Degrading Proteins, Making Medicines

MRT-2359 Phase 1/2 Clinical Data Update

December 16, 2025

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, our ability to successfully complete research and further development and commercialization of our drug candidates in current or future indications, including the timing and results of our clinical trials and our ability to conduct and complete clinical trials, statements regarding the promising interim results from our ongoing Phase 1/2 clinical study evaluating MRT-2359 in combination with enzalutamide in heavily pretreated patients with metastatic CRPC, our expectations regarding the clinical activity observed with MRT-2359 in combination with enzalutamide in heavily pretreated mCRPC patients and the significant opportunity for MRT-2359 in the rapidly evolving treatment landscape of prostate cancer, our plans to initiate a signal-confirming Phase 2 study evaluating MRT-2359 in combination with a second generation AR inhibitor in mCRPC patients with AR mutations and timing thereof, with potential to expand into additional patient subsets, the potential for the data from this study to confirm MRT-2359's clinical activity and position the program for advancement into registrational studies, the clinical significance of the clinical data read-out at upcoming scientific meetings and timing thereof, our plans to present interim Phase 1 data on MRT-8102 in early 2026, statements around our ability to capitalize on and potential benefits resulting from our research and translational insights, 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, 2024, filed with the U.S. Securities and Exchange Commission on March 20, 2025, 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.

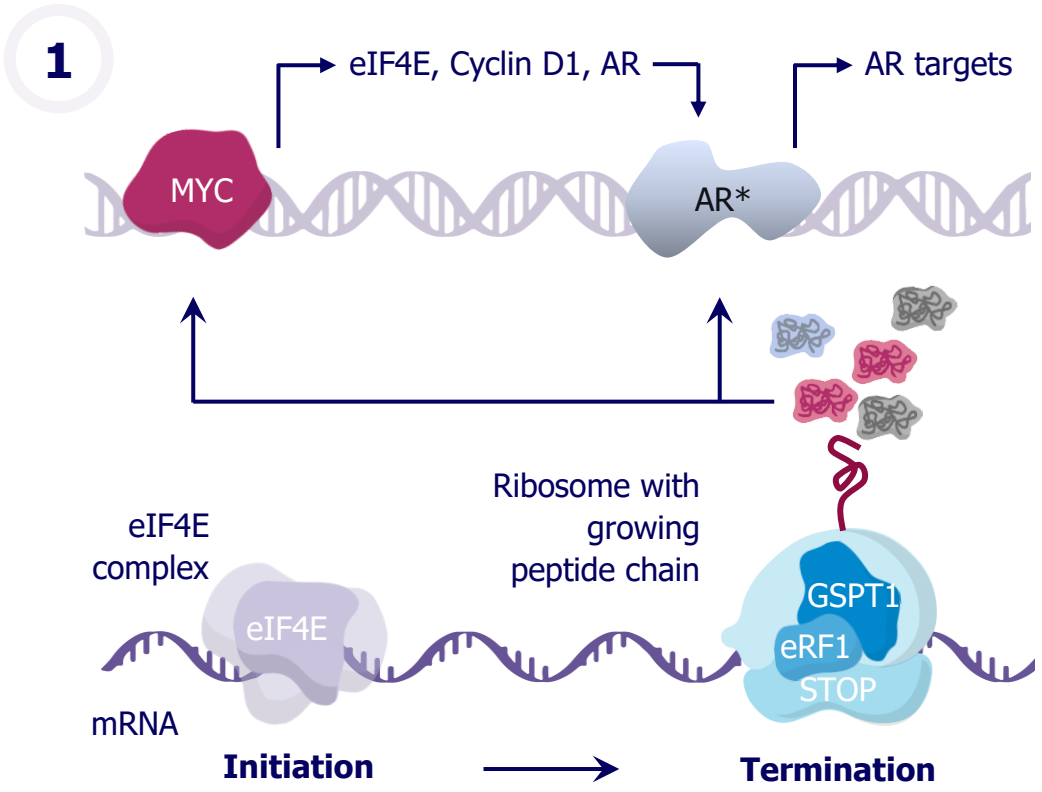
Summary

- MRT-2359 in combination with enzalutamide achieved compelling clinical activity in a subset of heavily pre-treated metastatic castration resistant prostate cancer (mCRPC) patients with androgen receptor (AR) mutations.
- Of the 4 patients with AR mutations:
  - 4 patients showed a PSA response, including 2 patients with PSA90 and 2 patients with PSA50 responses
  - 2 patients showed RECIST partial responses (1 confirmed, 1 unconfirmed)
  - 2 patients had stable disease, leading to a 100% disease control rate in the AR mutant population
  - 2 patients remained on therapy for 10 cycles or longer and 3 of 4 patients remained on drug as of data cut off on December 3rd
- 5 additional patients without AR mutations had stable disease per RECIST, several of which associated with tumor size reductions of target lesions, resulting in an overall disease control rate (DCR) of 64% in a total of 14 evaluable patients
- Combination of MRT-2359 and enzalutamide was well tolerated with mild or moderate manageable GI adverse events (AEs) being the most frequent toxicities
- Data support potential of combination of MRT-2359 with 2nd generation androgen receptor inhibitors for mCRPC patients with AR mutations (up to 30% of 2nd line+ mCRPC), with additional potential in earlier line settings or in combination with other agents

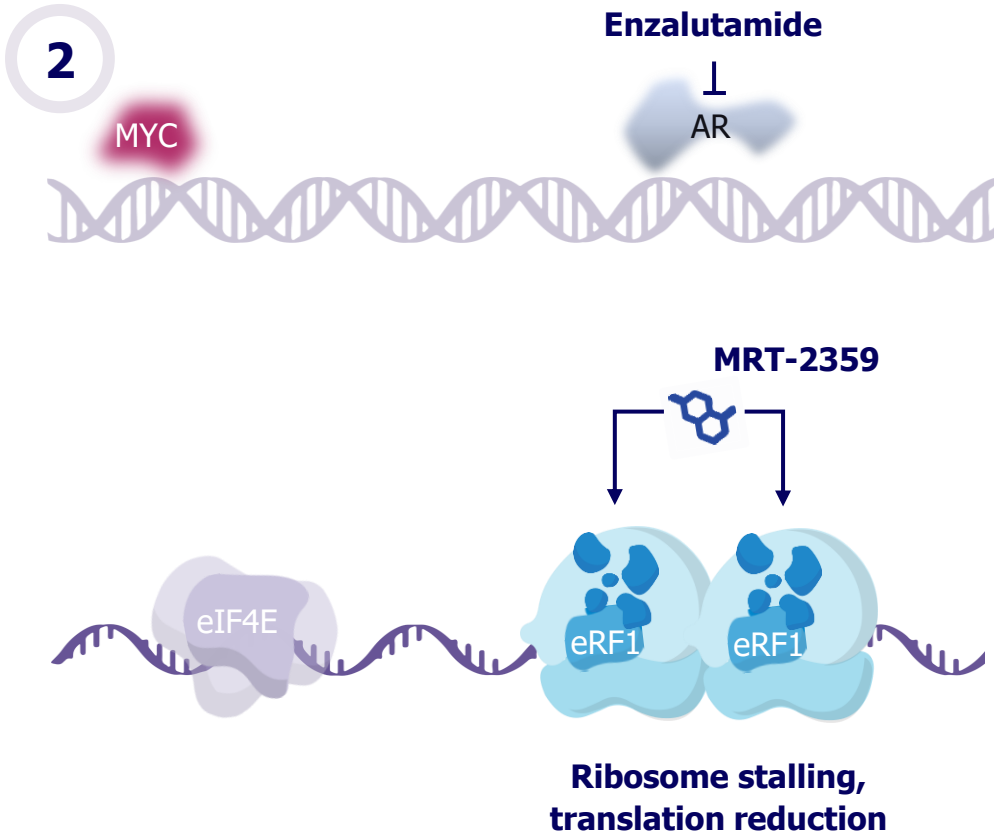
Therapeutic Rationale in mCRPC

MRT-2359 Exploits Key Therapeutic Vulnerabilities in Therapy-Resistant CRPC

Therapy-resistant mCRPC is characterized by increased MYC, E2F, AR and other oncogenic pathways activity



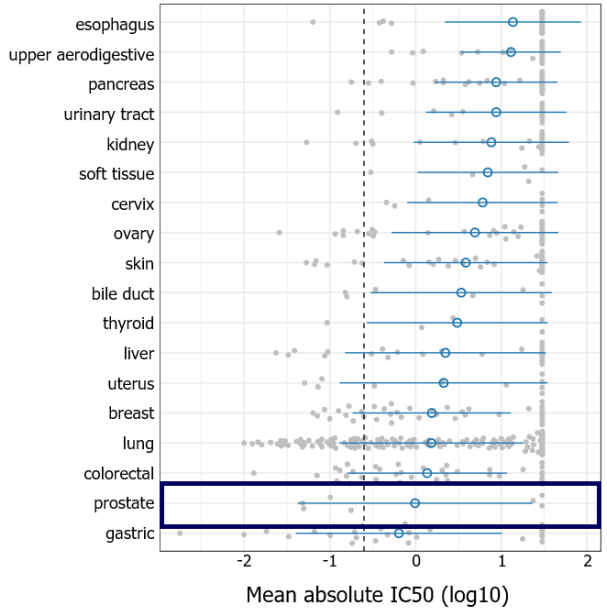
MRT-2359 + enzalutamide suppress multiple oncogenes including AR*, MYC and Cyclin D1



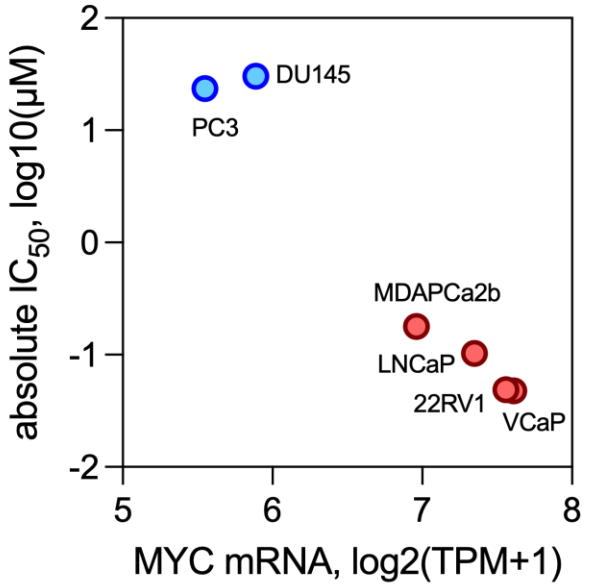
** AR WT and variants (mutants and V7).*

Pharmacogenomic Profiling Identified AR/MYC-positive Prostate Cancer Cell Lines as Exquisitely Sensitive to MRT-2359

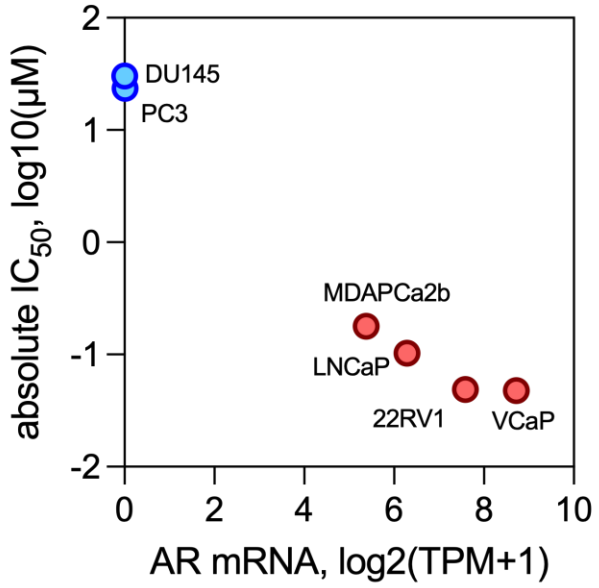
Cell Line Panel



Prostate Cell Lines



Prostate Cell Lines

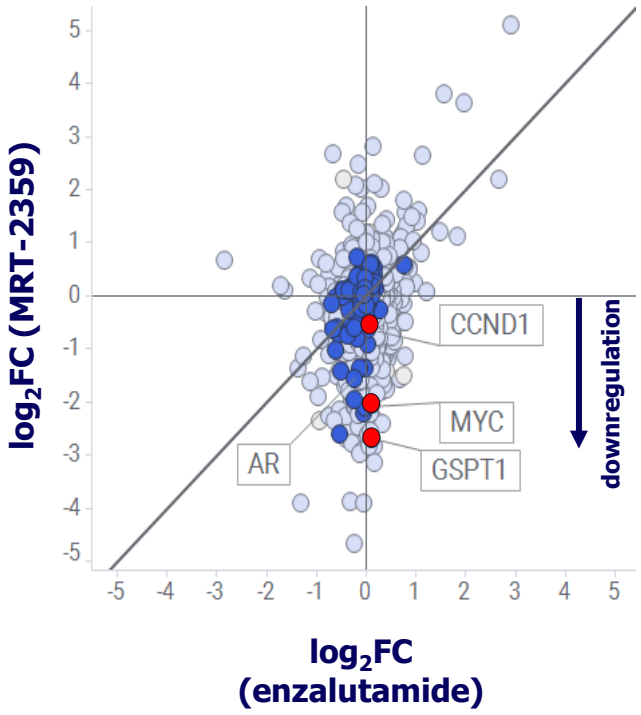


AR-positive AR-negative

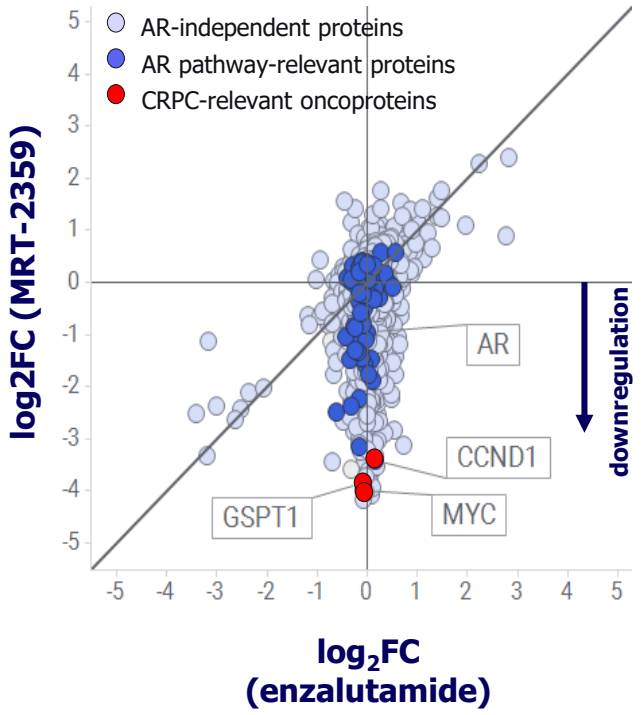
- Unbiased pharmacogenomic analysis identified prostate lineage as highly sensitive to MRT-2359
- Selective sensitivity noted in MYC/AR+ lines; minimal sensitivity in AR negative lines

Proteomics Analysis Revealed Modulation of AR and MYC/E2F Pathway by MRT-2359

VCaP model (AR-V7 low)



22RV1 model (AR-V7 high)



- MRT-2359 treatment significantly reduced abundance of several CRPC-relevant oncoproteins
  - AR abundance (WT and V7) and proteins regulated by AR were significantly reduced across cell lines
  - Other CRPC-relevant oncogenes such as MYC and Cyclin D1, a member of the E2F pathway, were also significantly reduced
- Notably, MRT-2359 was more effective than enzalutamide at reducing AR activity

MRT-2359 in Combination with Enzalutamide or Pluvicto Demonstrated Increased Activity Over Monotherapies In Xenograft Models

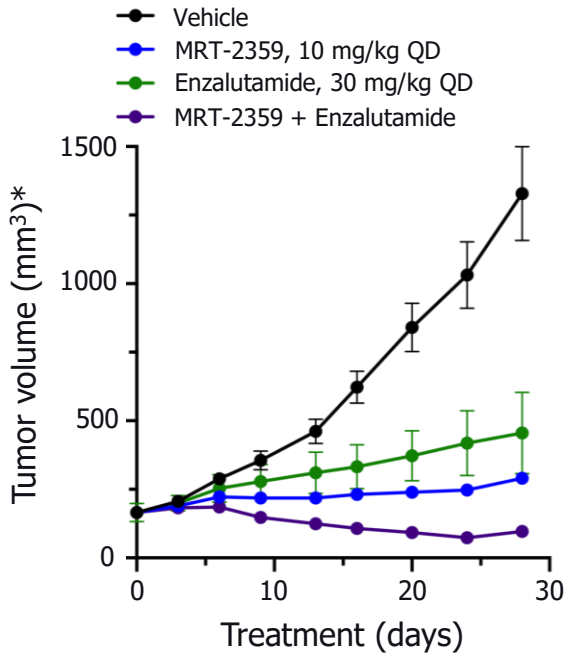
MRT-2359 + enzalutamide activity across AR mutant and AR-V7 low CDX models

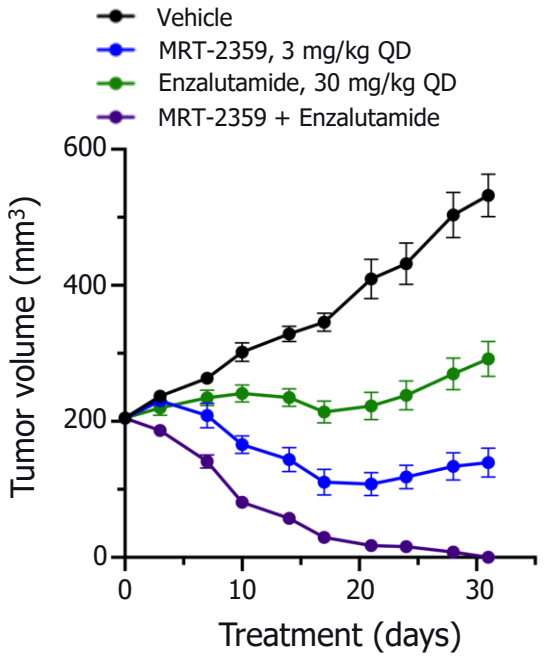
MRT-2359 + Pluvicto in AR-V7 CDX model

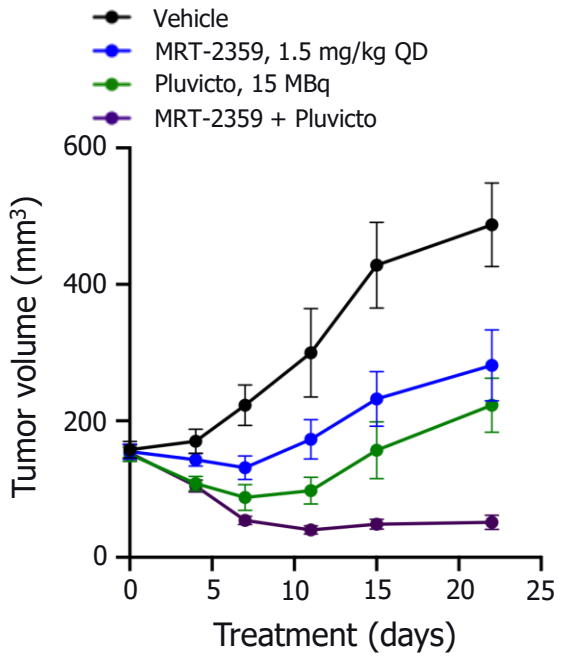
LNCaP AR Mutant (Mut), AR-V7 negative

VCAP AR amplified, AR-V7 low

22Rv1 AR-V7 high







- MRT-2359 + enzalutamide drove tumor regressions in CDX models of CRPC with various AR alterations including LNCaP and VCaP
- MRT-2359 + Pluvicto improved activity over single agents in enzalutamide-resistant, AR-V7 expressing 22Rv1 model

*Mean ± SEM

MRT-2359 Clinical Data Update

MRT-2359 Phase 1/2 Clinical Study Design

Phase 1: Dose Escalation

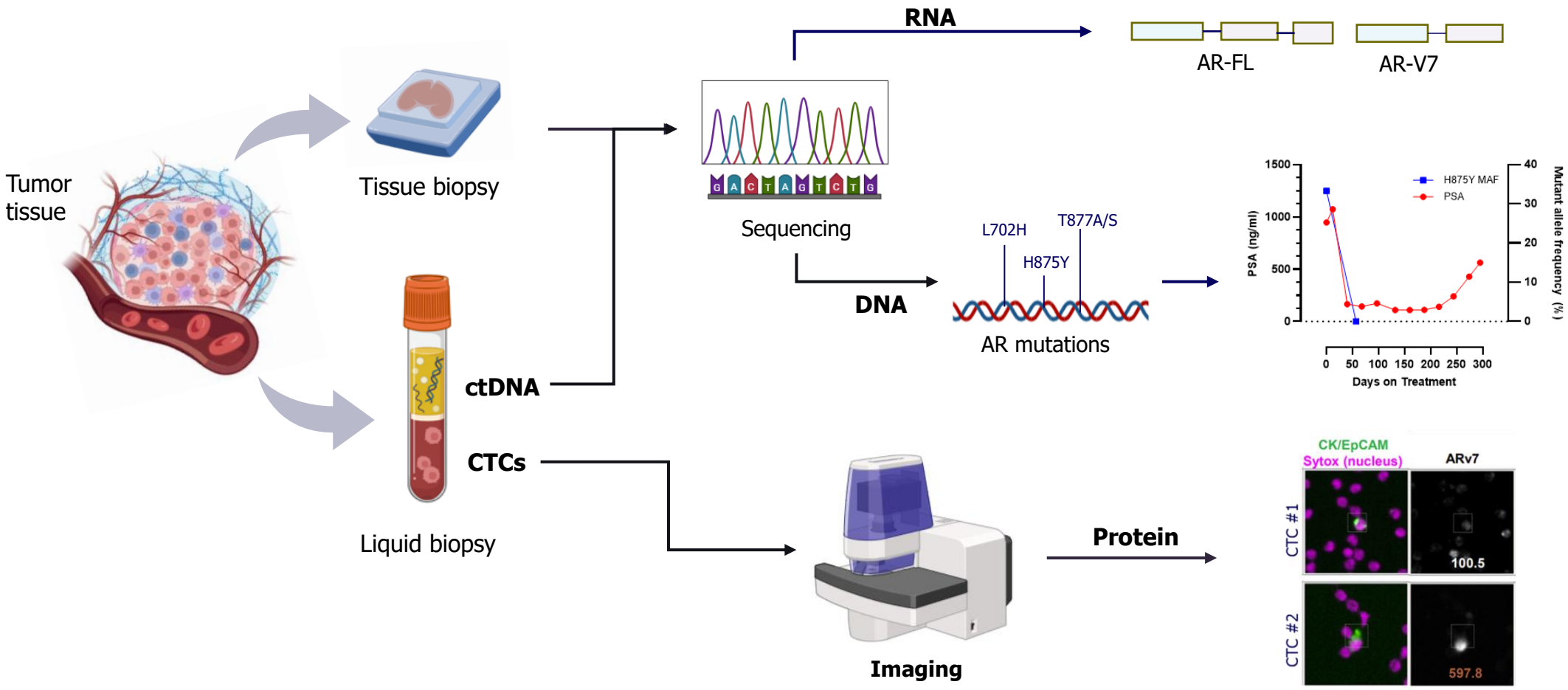
Monotherapy of MRT-2359 in lung cancer, high-grade neuroendocrine tumors and solid tumors with N-/L-MYC amplification

Phase 2: Expansion Cohort

Combination of MRT-2359 with enzalutamide in heavily-pretreated metastatic castration resistant prostate cancer (CRPC)

Well-tolerated dose level | 5/9 = 5 days on drug, 9 days off drug | 21/7 = 21 days on drug, 7 days off drug | RP2D = recommended Phase 2 dose

Biomarker Profiling of Tumor and Liquid Biopsies



- Identify key AR alterations in tumor biopsies, ctDNA, and CTCs, including AR mutations and AR-V7 transcripts
- Verify non-neuroendocrine histology through RNAseq

Notes: ctDNA = circulating tumor DNA. CTC = circulating tumor cell

Patient Demographics, Clinical Characteristics and Prior Therapies: MRT-2359 Compared to Mevrometostat Phase I Trial

Patient Characteristics	MRT-2359 + Enzalutamide Total (N=20)	Mevrometostat + Enzalutamide Phase I total (N=47)[1]
Age, median (range), years	72 (54-83)	70 (53 – 87)
Race, N (%)		
White	12 (60)	40 (85)
Black	6 (30)	4 (9)
Asian	0 (0)	2 (4)
Other	2 (10)	1 (2)
ECOG performance status, N (%)		
0 or 1	20 (100)	47 (100)
Histology subtype, N (%)		
Adenocarcinoma	17 (85)	47 (100)
Neuroendocrine[2]	3 (15)	ND[3]
Lesions at baseline, n (%)		
Bone only	0 (0)	16 (34)
Soft tissue only	1 (5)	10 (21)
Liver metastases	6 (30)	ND[3]
Number of prior lines of therapy, median (range)	4 (1-18)	ND[3]
Prior abiraterone, second gen ARi naive N (%)	5 (25)	20 (43)
Prior second gen ARi +/- abiraterone N (%)	15 (75)	27 (57)
Prior docetaxel and/or cabazitaxel N (%)	16 (80)	23 (49)
Prior Pluvicto N (%)	11 (55)	ND[3]
Baseline PSA, ng/mL, median (range)	17.4 (1.6 – 4,578)	49.9 (0-9,650)

Data cut-off December 03, 2025

Notes: [1] Mevrometostat + enzalutamide data from Schweizer et al. ASCO (2024). [2] Identified by RNAseq analysis of study tumor biopsies collected before dosing. [3] ND, not disclosed.
Comparisons between MRT-2359 and other therapies represented herein are based on post-hoc analyses comparing MRT-2359 clinical information with publicly available information for other therapies. Any comparisons use information from different clinical trials, conducted by different parties, at different points in time, with differences in trial designs and patient populations. No head-to-head clinical trials have been conducted, cross-trial comparisons should not be made, and this information is provided only for illustrative purposes.

Combination of MRT-2359 and Enzalutamide was Well Tolerated and May be Favorable over EZH2 Inhibitors

Treatment-Related AEs Occurring in >15% Patients

Dose Level	MRT-2359 0.5 mg and Enzalutamide 160 mg N=14				MRT-2359 0.75 mg and Enzalutamide 160 mg N=6				Total N=20
CTC AE V5 Grade	**G1 (%)**	**G2 (%)**	**G3 (%)**	**G4 (%)**	**G1 (%)**	**G2 (%)**	**G3 (%)**	**G4 (%)**	**All grades**
Fatigue	3 (21)	2 (14)	1 (7)	0	2 (33)	2 (33)	0	0	10 (50)
Diarrhea	5 (36)	0	1 (7)	0	4 (67)	0	0	0	9 (45)
Nausea	1 (7)	2 (14)	0	0	1 (17)	2 (33)	0	0	7 (35)
Arthralgia	3 (21)	1 (7)	0	0	1 (17)	1 (17)	0	0	6 (30)
Decreased appetite	1 (7)	1 (7)	0	0	2 (33)	1 (17)	1 (17)	0	6 (30)
Vomiting	1 (7)	1 (7)	0	0	1 (17)	3 (50)	0	0	6 (30)
Neutropenia	2 (14)	0	1 (7)	0	0	0	2 (33)	0	5 (25)
Muscular weakness	2 (14)	1 (7)	0	0	0	0	1 (17)	0	4 (20)

- Combination of MRT-2359 and enzalutamide was well tolerated
- Most frequent AEs were GI symptoms (nausea, diarrhea, vomiting), which were classified as mild or moderate and were manageable and not therapy limiting

Data cut-off December 03, 2025

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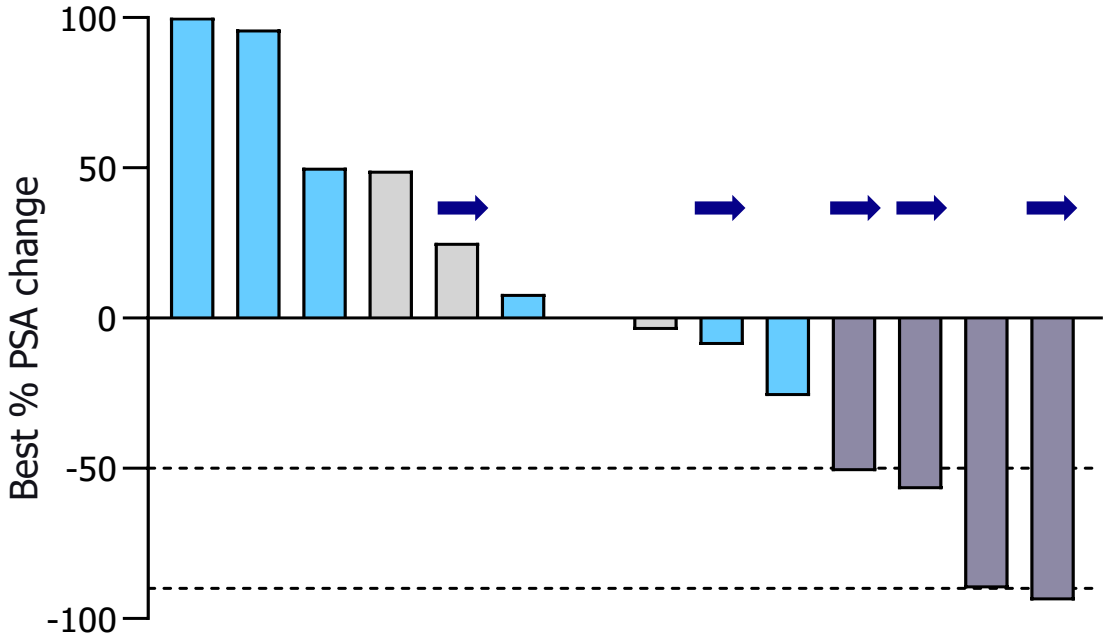
MRT-2359 and Enzalutamide Achieved High PSA Response Rate in AR Mutant mCRPC



AR status	V7	V7	V7	WT	WT	V7	V7	WT	V7	V7	Mut	Mut*	Mut	Mut
RECIST Response	PD	PD	SD	PD	SD	SD	SD	PD	SD	PD	SD	SD	PR	PR
RECIST %	0	-13	0	+29	-9	+12	-2	+67	-16	-7	-20	0	-62	-61
abi	+	-	+	-	+	+	+	-	+	-	+	+	+	+
2nd gen ARi	+	+	+	+	-	+	+	+	+	+	+	-	-	+
Docetaxel	+	+	+	+	-	+	-	+	+	+	+	+	+	+
Pluvicto	+	+	-	+	-	+	-	+	+	-	-	+	+	+
Dosing (mg)	0.75	0.75	0.5	0.5	0.5	0.75	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

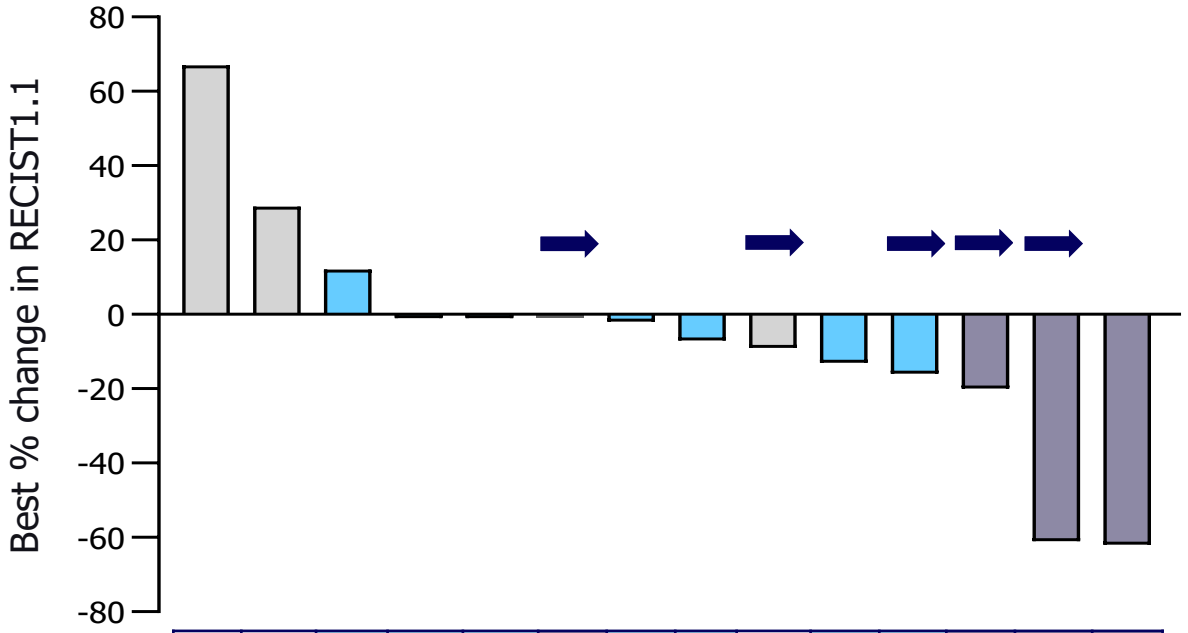
Data cut-off December 03, 2025
** Further deepening of PSA response to -68% confirmed after data cut-off*

- MRT-2359 + enzalutamide achieved 100% PSA response rate; PSA response in 4 of 4 heavily pretreated patients with AR mutations
  - PSA50 (n=2)
  - PSA90 (n=2)
- PSA response rate in overall population suggests activity at least comparable to data shown in Phase 1 study of mevrometostat + enzalutamide

Note: Comparisons between MRT-2359 and other therapies represented herein are based on post-hoc analyses comparing MRT-2359 clinical information with publicly available information for other therapies. Any comparisons use information from different clinical trials, conducted by different parties, at different points in time, with differences in trial designs and patient populations. No head-to-head clinical trials have been conducted, cross-trial comparisons should not be made, and this information is provided only for illustrative purposes.

MRT-2359 plus Enzalutamide Achieved Tumor Regressions in AR Mutant mCRPC

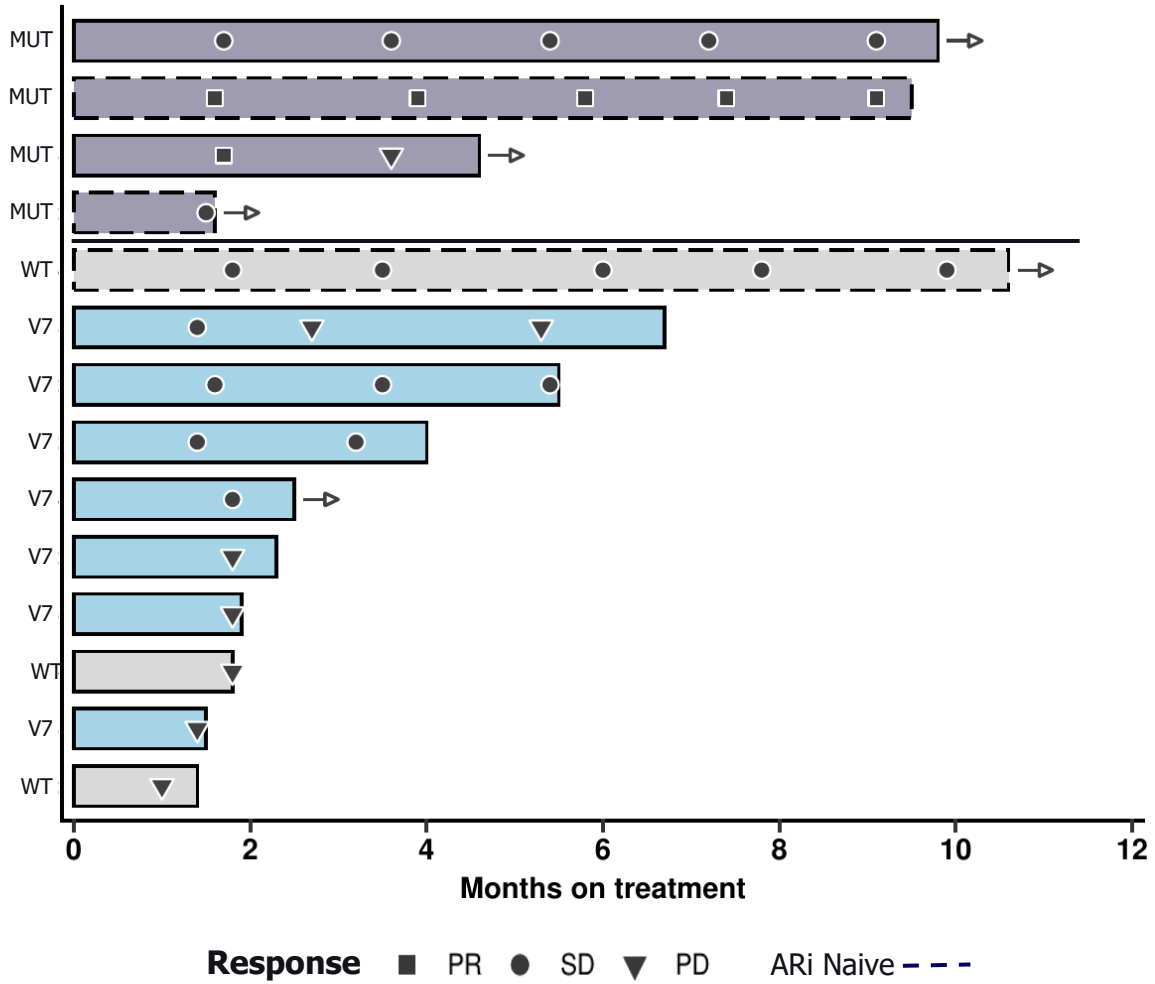
Best % change in RECIST in patients spanning AR alterations



AR status	WT	WT	V7	V7	V7	Mut	V7	V7	WT	V7	V7	Mut	Mut	Mut
RECIST Response	PD	PD	SD	PD	SD	SD	SD	PD	SD	PD	SD	SD	PR	PR
RECIST %	+67	+29	+12	0	0	0	-2	-7	-9	-13	-16	-20	-61	-62
PSA	-4	+49	+8	+100	+50	-57	-0.3	-26	+25	+96	-9	-51	-94	-90
Abiraterone	-	-	+	+	+	+	+	-	+	-	+	+	+	+
2nd gen ARi	+	+	+	+	+	-	+	+	-	+	+	+	+	-
Docetaxel	+	+	+	+	+	+	-	+	-	+	+	+	+	+
Pluvicto	+	+	+	+	-	+	-	-	-	+	+	-	+	+
Dose (mg)	0.5	0.5	0.75	0.75	0.5	0.5	0.5	0.5	0.5	0.75	0.5	0.5	0.5	0.5

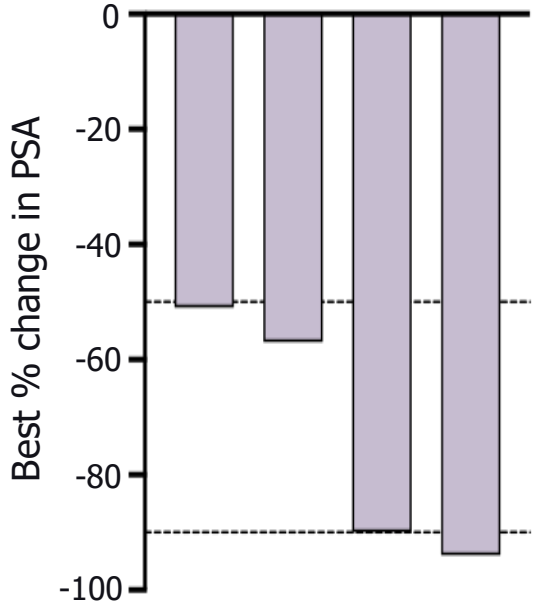
Data cut-off December 03, 2025

Durable disease control noted in mutant and ARi naïve patients



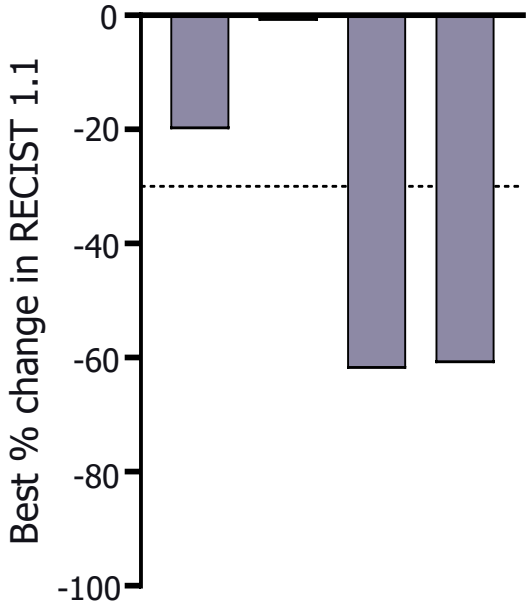
Compelling Activity in Heavily Pretreated Patients with AR Mutations

Best % change in PSA



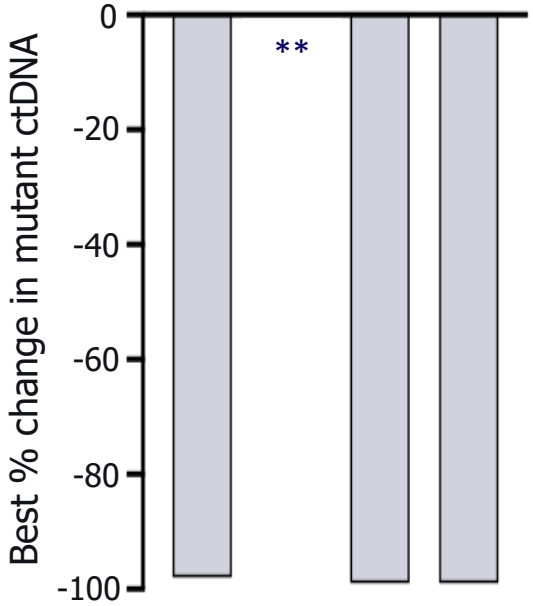
Response	SD	SD*	PR	PR
RECIST %	-20	0	-62	-61
Abiraterone	+	+	+	+
2nd gen ARi	+	-	-	+
Docetaxel	+	+	+	+
Pluvicto	-	+	+	+

Best % change in RECIST



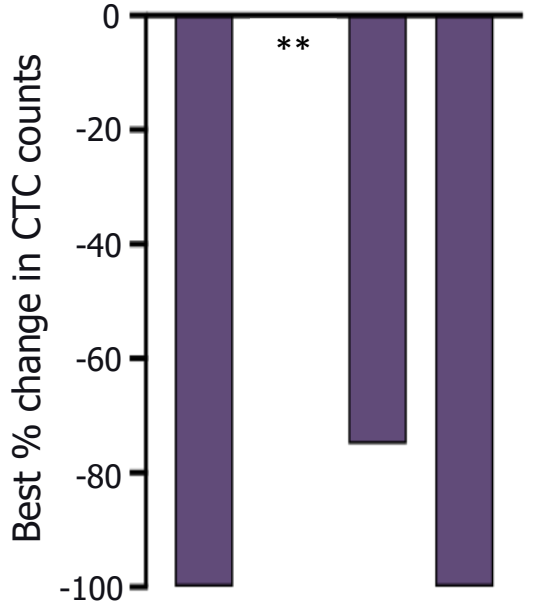
SD	SD	PR	PR
-20	0	-62	-61
+	+	+	+
+	-	-	+
+	+	+	+
-	+	+	+

Best % change in ctDNA



SD	SD	PR	PR
-20	0	-62	-61
+	+	+	+
+	-	-	+
+	+	+	+
-	+	+	+

Best % change in CTC counts



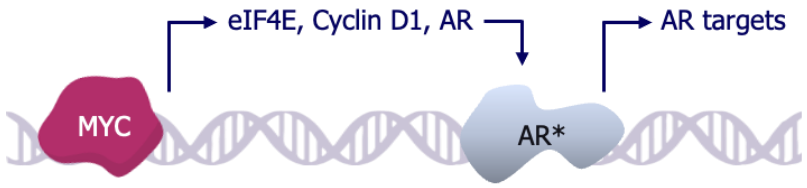
SD	SD	PR	PR
-20	0	-62	-61
+	+	+	+
+	-	-	+
+	+	+	+
-	+	+	+

Data cut-off December 03, 2025
** Further deepening of PSA response to -68% confirmed after data cut-off*

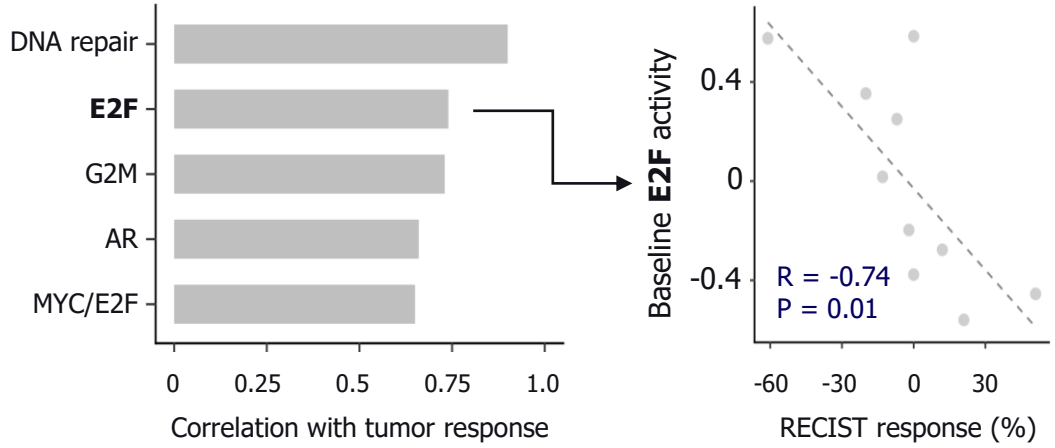
***Data pending*

Analysis of Tumor Biopsies Supports MRT-2359 Mode of Action – Correlation of Activity with and Modulation of MYC, E2F and AR Pathway

Unbiased Post-Hoc Analysis of RNAseq from tumor biopsies identified MYC, E2F and AR Activity as key predictors of tumor shrinkage*

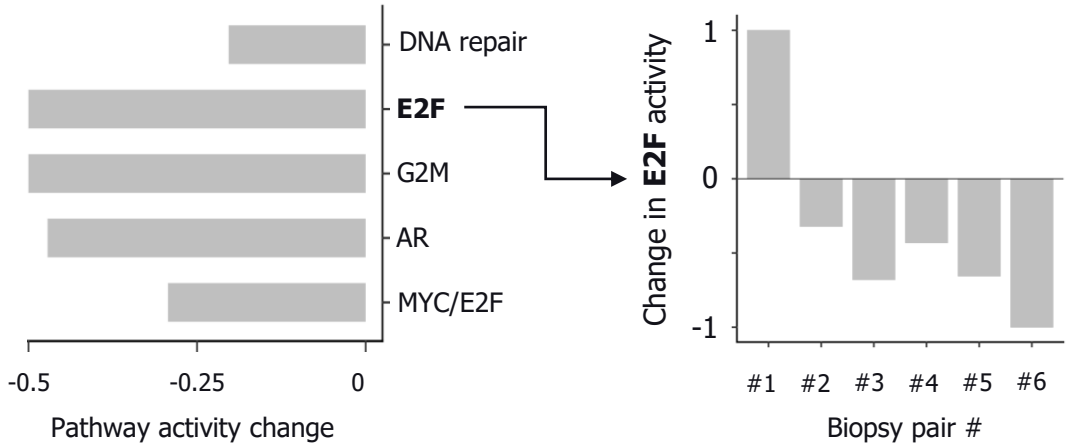


Promote mCRPC growth



Treatment reduced multiple key pathway signatures**

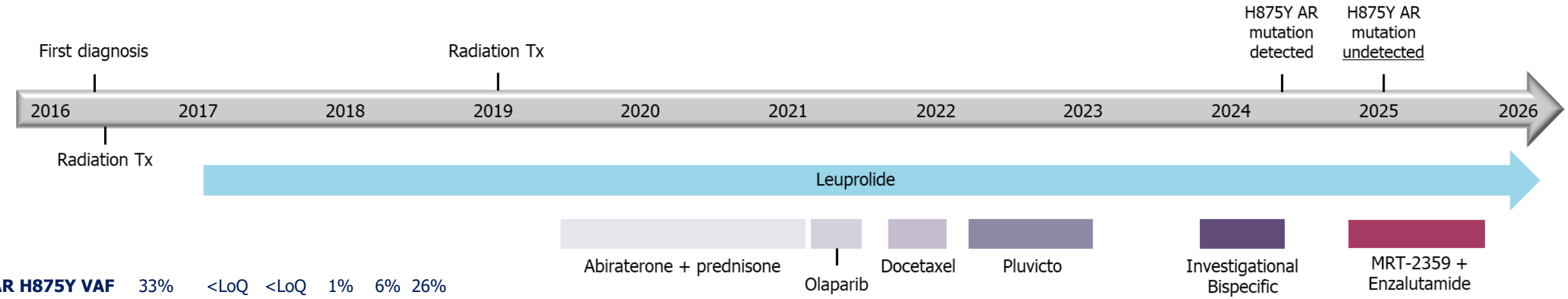
Inhibit mCRPC growth

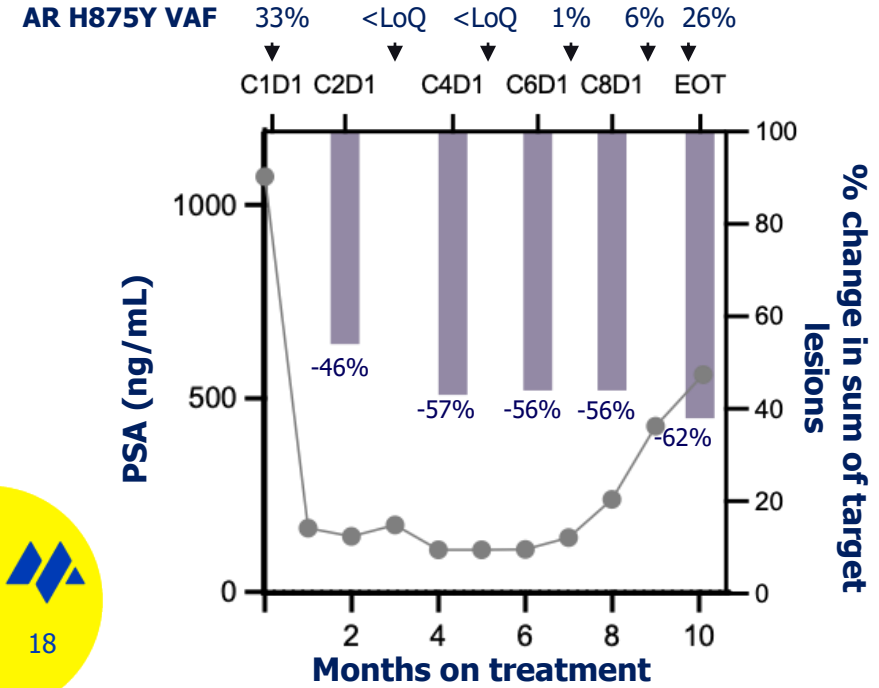


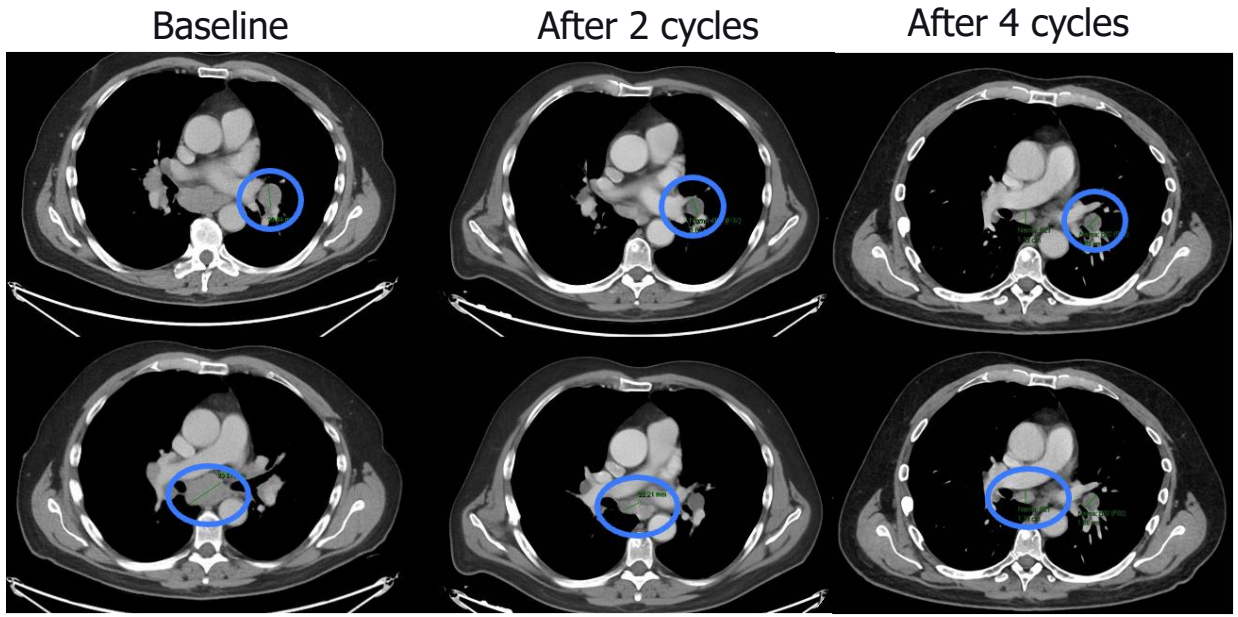
Data cut-off December 03, 2025

***Top 5 of 7 statistically significant pathways shown in plots; **Pathway level analysis in post-vs pre-treatment biopsies shown for pathways from analysis in left plot.*

Confirmed PR and PSA90 Response in mCRPC with Activating AR Mutation

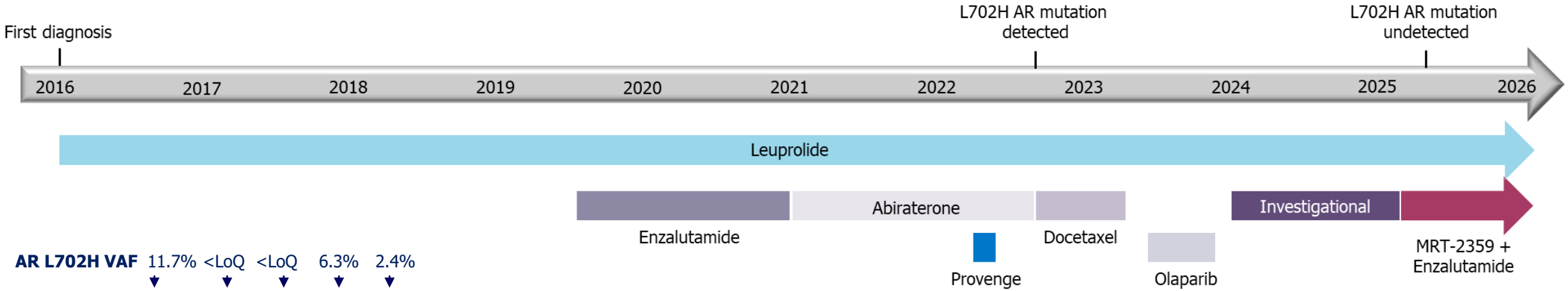


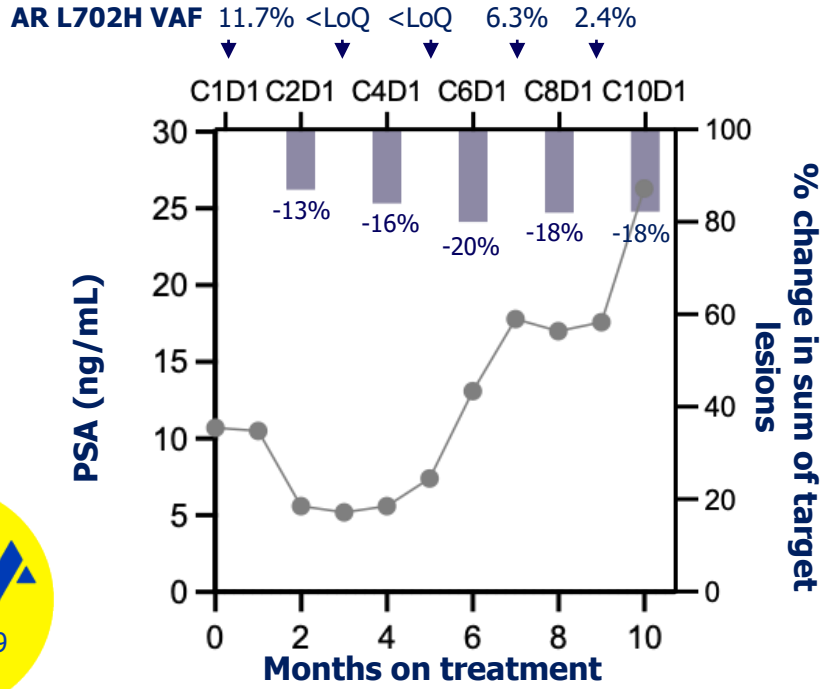


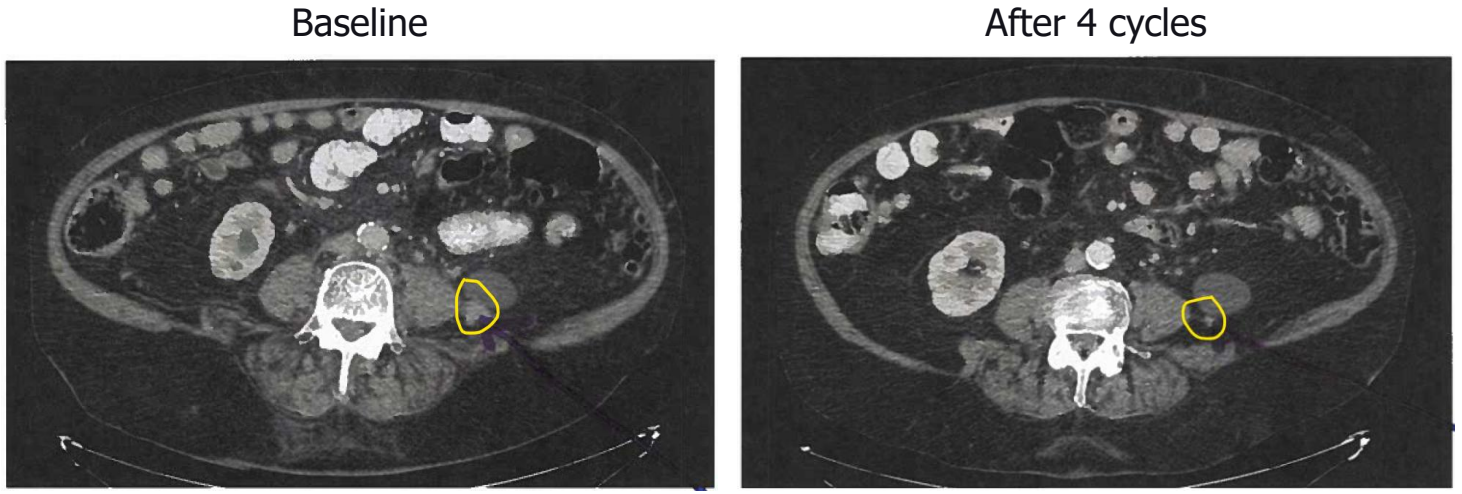


Data cut-off December 03, 2025

Confirmed SD and PSA50 in mCRPC patient with Activating AR Mutation







Data cut-off December 03, 2025

Next Steps

MODeFIRe-1* Phase 2 MRT-2359 Phase 2 Study in CRPC (up to 25 pts)

Enrollment

Simon's 2-Stage Design
(up to 25 pts)

mCRPC with AR mutations
PSA +/- RECIST measurable

Treatment

MRT-2359 0.5mg (21/7) +
2nd gen ARi (apa, daro, or enza)

28-day cycles

- Planned study initiation in 2026, US-only
- Enrollment completion ~12 months after initiation
- Endpoints include PSA response, RECIST, DoR, rPFS, and safety

Potential to expand to other AR driven populations, including patients without prior 2nd generation AR inhibitors

** MODeFIRe-1 Trial: Molecular Degrader For Inhibitor Resistance*

Summary

Summary and Next Steps

- MRT-2359 in combination with enzalutamide achieved compelling clinical activity (100% PSA response) in a subset of heavily pre-treated metastatic castration resistant prostate cancer (mCRPC) patients with androgen receptor (AR) mutations.
- Overall disease control rate (DCR) of 64% in a total of 14 evaluable patients
- Combination of MRT-2359 and enzalutamide was well tolerated with mild or moderate manageable GI adverse events (AEs) being the most frequent toxicities
- Data support potential of combination of MRT-2359 with 2nd generation androgen receptor inhibitors for mCRPC patients with AR mutations (up to 30% of 2nd line+ mCRPC), with additional potential in earlier line settings or in combination with other agents
- Updated data from the Phase 1/2 study expected to be presented at ASCO Genitourinary Cancers Symposium in February 2026
- Planning to initiate a signal-confirming 2-stage Phase 2 study of MRT-2359 in combination with 2nd generation AR inhibitor to target AR-mutated mCRPC in 2026

Monte Rosa Pipeline and Upcoming Milestones

	Target	Compound	Indication(s)	Discovery	IND-Enabling	Clinical	Next Anticipated Milestone
Immunology & Inflammation	VAV1 *Licensed to Novartis**	MRT-6160	Immune-mediated Diseases				Multiple Phase 2 initiations
Immunology & Inflammation	NEK7	MRT-8102	IL-1β/NLRP3-driven Inflammatory Diseases				Phase 1 interim data in early 2026
Immunology & Inflammation	NEK7	CNS Optimized	IL-1β/NLRP3-driven Inflammatory Diseases				IND submission in 2026
Oncology	GSPT1	MRT-2359	Castration-resistant Prostate Cancer				Phase 2 initiation in 2026
Oncology	CCNE1/ CDK2	Discovery	CCNE1 Amplified Tumors ER+ Breast Cancer				IND submission in 2026
Various	Multiple Targets *Includes those licensed/optioned to Roche and Novartis*	Discovery	I&I, Oncology, Genetic and Neurological Diseases				Undisclosed

* Novartis has exclusive worldwide rights to develop, manufacture and commercialize MRT-6160 and other VAV1 MGDs. Monte Rosa is eligible for up to $2.1B in development, regulatory, and sales milestones, beginning upon initiation of Phase 2 studies, and is also eligible for 30% US P&L share and ex-US tiered royalties.
Notes: IND = investigational new drug. ER = endocrine receptor. I&I = immunology and inflammation.

Q&A

Thank you

Monte Rosa Therapeutics