# #161: MRT-2359 in Combination with Enzalutamide Suppresses Multiple Oncogenic Pathways to Drive Deep and Durable PSA and RECIST Responses in Heavily Pretreated, Metastatic Castration-Resistant Prostate Cancer Harboring AR Mutations


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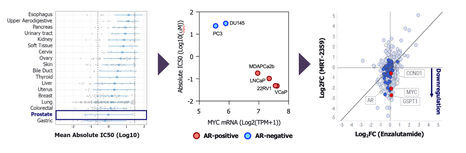
## Introduction

MYC-driven cancers depend on enhanced translation of lineage-specific oncoproteins to support rapid growth (1, 2). This vulnerability was exploited therapeutically with the potent molecular glue degrader MRT-2359 that disrupted translation through selective degradation of the translation termination factor GSPT1. An unbiased pharmacogenomic screen identified the prostate lineage as one of the most sensitive to MRT-2359 treatment. This exquisite potency was confirmed in AR-dependent prostate cancer (PCa) cell lines bearing high expression of MYC. MYC/AR-negative neuroendocrine PCa lines demonstrates minimal/no response to MRT-2359 (**Figures 1, 2**).

Progression of PCa to metastatic castration resistant-PCa (mCRPC), an aggressive, incurable form of PCa, occurs when tumors stop responding to androgen deprivation therapy. Numerous mechanisms, including emergence of AR mutations that reactivate the AR pathway and blunt response to hormone therapies including novel hormonal agents (NHA), become more prevalent in the androgen deprivation setting (3, 4). Mechanistically, MRT-2359 treatment reduced cellular abundance of many PCa-relevant oncoproteins including AR, MYC and Cyclin D1-E2F that correlated with robust anti-tumor activity across multiple preclinical models of mCRPC. Interestingly, combination with enzalutamide further improved anti-tumor responses in models harboring WT, AR-V7 or AR mutations through even greater suppression of AR signaling than achieved with MRT-2359 monotherapy alone (**Figures 1, 2**).

Here, we report preliminary results from an ongoing expansion portion of the Phase 1/2 study evaluating the safety/tolerability and preliminary antitumor activity of MRT-2359 in combination with enzalutamide in heavily pretreated mCRPC with RECIST 1.1 measurable disease **(NCT05546268)**.

**Pharmacogenomic Screen in Lineage Agnostic Cell Line Panel** | **Proliferation Potency Across Prostate Lines** | **Unbiased Proteomics Analysis in VCaP Line**




**MRT-2359 + Enzalutamide Activity Across AR Mutant and AR-V7 Low CDX Models** | **MRT-2359 + Pluvicto in AR-V7 CDX Model**

**LNCaP** AR Mutant, AR-V7 Negative | **VCAP** AR amplified, AR-V7 Low | **22Rv1** AR-V7 High

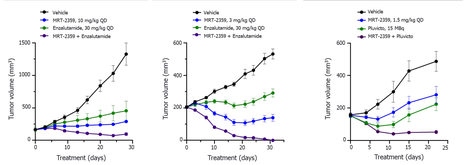



**Figure 1. MRT-2359 demonstrates efficacy in prostate cancer models both as a monotherapy and in combination with agents spanning multiple MoAs and modalities.** *Top*, MRT-2359 treatment reduces abundance of multiple oncoproteins in MYC high/AR-dependent (red dots, middle plot) PCa lines that leads to robust anti-proliferative activity. Blue dots represent AR and AR target proteins, red dots represent key PCa-relevant, AR-independent oncoproteins (*top, right*). *Bottom*, MRT-2359 exhibits exquisite anti-tumor activity across a number of AR-dependent prostate cancer cell line-derived xenograft models both as a monotherapy or in combination with enzalutamide (*left, middle*) or Pluvicto (*right*).

**Therapy-resistant mCRPC is characterized by increased oncogenic pathway activity** | **MRT-2359 + enzalutamide suppress multiple oncogenes including AR, MYC and Cyclin D1**

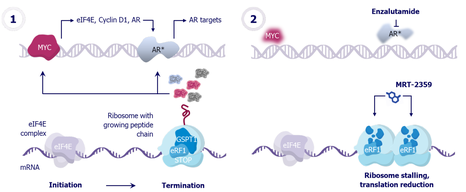



**Figure 2. MRT-2359 and enzalutamide combination exploits key therapeutic vulnerabilities in therapy-resistant CRPC.** *Left*, MYC high PCa cells present high baseline oncogenic pathway activity, including MYC, AR and Cyclin D1/E2F signaling. *Right*, MRT-2359 suppresses oncogenic pathway signaling through reducing protein translation. Combination with enzalutamide further suppresses AR-mediated signaling. *All AR variants (WT, V7, mutants).

## Methods

**Clinical study design**

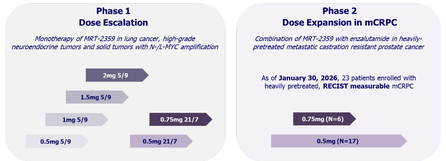



**Figure 3. MRT-2359 monotherapy and combination trial designs.** *Left*, monotherapy dose escalation study in lung cancer, high-grade neuroendocrine tumors and solid tumors with N-/L-MYC amplification. 5/9 (5 days on drug, 9 days off drug) and 21/7 (21 days on drug, 7 days off drug) schedules were assessed. *Right*, dose exploration and expansion study in heavily pretreated, metastatic castration resistant PCa. 0.5 and 0.75mg doses were explored and 0.5mg was selected as RP2D in combination with 160mg enzalutamide.

**Study Objectives (Phase 2)**

- Primary: Preliminary antitumor activity of MRT-2359
- Secondary: Safety, tolerability, antitumor activity, and PK profile
- Exploratory: PD effect, potential mechanisms of resistance, and additional molecular profiling

**Patients (Major eligibility criteria)**

- Non-neuroendocrine mCRPC prostate cancer patients with a focus on the following patient subsets:
  - Have received prior abiraterone but not a 2nd generation ARi
  - Harbor mutations in AR such as L702H, AR T878A/S, AR H875Y, or similar pathogenic mutations detected by ctDNA or molecular testing of tumor tissue
- At least one measurable lesion according to RECIST v1.1
- ECOG ≤ 2

## Results

**Patient disposition, demographics and baseline disease characteristics**

As of January 30, 2026, **23** heavily pretreated patients received MRT-2359 + enzalutamide (**Table 1**) and 4 patients (17%) remain on therapy. There were no treatment discontinuations for AEs.

Reasons for treatment discontinuation:
- Radiological or Clinical Progression – 13 (68%)
- Development of intercurrent medical condition – 1 (5%)
- Investigator Decision – 1 (5%)
- Withdrawal of Consent – 3 (16%)
- Death – 1 (5%)

**Table 1:** Patient demographics, clinical characteristics and prior therapies.

| Patient Characteristics | MRT-2359 + Enzalutamide Total (N=23) |
|---|---|
| **Age, median (range), years** | 71 (54-83) |
| **Race, N (%)** | |
| White | 14 (61) |
| Black | 7 (30) |
| Asian | 0 (0) |
| Other | 2 (9) |
| **ECOG performance status, N (%)** | |
| 0 | 9 (39) |
| 1 | 12 (52) |
| 2 | 2 (9) |
| **Histology subtype, N (%)** | |
| Adenocarcinoma | 20 (87) |
| Adenocarcinoma with neuroendocrine differentiation[1] | 3 (13) |
| **Sites of Disease at baseline, n (%)** | |
| RECIST measurable disease | 23 (100) |
| Soft tissue only | 1 (5) |
| Liver metastases | 6 (27) |
| **Number of prior lines of therapy, median (range)** | 5 (1-18) |
| Prior abiraterone, second gen ARi naive N (%) | 5 (22) |
| Prior second gen ARi +/- abiraterone N (%) | 18 (78) |
| Prior docetaxel and/or cabazitaxel N (%) | 19 (83) |
| Prior Pluvicto N (%) | 13 (57) |
| **Baseline PSA, ng/mL, median (range)** | 19.66 (0.66 – 4989) |

[1] Identified by RNAseq analysis of study tumor biopsies collected before dosing.

## Safety

- One (4%) patient had a dose-limiting toxicity (DLT) (grade 3 stomatitis associated with pain)
- AEs suspected to be drug-related occurring in ≥20% of patients shown in **Table 2**
  - Most common treatment-related, AEs were fatigue (N=12, 52%), diarrhea (N=11, 48%), and nausea (N=8, 35%) which were classified as mild or moderate and were manageable and not therapy limiting
- On the basis of favorable AE profile (**Table 2**) and superior clinical activity (**Figure 4**), 0.5mg 21/7 dose was prioritized for remainder of Ph2 expansion

**Table 2: Treatment-related adverse events occurring in ≥20% of patients.**

| Dose Level | MRT-2359 0.5mg and Enzalutamide 160mg N=17 | | | | MRT-2359 0.75mg and Enzalutamide 160mg N=6 | | | | Total N=23 |
|---|---|---|---|---|---|---|---|---|---|
| **CTC AE V5 Grade** | **G1 (%)** | **G2 (%)** | **G3 (%)** | **G4 (%)** | **G1 (%)** | **G2 (%)** | **G3 (%)** | **G4 (%)** | **All grades** |
| **Fatigue** | 3 (18) | 4 (24) | 1 (6) | 0 | 2 (33) | 2 (33) | 0 | 0 | 12 (52) |
| **Diarrhea** | 5 (29) | 1 (6) | 1 (6) | 0 | 4 (67) | 0 | 0 | 0 | 11 (48) |
| **Nausea** | 1 (6) | 3 (18) | 1 (6) | 0 | 1 (17) | 2 (33) | 0 | 0 | 8 (35) |
| **Decreased appetite** | 1 (6) | 2 (12) | 0 | 0 | 2 (33) | 1 (17) | 1 (17) | 0 | 7 (30) |
| **Vomiting** | 1 (6) | 2 (12) | 0 | 0 | 1 (17) | 3 (50) | 0 | 0 | 7 (30) |
| **Anemia** | 3 (18) | 1 (6) | 0 | 0 | 0 | 0 | 2 (33) | 0 | 6 (26) |
| **Arthralgia** | 3 (18) | 1 (6) | 0 | 0 | 1 (17) | 1 (17) | 0 | 0 | 6 (26) |
| **Lymphopenia** | 1 (6) | 0 | 3 (18) | 0 | 0 | 0 | 1 (17) | 0 | 5 (22) |
| **Muscular Weakness** | 2 (12) | 2 (12) | 0 | 0 | 0 | 0 | 1 (17) | 0 | 5 (22) |
| **Neutropenia** | 2 (12) | 0 | 1 (6) | 0 | 0 | 0 | 2 (33) | 0 | 5 (22) |

## Efficacy in Evaluable Patients

- As of data cutoff on January 30, 2026, 33% of patients (5 of 15) showed PSA response, 13% (2 of 15) RECIST partial response (PR) and the overall disease control rate (DCR) was 67% (10 of 15) with 10 patients presenting tumor size reductions of target lesions (**Figure 4**)
- In a subset analysis, compelling efficacy was noted in a cohort of 5 heavily pretreated patients with AR mutations (**Figures 4-5, 7-9**);
  - 5 of 5 patients (100%) showed a PSA response, including 2 patients with PSA90 and 3 patients with PSA50 responses
  - 2 of 5 patients showed RECIST PR (1 confirmed, 1 unconfirmed) and 3 patients had stable disease, leading to a 100% DCR
  - 2 patients remained on therapy for 10 cycles or longer and 2 of 5 patients remain on drug as of data cutoff on January 30, 2026

**Best % change in PSA in AR-WT, -V7 and mutant patients** | **Best % change in RECIST in AR-WT, -V7 and mutant patients**

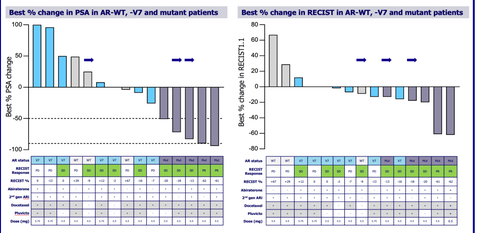



**Figure 4. PSA and RECIST waterfall plots of all evaluable patients.** Plot of best % change in PSA (*left*) and sum of diameter of target lesions (*right*) from baseline in WT (grey bars), AR-V7 (blue bars) and AR mutant (purple bars) patients. Dose level and prior treatments shown in table below. Blue arrows reflect on-treatment status as of data cutoff.

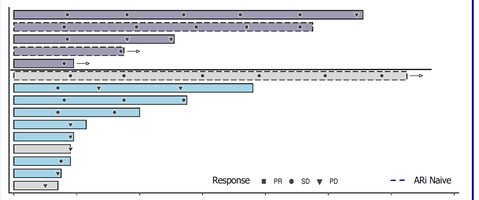



**Figure 5. Swimmer plot of all evaluable patients.** Swimmer plot showing response at every scan (PR, solid square; SD, solid circle; PD, solid inverted triangle) and duration of treatment in months in WT (grey bars), AR-V7 (blue bars) and AR mutant (purple bars) patients. Arrows reflect on-treatment status. Dashed line reflects second generation ARi naive status.

## Efficacy in Patients with AR Mutations

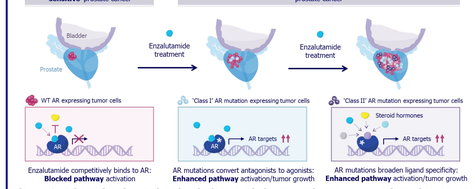



**Figure 6. Schematic of two functional classes of therapy-resistant AR mutations that emerge following treatment with AR antagonists (5).** Following prolonged treatment with enzalutamide, 2 functional classes of mutations in AR might emerge. *Middle*, **class 1,** antagonist-to-agonist switch mutations that activate AR signaling in the presence of AR antagonist(s). *Right*, **class 2,** mutations that broaden ligand specificity and allow AR activation in response to diverse array of steroid hormones in addition to testosterone. Class 2 mutations are more relevant to present study as they might serve as surrogates for AR pathway activity.

**Best % change in PSA** | **Best % change in RECIST** | **Best % change in ctDNA** | **Best % change in CTC counts**

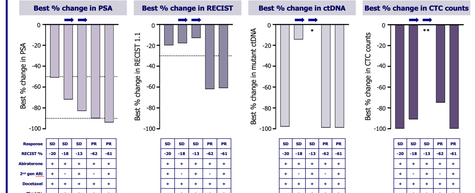



**Figure 7. Best % change in PSA, sum of diameters of target lesions, variant allele frequency and CTC counts in 5 of 5 AR mutant patients.** All patients showed a PSA response, 2 of 5 showed RECIST partial responses and 3 of 5 presenting stable disease. A significant decrease in mutant allele frequency and total CTC counts were noted in 4 of 5 patients for which data is available. Blue arrows reflect on-treatment status as of data cutoff. *QC failed. **data pending for 5th patient.

## Case Studies

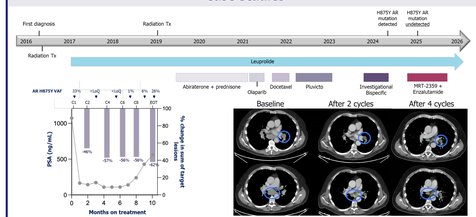



**Figure 8. Treatment history and response in heavily pretreated patient bearing an AR H875Y mutation.** C, cycle of treatment.

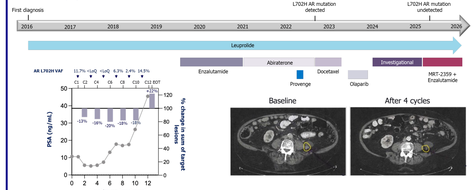



**Figure 9. Treatment history and response in heavily pretreated patient bearing an AR L702H mutation.** Patient discontinued treatment due to rebound in PSA although reduction in target lesions was maintained. C, cycle of treatment.

## Proof-of-Modulation of Target Oncogenic Pathways

**Unbiased Post-Hoc Analysis of RNAseq from tumor biopsies identified MYC, E2F and AR Activity as key predictors of tumor shrinkage*** | **Treatment reduced multiple key pathway signatures****

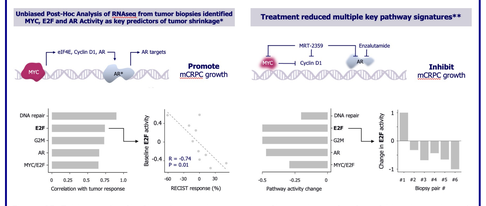



**Figure 10. Evidence of activation of several oncogenic pathways in pre-treatment biopsies and proof-of-modulation of target PCa-relevant oncogenic pathways in post-treatment tumor biopsies.** *Left*, oncogenic pathways significantly activated in pre-treatment biopsies. * Top 5 of 7 statistically significant pathways shown. *Right*, significantly reduced signaling output of pathways highlighted in left plot following treatment. ** Pathway level analysis in post-vs pre-treatment biopsies shown for pathways analyzed in left plot.

## Conclusions and Future Development

- MRT-2359 + enzalutamide combination was well tolerated in mCRPC patients
  - All AEs were manageable, with the most common study drug-related AEs being fatigue, diarrhea, nausea and decreased appetite
- Of all evaluable patients, the overall RECIST DCR was 67% (10 of 15) with 10 of 15 associated with tumor size reductions of target lesions
  - Compelling combination activity was noted in subset of 5 patients harboring AR mutations with 100% PSA50/90 response, 40% RECIST PR and 100% RECIST DCR
- Based on the compelling efficacy in AR mutation subset, a signal-confirming Phase 2 study of MRT-2359 in combination with a second-generation AR inhibitor will be pursued in AR mutant patients
  - Expected enrollment: Up to 25 patients with mCRPC and AR mutations
  - Potential to expand into additional patient subsets, including patients naive to 2nd generation AR inhibitors and/or in combination with other agents
  - Endpoints: PSA response, RECIST response, duration of response, radiographic progression free survival, and safety

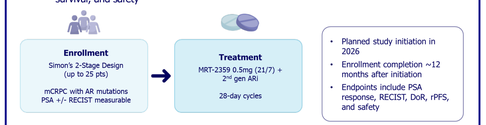



**Figure 11. MODeFIRe-1 (Molecular Degrader For Inhibitor Resistance) phase 2 signal confirming study design and main endpoints.**

## References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