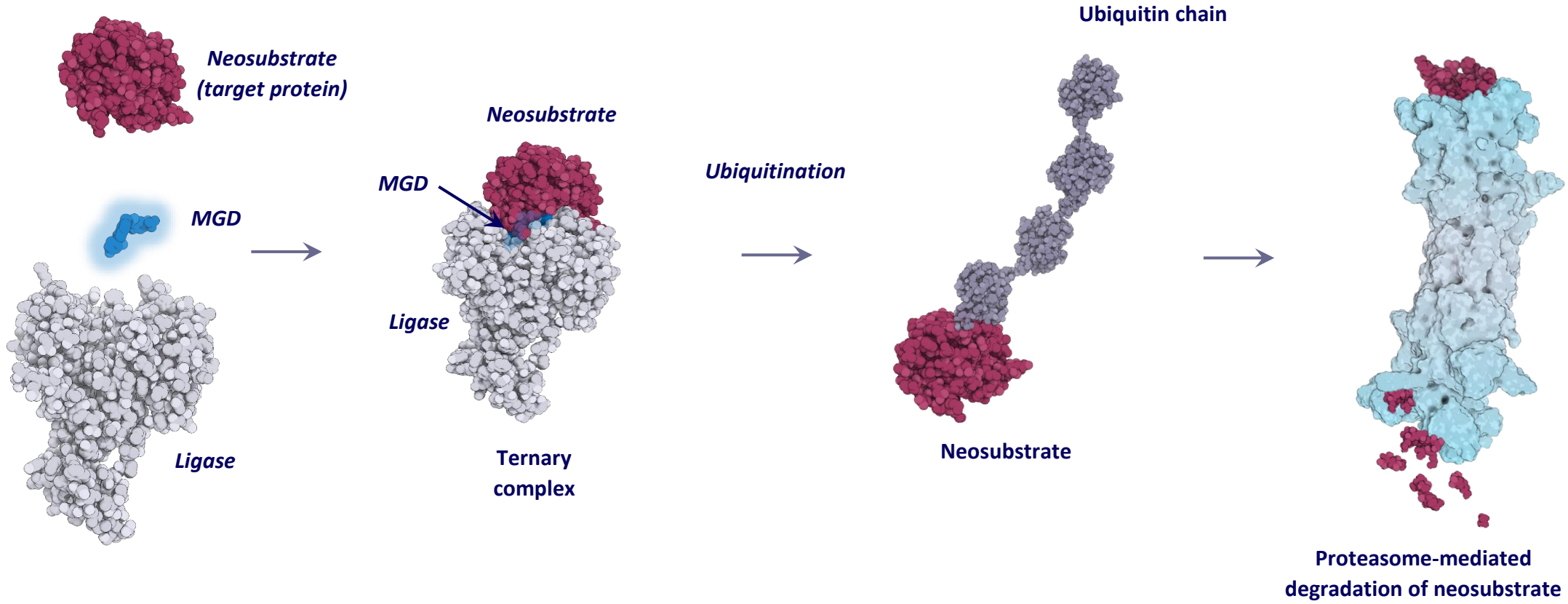
Filip Janku, MD, PhD
Chief Medical Officer
Monte Rosa Therapeutics

Monte Rosa Therapeutics

Forward-Looking Statements

This communication includes 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 herein include, but are not limited to, statements about our ability to grow our product pipeline, statements around the Company's QuEEN™ discovery engine and its potential to identify novel degradable protein targets and rationally designed MGDs with unprecedented selectivity, statements around the potential of the Company's MGDs against a broad spectrum of targets, statements about the advancement and timeline of our preclinical and clinical programs and our pipeline and the various products therein, statements about the ongoing clinical development of our GSPT1 degrader referred to as MRT-2359, including our expectations for the nature, significance, and timing for our disclosure of any updated data from our Phase 1/2 clinical trial of MRT-2359 in MYC-driven solid tumors in the second half of 2024, statements about Phase 2 development of MRT-2359, including timing of initiation and enrollment of any Phase 2 expansion cohorts in the second half of 2024, statements about the ongoing Phase 1 SAD/MAD study for the VAV1-directed degrader, referred to as MRT-6160 and our expected timing of disclosure of initial clinical data therefrom, our expectations of indications for the potential future clinical development for a VAV1-directed degrader, including MRT-6160, including the relevance of preclinical data for such indications, and our expectations regarding the potential clinical benefit for a VAV1-directed degrader, including MRT-6160, statements concerning our expectations regarding our ability to nominate and the timing of our nominations of additional targets, product candidates, and development candidates, statements regarding regulatory filings for our development programs, including the planned timing of such regulatory filings, such as IND applications, and potential review by regulatory authorities, our use of capital, expenses and other financial results in the future, availability of funding for existing and future programs, statements related to our strategic agreements, goals of such agreements and any related milestone, royalty or other payments related thereto, statements about the transaction with Novartis, including the closing thereof, as well as our expectations of success for our programs, strength of collaboration relationships and the strength of our financial position, among others. By their nature, these statements are subject to numerous risks and uncertainties, including those risks and uncertainties set forth in our most recent Annual Report on Form 10-K for the year ended December 31, 2023, filed with the U.S. Securities and Exchange Commission on March 14, 2024, and any subsequent filings, 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.

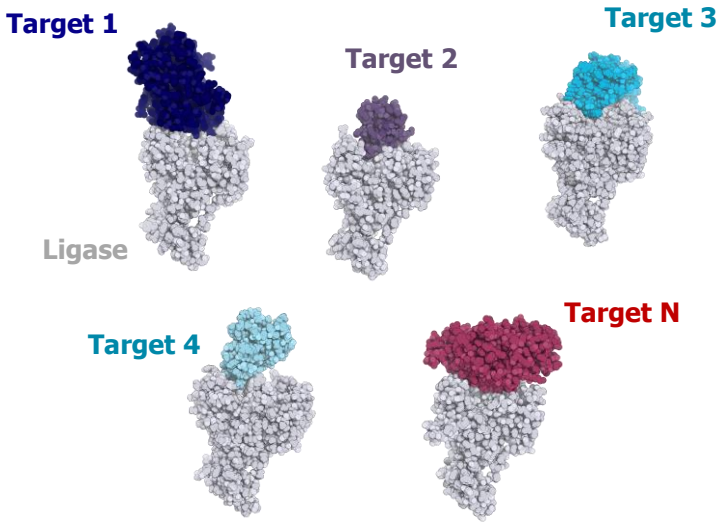
Our Molecular Glue Degraders (MGDs) Edit the Proteome



Monte Rosa's rationally designed MGDs have potential applications in Oncology, Immunology, Neuroscience and other therapeutic areas

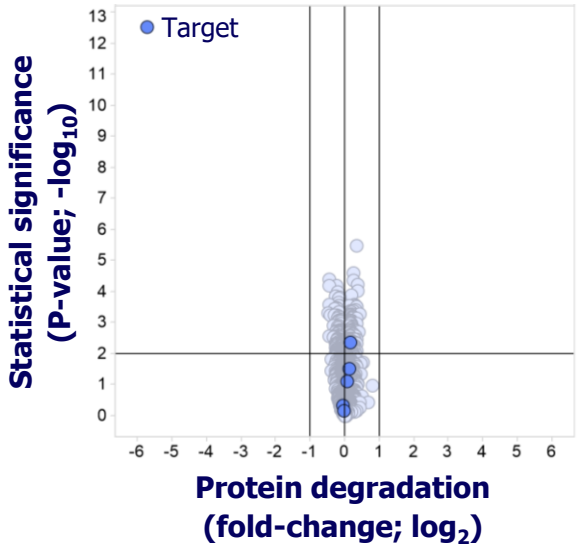
Key Advantages of Our Rationally Designed MGDs

Unique Target Space



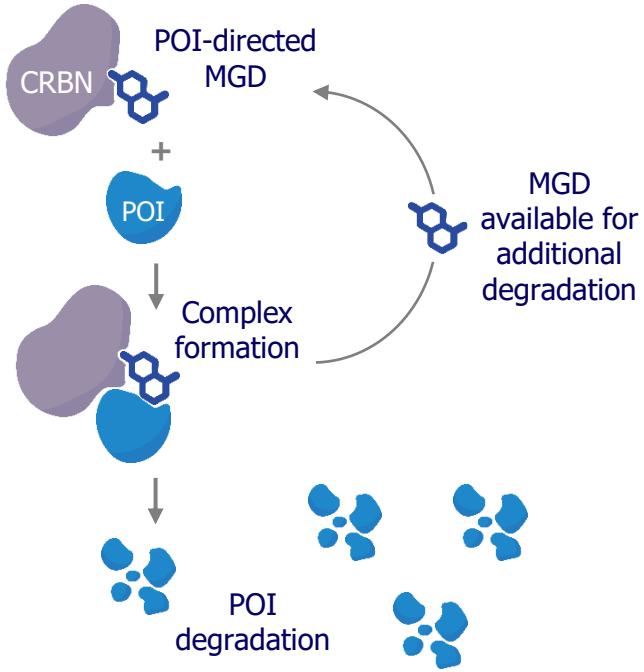
Disease-agnostic platform with initial focus on highly credentialed, undruggable oncology and immunology/inflammation targets

Unprecedented Selectivity



Unique insights into anatomy of protein-protein-MGD interaction allows unprecedented MGD selectivity

Catalytic Mechanism of Action

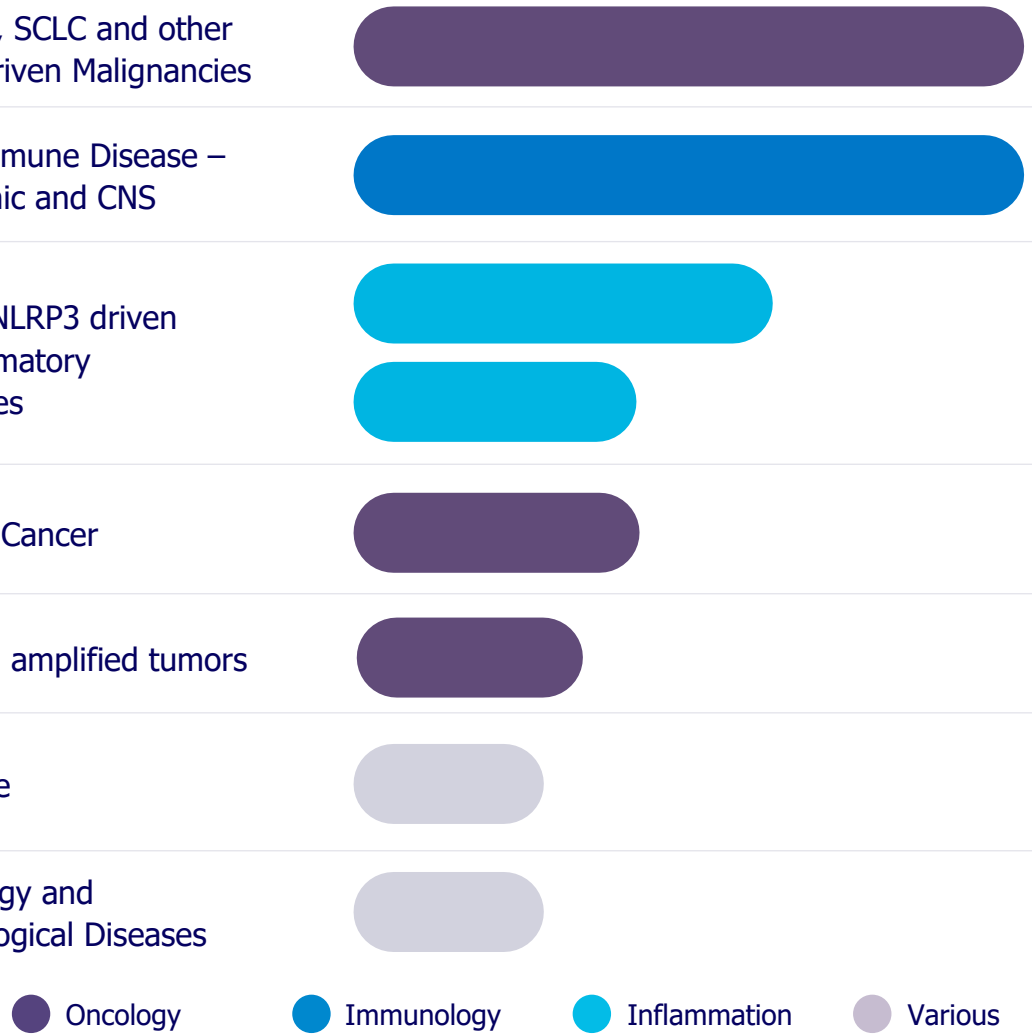


Long lasting, catalytic protein degradation effect creates differentiated target product profiles

POI = protein of interest

Monte Rosa Pipeline and Upcoming Milestones

Target	Compound	Indication(s)	Next Anticipated Milestone	Ownership
GSPT1	MRT-2359	NSCLC, SCLC and other MYC-driven Malignancies	RP2D and Phase 1 data in H2 2024	Monte Rosa
VAV1	MRT-6160	Autoimmune Disease – Systemic and CNS	Phase 1 data in Q1 2025	NOVARTIS *
NEK7	MRT-8102	IL-1β/NLRP3 driven Inflammatory Diseases	IND submission in H1 2025	Monte Rosa
	LO (2nd generation)		Development candidate	Monte Rosa
CDK2	LO	Breast Cancer	Development candidate in 2024	Monte Rosa
CCNE1 (Cyclin E1)	LO	CCNE1 amplified tumors	Development candidate	Monte Rosa
Discovery Targets	-	Multiple	Lead optimization	Monte Rosa
Discovery Targets	-	Oncology and Neurological Diseases	Undisclosed	Roche

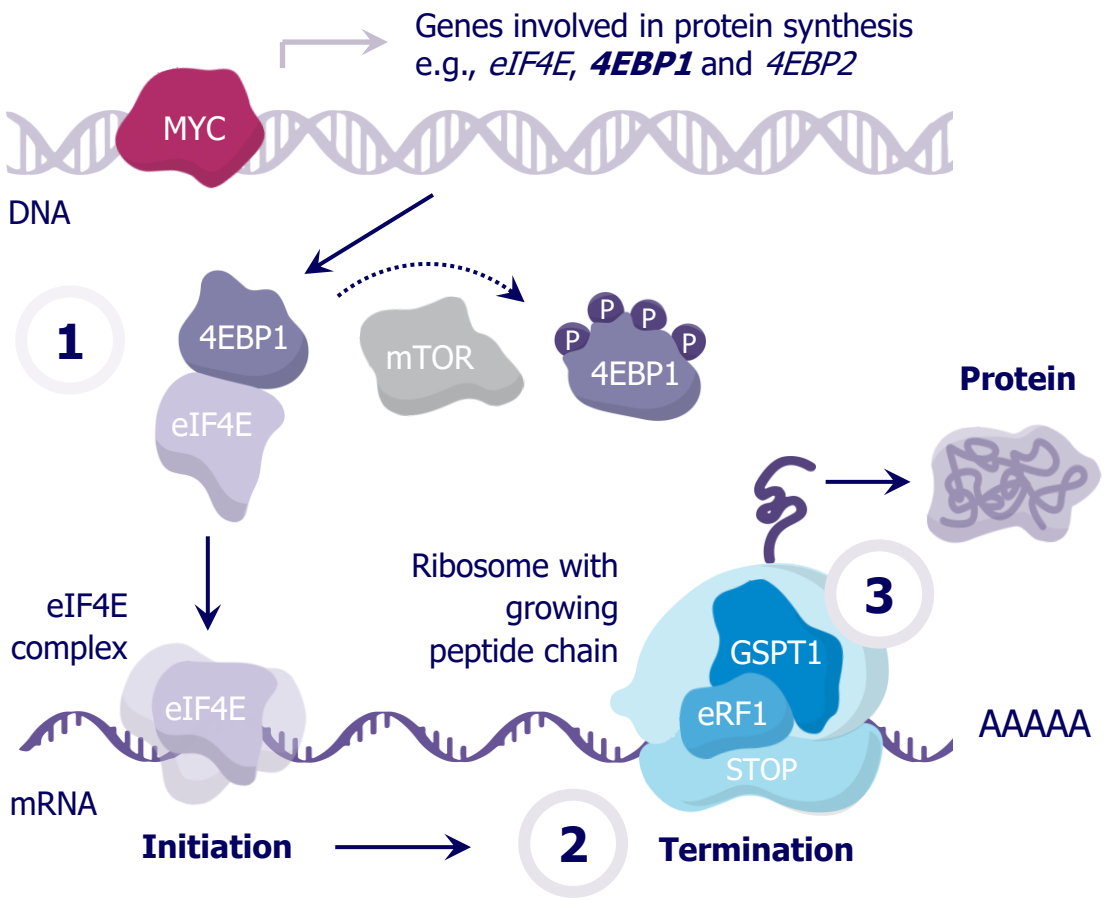


* Monte Rosa has signed an exclusive global license agreement with Novartis for this asset. This transaction is subject to customary closing conditions, including regulatory clearance.

Monte Rosa Therapeutics

GSPT1/MRT-2359

Targeting MYC-driven Tumors and Their Addiction to Protein Translation Through GSPT1 Degradation



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

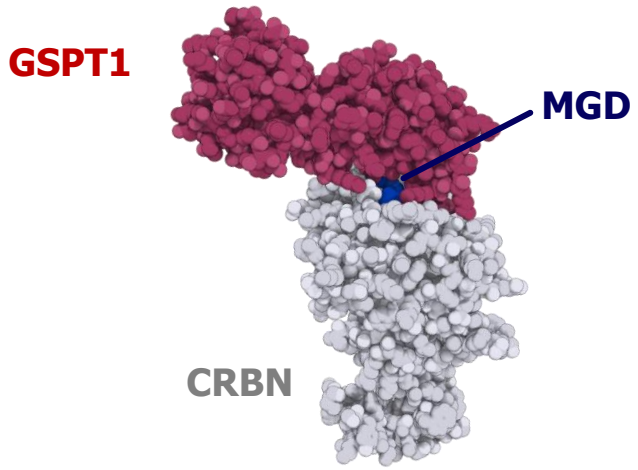
Therapeutic vulnerability

GSPT1 is a therapeutic vulnerability of MYC-driven tumors
leading to preferential activity of GSPT1 MGDs

MRT-2359 is a Potent and Highly Selective GSPT1-directed MGD

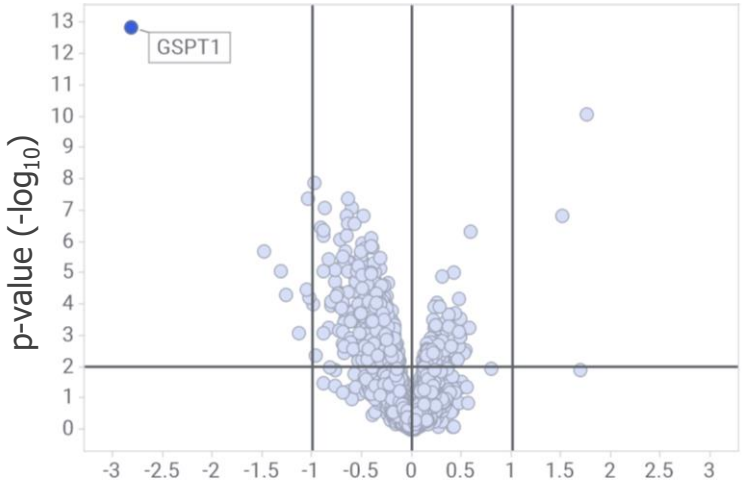
MRT-2359 is a potent GSPT1-directed MGD

Ternary complex modelling



in vitro data	
CRBN binding, K_i	113 nM
Ternary complex, EC_{50}	< 7 nM
Degradation, DC_{50} (in disease relevant cell lines)	1 - 20 nM

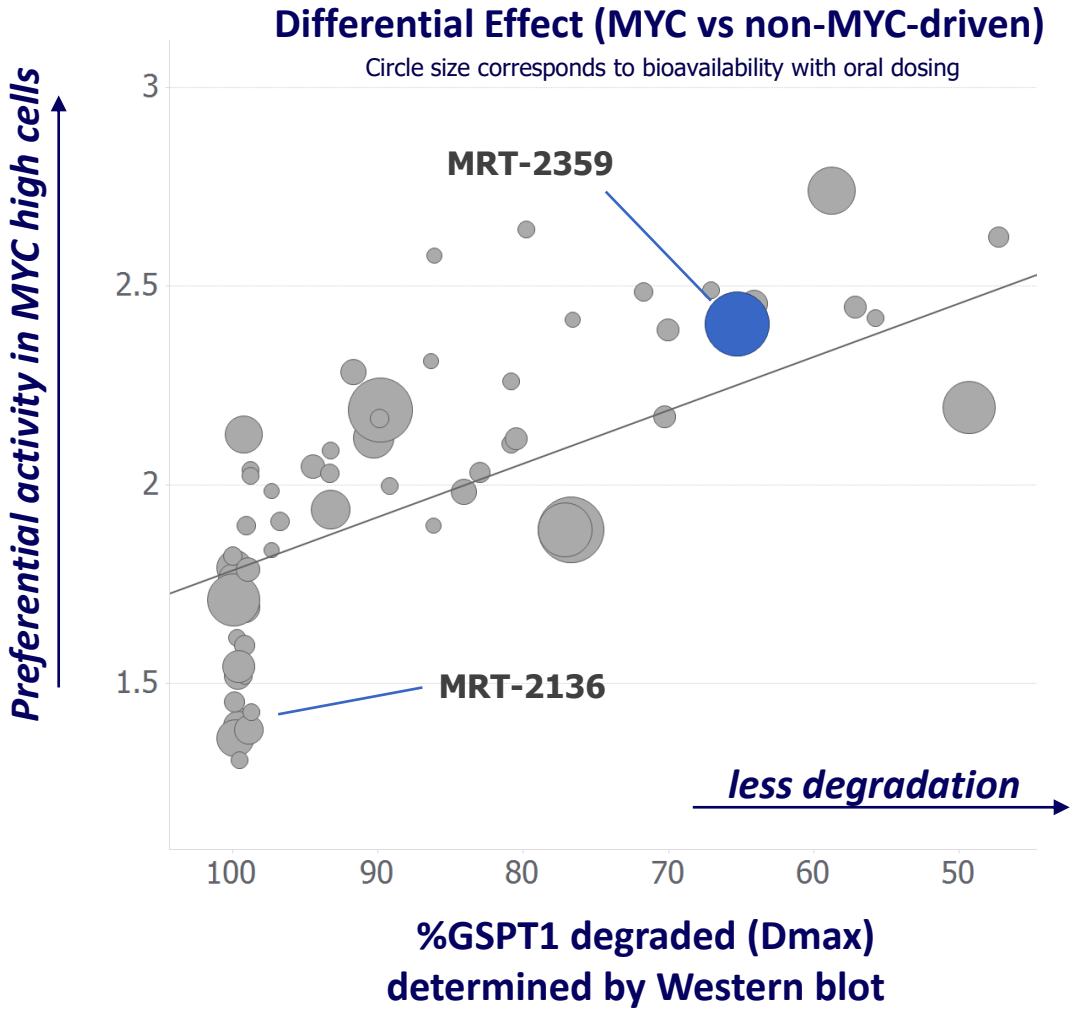
MRT-2359 induces selective GSPT1 degradation and shows favorable ADME/DMPK profile



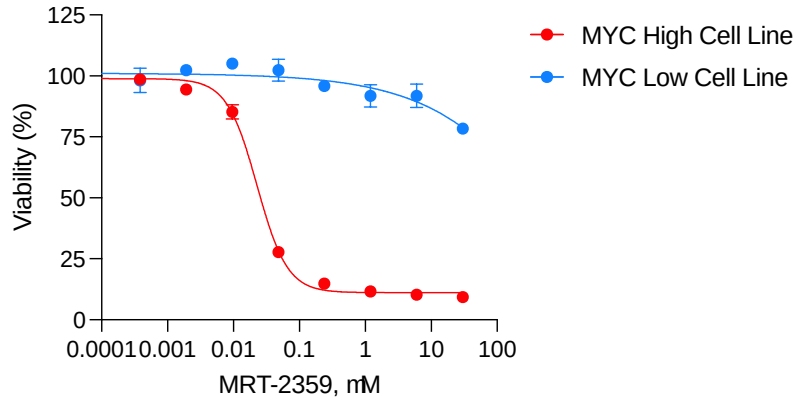
No degradation of other known cereblon neosubstrates

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

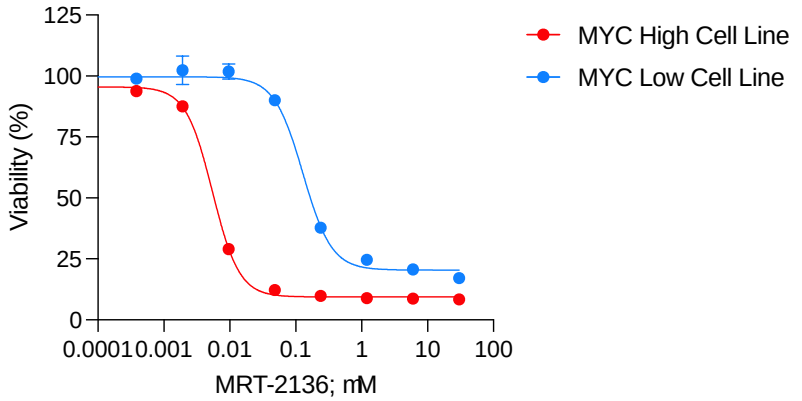
MRT-2359 Has Optimized Depth of Degradation To Achieve Preferential Activity in MYC High Cancer Cells



MRT-2359 displays preferential activity in MYC driven NSCLC cells

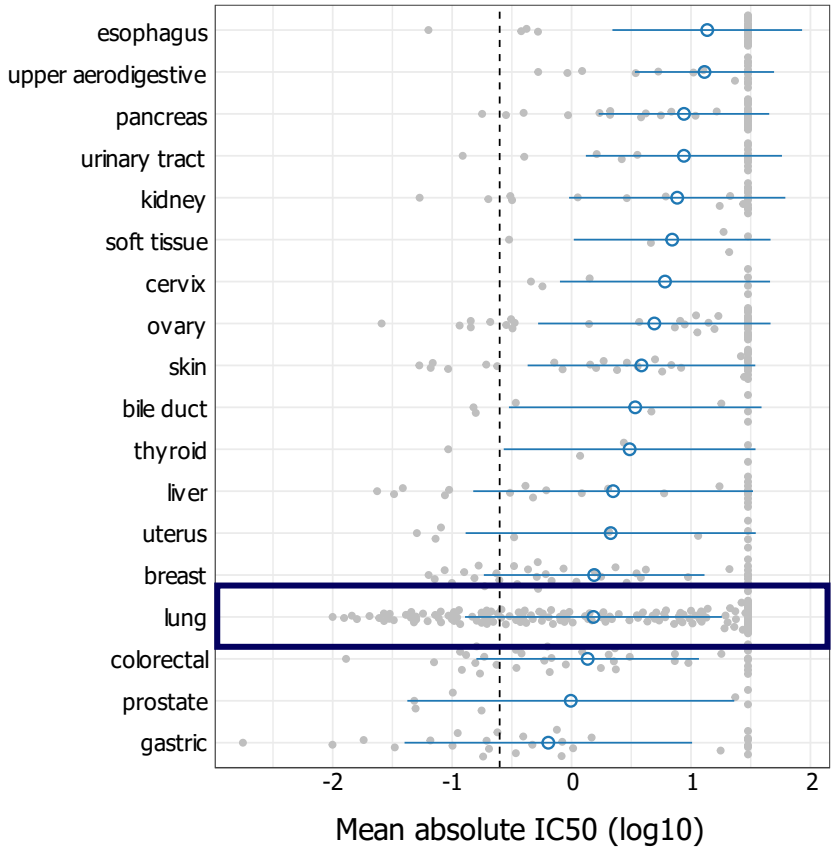


Non-optimal GSPT1 MGD (MRT-2136) shows limited preferential activity

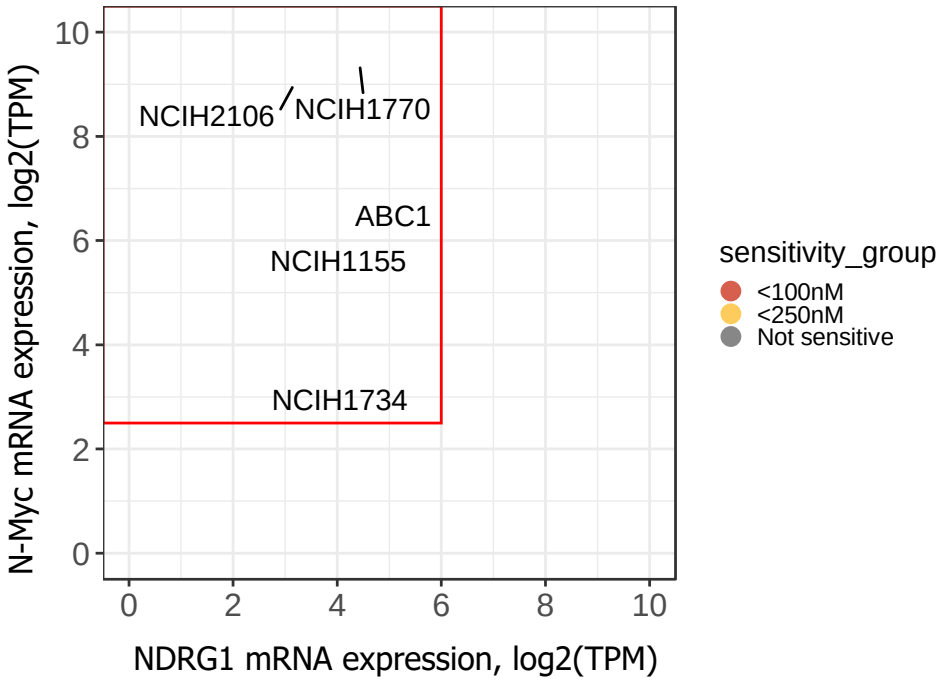


Pharmacogenomic Profiling Identifies Multiple MYC-Driven Tumor Types With Sensitivity to MRT-2359 – Non-small Cell Lung Cancer

Pharmacogenomic profiling of cancer cell lines identifies …



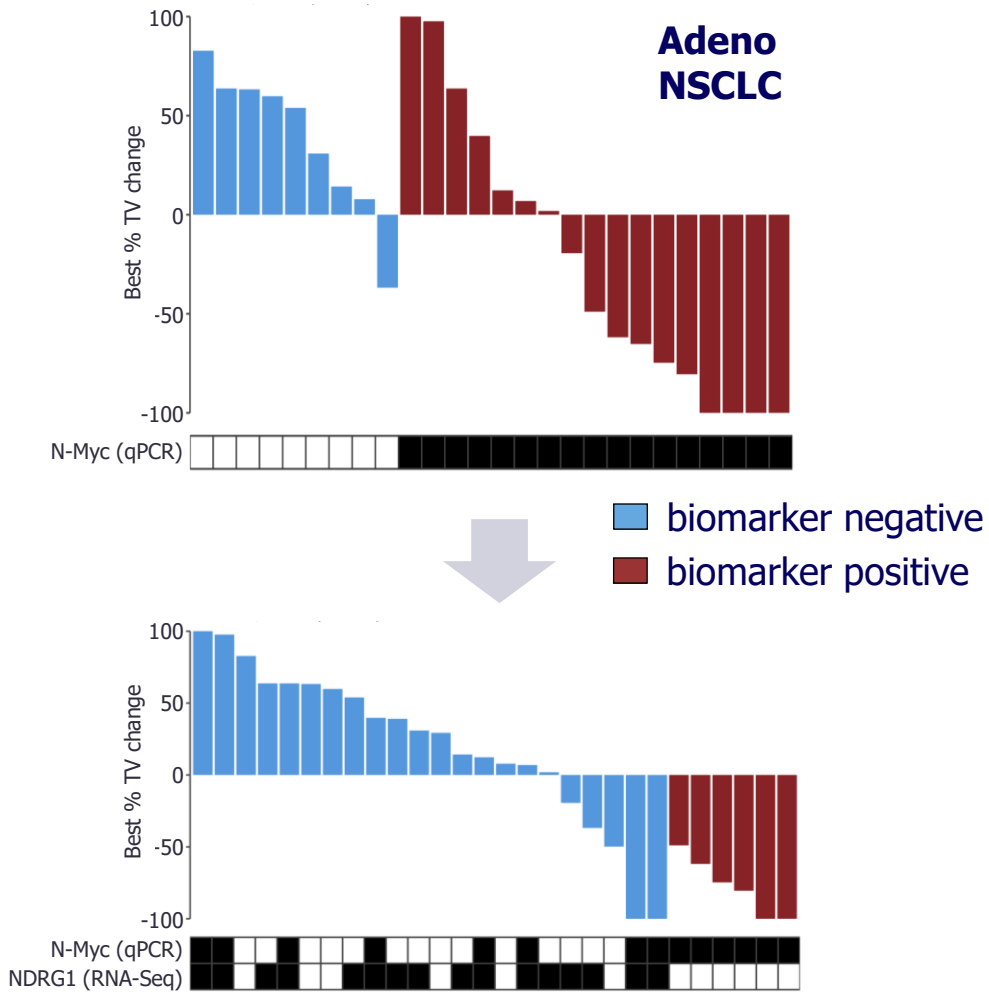
… N-Myc high / NDRG1 low NSCLC as potential indication



Preclinical Validation of Activity of MRT-2359 in Lung Cancer PDX Models

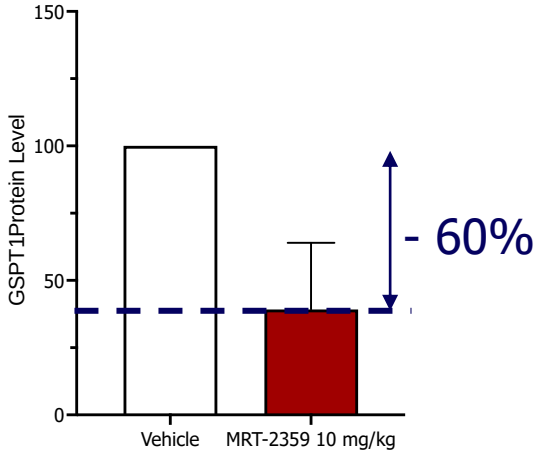
Collection of PDX models

MRT-2359
10 mg/kg QD



PD modulation

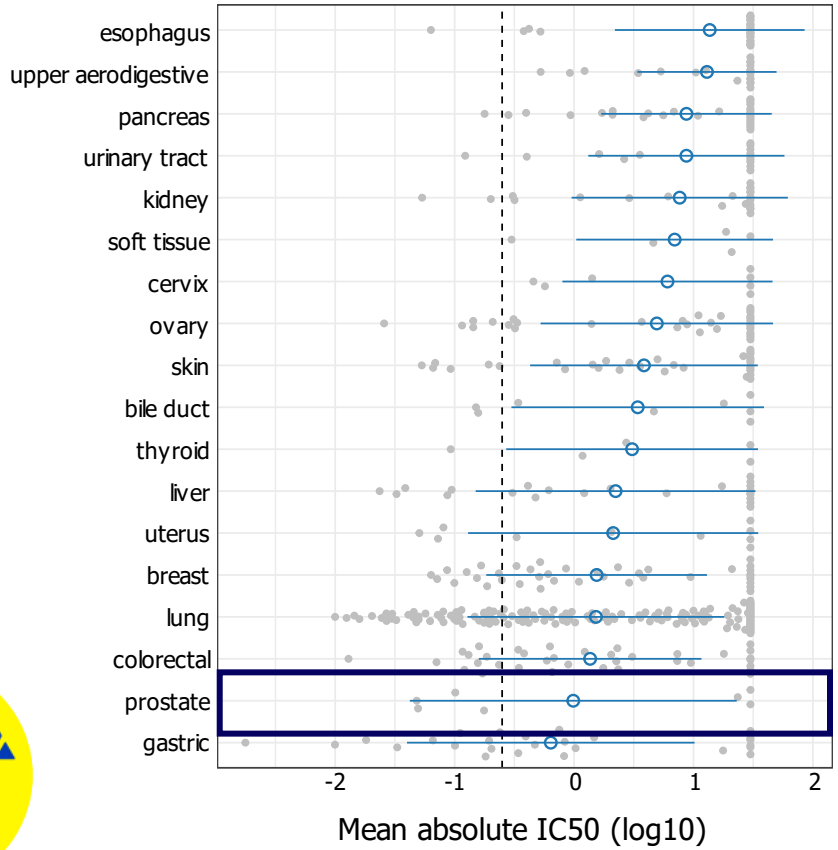
Targeted mass spectrometry
in 7 representative models



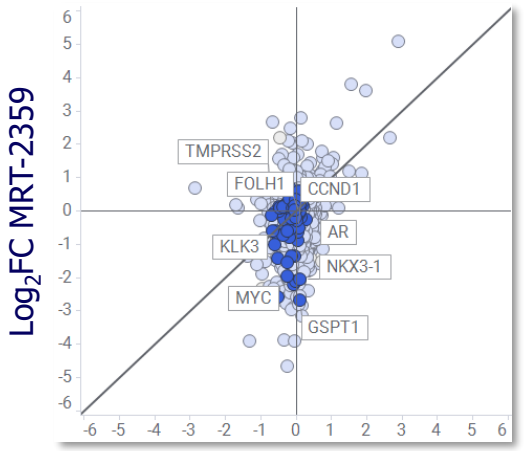
Pharmacogenomic Profiling Identifies Multiple MYC-Driven Tumor Types With Sensitivity to MRT-2359 – Prostate Cancer

Pharmacogenomic profiling of cancer cell lines identifies …

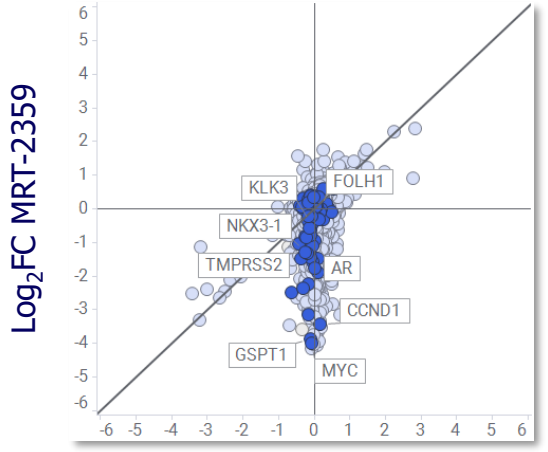
… AR positive prostate cancer as potential indication – MRT-2359 reduces expression of GSPT1, MYC, CCND1 and AR Signature



VCaP (AR-V7 low)

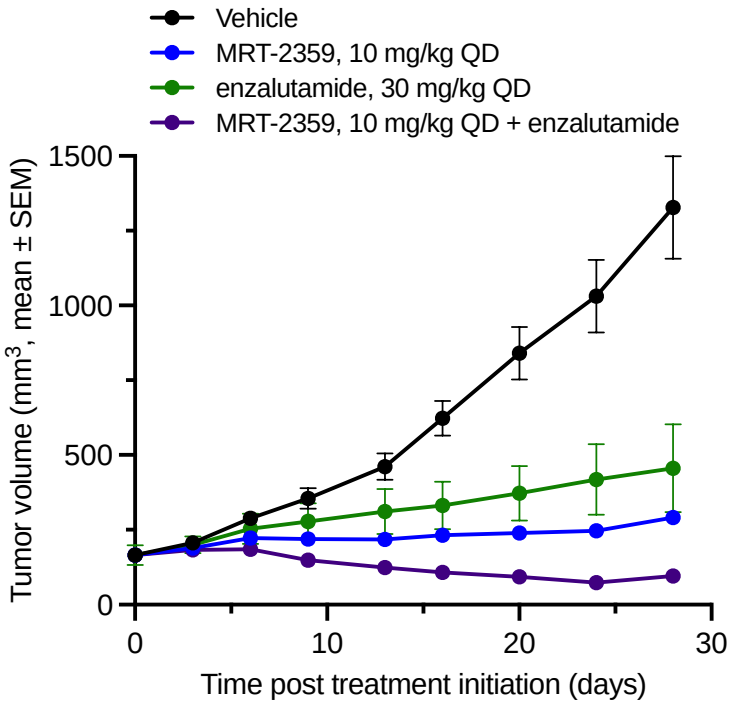


22RV1 (AR-V7 high)

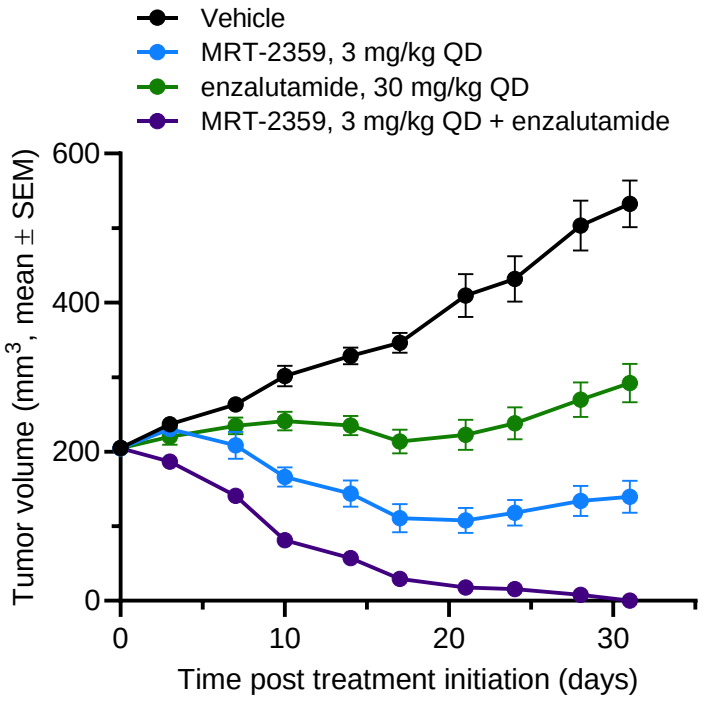


MRT-2359 Leads to Tumor Regressions in Preclinical Models of Castration Resistant Prostate Cancer and ARV7-driven Prostate Cancer

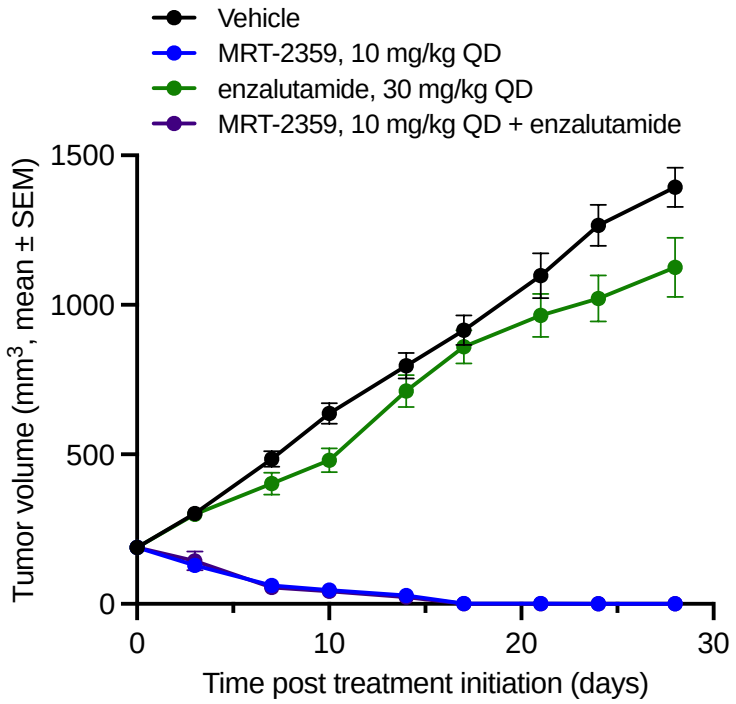
LNCaP model (AR-V7 negative)



VCaP model (AR-V7 low)



22RV1 model (AR-V7 high)



MRT-2359-001 Phase 1/2 Clinical Study Design

Phase 1: Dose Escalation

Lung cancer, high-grade neuroendocrine tumors and solid tumors with N-/L-MYC amplification

RP2D (expected H2 2024)

- 2mg 5/9
- 1.5mg 5/9
- 1mg 5/9
- 0.5mg 5/9
- DL X 21/7
- 0.75mg 21/7
- 0.5mg 21/7

Backfill: Up to 6 additional pts for each dose level

5/9 = 5 days on drug, 9 days off drug.
21/7 = 21 days on drug, 7 days off drug.

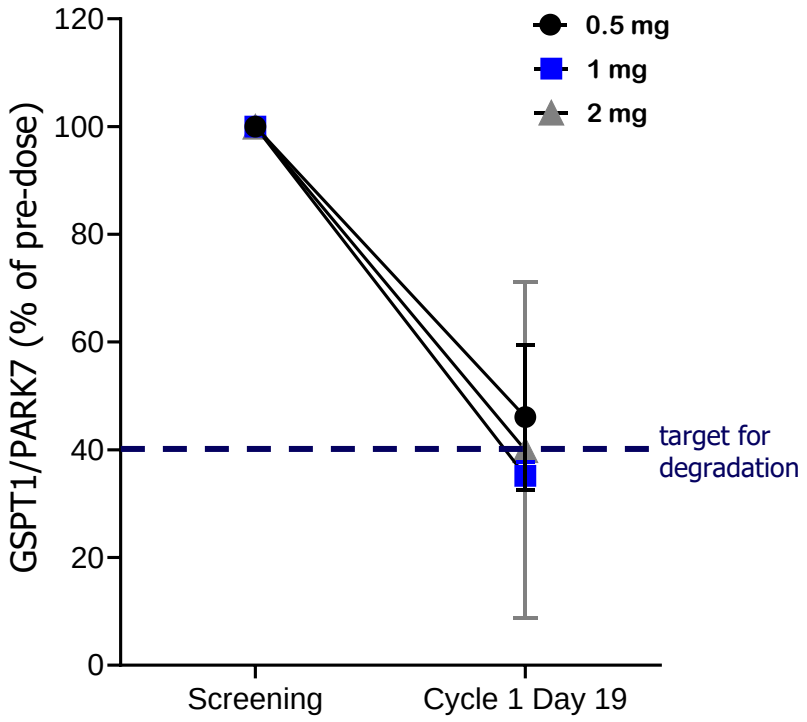
Phase 2: Expansion Cohorts

- NSCLC*
- SCLC**
- N-MYC/L-MYC amplified tumors
- HR+/Her2- Breast cancer (+Fulv)
- Prostate cancer (+Enza)

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

MRT-2359 Induces Optimal GSPT1 Degradation in Tissue Biopsies*

MRT-2359 reduced GSPT1 protein expression in human tissue biopsies

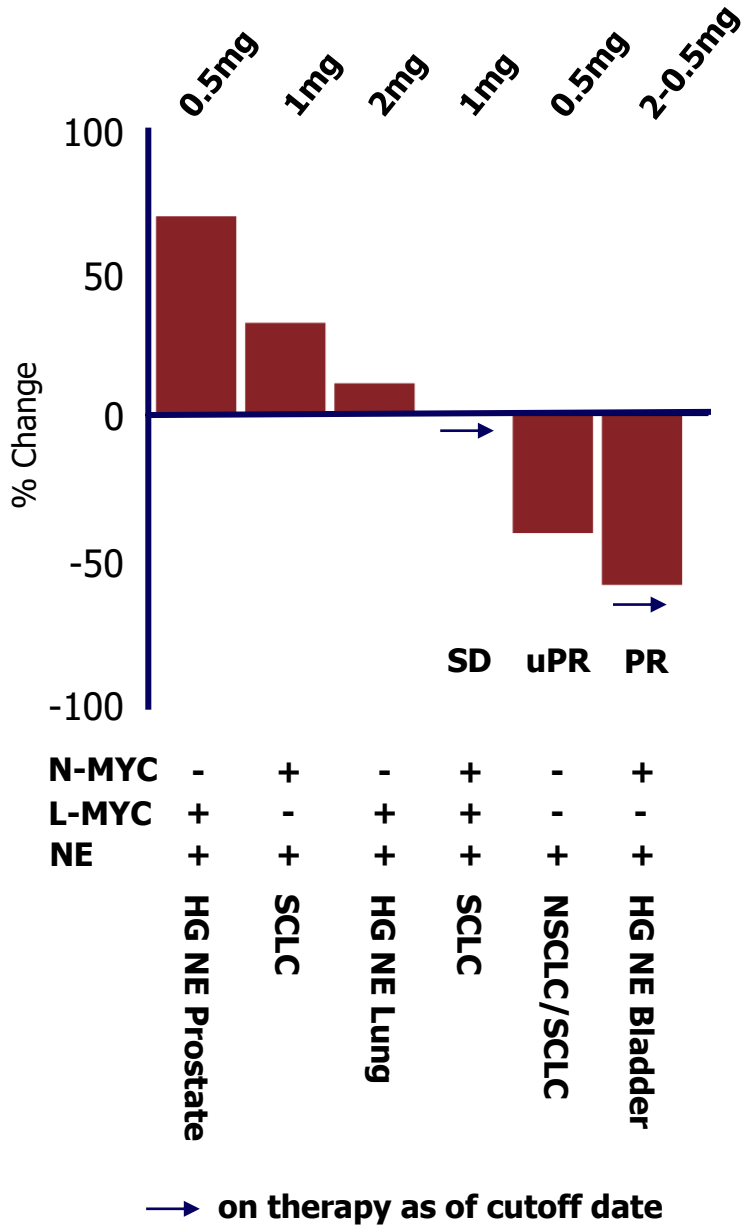


- GSPT1 degradation assessed from pre-treatment screening biopsies and biopsies taken at day 19
- Matched biopsies obtained from 11 patients across the 3 cohorts analyzed
- GSPT1 expression assessed using targeted mass spectrometry
- PD modulation seen in tissue biopsies in line with PD modulation seen preclinically at efficacious dose levels using same assay (targeted mass spectrometry)

* Based on optimal PD modulation in preclinical studies as presented on 10/17/23

MRT-2359-001 – Preliminary Efficacy Data*

- As of September 7th, 2023, of 15 evaluable patients treated across 3 cohorts, tumors from 6 patients were identified as biomarker positive
- Of these 6 biomarker positive patients, 2 have experienced a PR (1 confirmed, 1 unconfirmed) and 1 patient has SD
  - PR (-59%) – HG NE bladder carcinoma
  - uPR (-41%) – NSCLC with SCLC/NE transformation
  - SD (0%) – SCLC (remains on therapy for > 4 months)
- In addition, one patient with NSCLC and unclear biomarker status remains on therapy for > 7 months with stable disease
- No clinical activity seen in biomarker negative patients



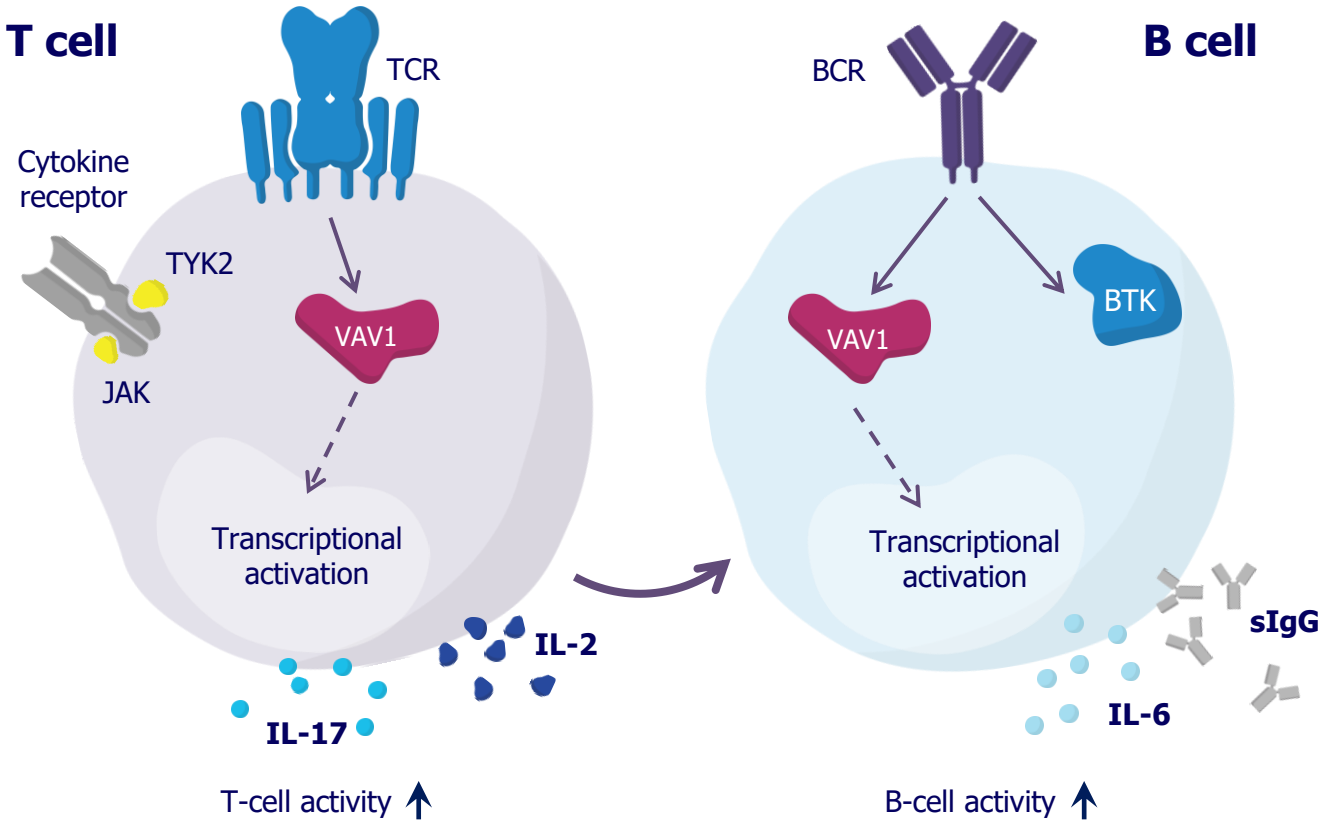
* as presented on 10/17/23

Monte Rosa Therapeutics

VAV1/MRT-6160

VAV1 is a Key Regulator of T- and B-cell Receptor Activity

VAV1-directed MGDs have the potential to modulate T- and B-cell function



VAV1 signaling increases cytokine production, proliferation, and differentiation

Therapeutic hypothesis:

- VAV1 is a pivotal scaffolding protein and signaling molecule downstream of both the T-cell and B-cell receptors – confirmed by multiple CRISPR screens & VAV1 knockout (KO) mice
- VAV1 degradation is predicted to impact both T- & B-cell function and has the potential to treat a broad set of autoimmune diseases

Clinical Opportunity:

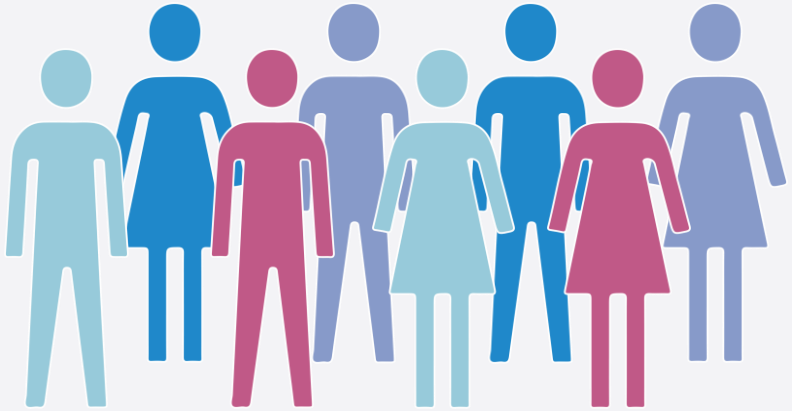
Autoimmune/inflammatory disorders including inflammatory bowel disease (4.1M patients), rheumatoid arthritis (6.2M patients), multiple sclerosis (1.3M patients), and myasthenia gravis (~300K patients)

TCR = T-cell receptor. BCR = B-cell receptor. IL-2, IL-17 and IL-6 are cell signaling molecules (cytokines) that promote immune response. sIgG is the most common circulating antibody.

Patient diagnosed prevalence #s, major markets (US, EU and JP): Decision Resources Group (DRG)

Unique Mechanism of VAV1 MGD May Achieve Broad Clinical Response

Response to single cytokine or cell-type specific therapies can be variable due to clinical heterogeneity

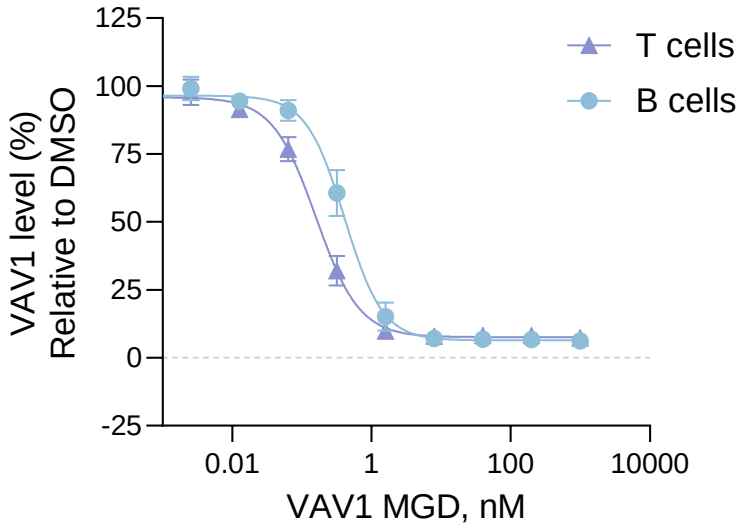


Potentially broadly responsive to VAV1 MGD

- Patients are currently treated by various drugs focused on single cytokine or cell-type specific therapies which best address specific endotypes
- Instead, deep modulation of multiple cytokine pathways with a first-in-class VAV1 oral MGD may benefit patients presenting a broad range of pathophysiology

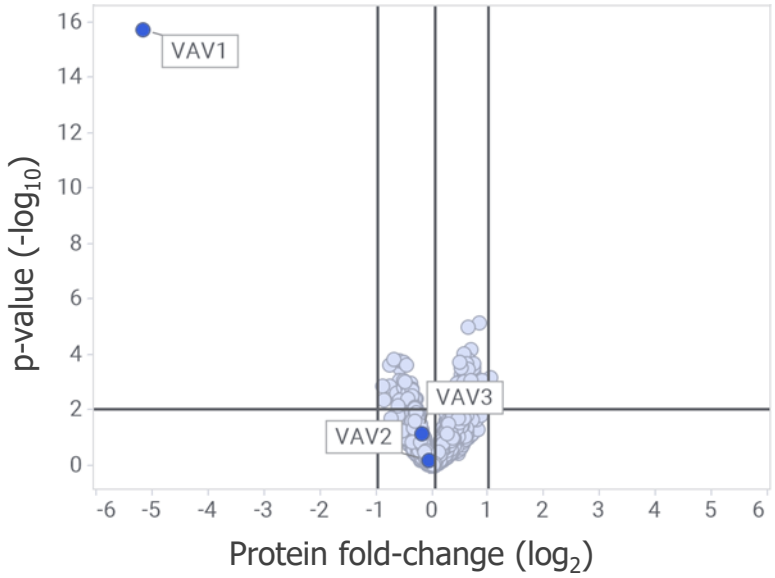
MRT-6160 is a Potent and Highly Selective VAV1-directed MGD

MRT-6160 is a potent VAV1-directed MGD



in vitro data	
CRBN binding, IC_{50}	670 nM
Ternary complex, EC_{50}	11 nM
Degradation, DC_{50} /D_{max} (Jurkat)	7 nM / 97 %

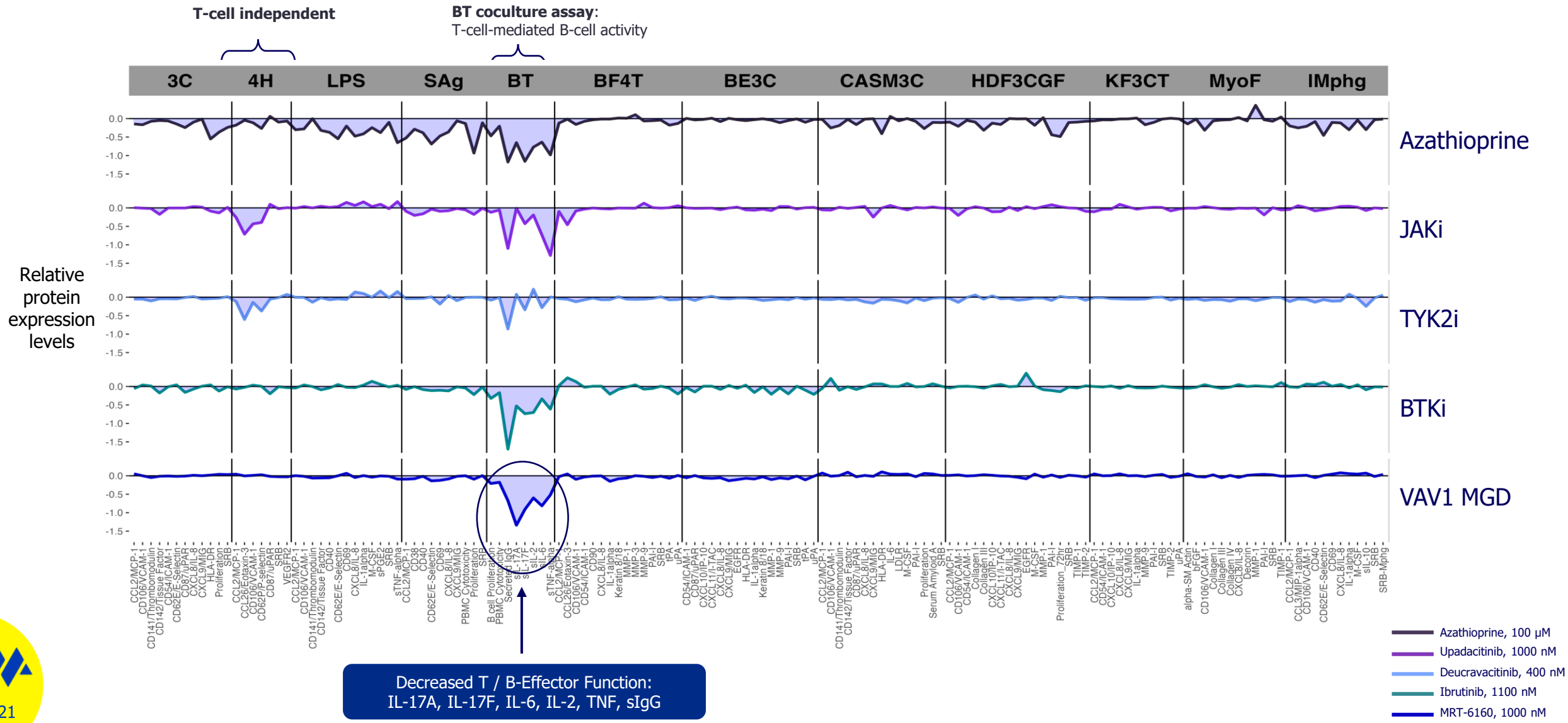
MRT-6160 induces highly selective VAV1 degradation and has a favorable ADME/DMPK profile



No degradation of other known cereblon neosubstrates

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

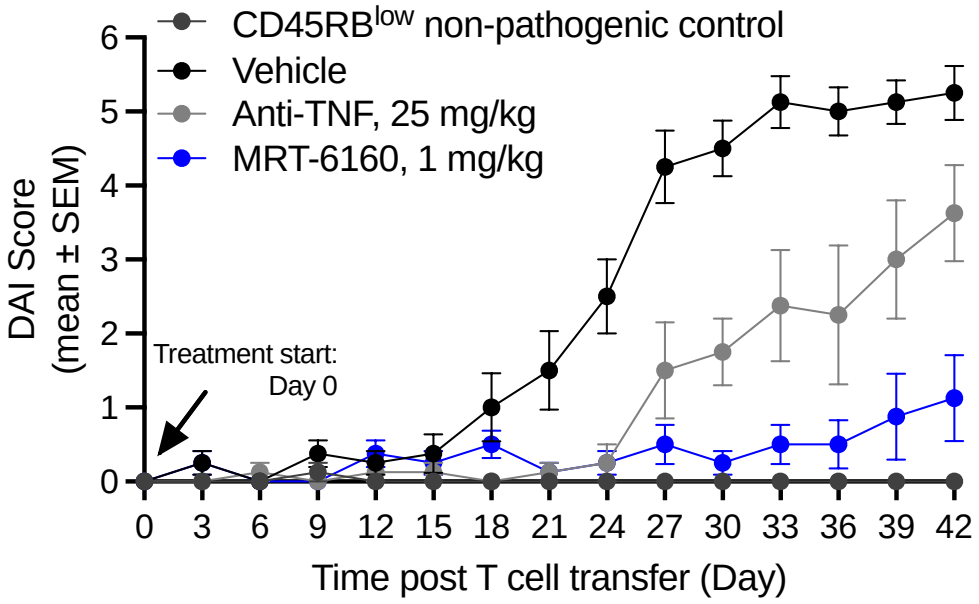
MRT-6160 Blocks T-cell-Mediated B-cell Activity in BioMAP® Profile



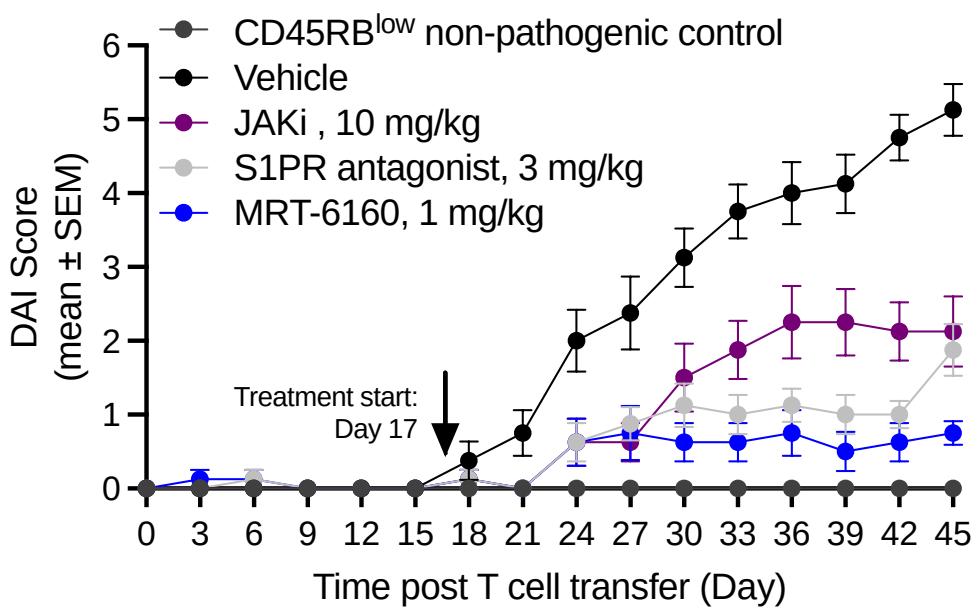
BioMAP® Diversity Plus Platform (Eurofins). Shark tooth plots show relative expression levels of indicated proteins in Drug treated vs. DMSO controls. 3C/4H, Venular endothelial cells; LPS/SAg, Venular endothelial cells + PBMC; BT, PBMC + B cells; BF4T, Bronchial epithelial cells + dermal fibroblasts; BE3C. Bronchial epithelial cells; CASM3C, Coronary artery smooth muscle cells; HDF5CGF, Dermal fibroblasts; KF3CT, keratinocytes + dermal fibroblasts; MyoF, lung fibroblasts; IMphg, macrophages + venular epithelial cells

MRT-6160 Ameliorates T Cell Transfer-Induced Colitis Better than Standard of Care

Treatment initiated at time of model induction on Day 0



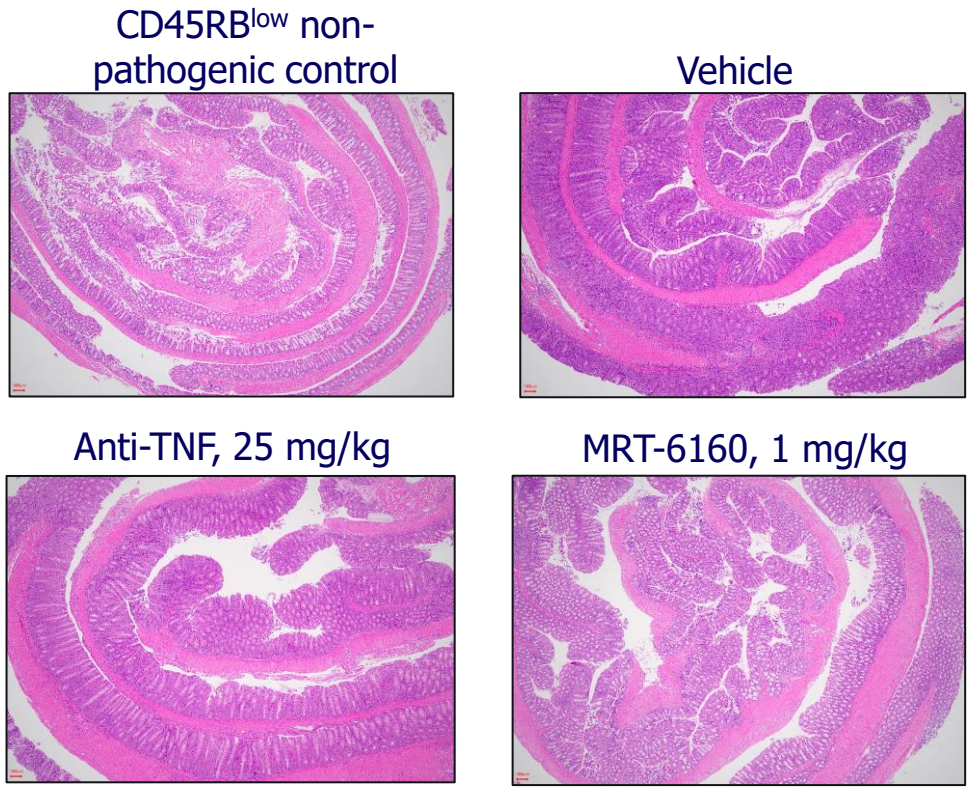
Treatment initiated in therapeutic setting on Day 17 following disease induction



Non-pathogenic CD45RB^{low} or pathogenic CD45RB^{high} cells were transferred into SCID mice to induce colitis. Mice were treated with vehicle, MRT-6160 (PO QD), or anti-TNF (IP Q3D) from Day 0 to Day 42 and assessed for disease every 3 days (*left*) or with vehicle, MRT-6160, or S1PR antagonist (etrasimod; PO QD), or JAKi (upadacitinib; PO BID) from Day 17 to Day 45 and assessed for disease every 3 days (*right*)

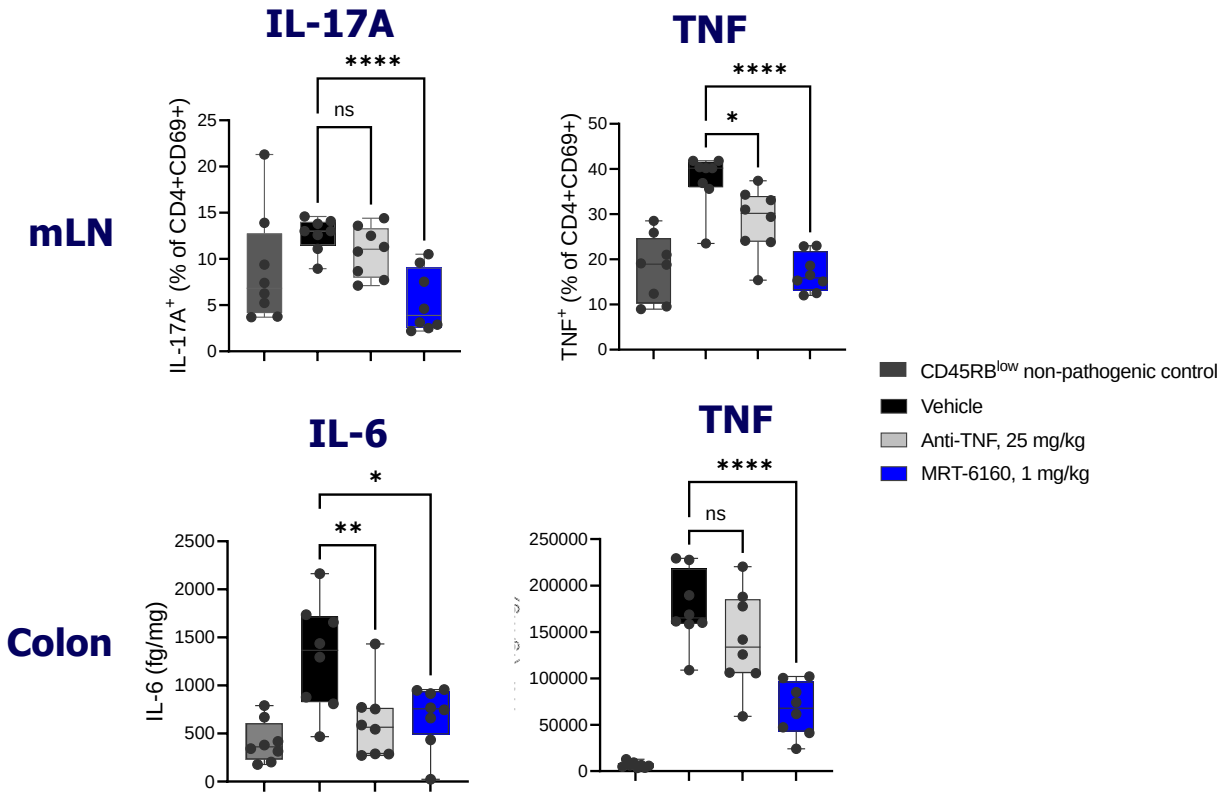
MRT-6160 Reduces Inflammation-Mediated Damage of the Colon and Cytokine Production in a T-Cell Transfer Model of Ulcerative Colitis

MRT-6160 reduces inflammation-mediated damage and swelling of the colon



Hematoxylin and eosin-stained histopathology sections from colon at end of study

MRT-6160 reduces cytokine production in the mesenteric lymph node and colon



Flow cytometric (*upper row*) and cytokine bead array (*lower row*) analysis of mesenteric lymph node CD4+ T cells and colon tissue respectively

Phase 1 Biomarker Strategy to Demonstrate MRT-6160 Pharmacodynamic Effects

Phase 1 SAD/MAD in Healthy Volunteers

Provide early insights into safety, PK/PD, and effects on key immunomodulatory signaling pathways

VAV1 protein degradation

- Flow cytometry on T and B cells: whole blood (WB)
- Targeted Mass Spec: PBMCs
- Potential: Mature B cell typing in MAD

Key downstream PD

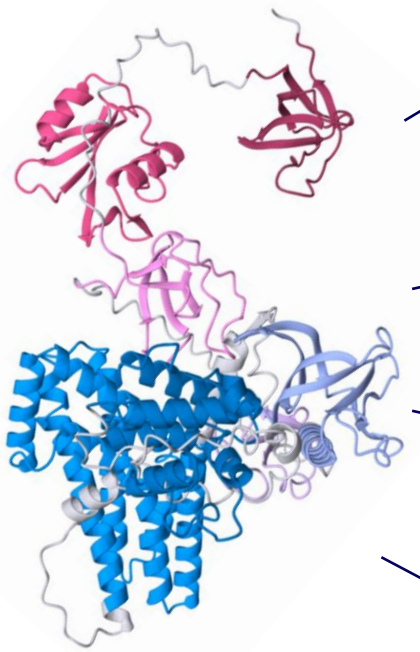
- Flow cytometry for CD69 protein on T & B cells: WB
- Immunoassay for IL-2, IL-6, IL-17, BAFF, CCL3/4
- hs C-reactive protein

Phase 1 SAD/MAD study ongoing, clinical data anticipated Q1 2025

VAV1 is an Upstream Targeting Node Associated with Clinically Validated Pathways

VAV1 signaling is associated with several T and B cell immunologic outcomes

Clinically validated pathway in autoimmune/inflammatory disease



VAV1

T cell activation

ORENCIA® (abatacept)

RINVOQ® upadacitinib

B cell activation/Plasma cell differentiation (Antibody production)

Rituxan® Rituximab

VYVGART® Hytrulo

Th17 response

Cosentyx® (secukinumab)

omvoh™ (mirikizumab-mrkz) 300 mg/15 mL infusion | 100 mg/mL injection

Pro-inflammatory cytokine production

HUMIRA® adalimumab

ACTEMRA® tocilizumab

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