Androgen Receptor Modulation Optimized for Response: Splice Variant (ARMOR3-SV) — Randomized, Open-label, Multicenter, Controlled Study of Galeterone vs Enzalutamide in Men with Metastatic Castration-Resistant Prostate Cancer (mCRPC) Expressing AR-V7 Splice Variant

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BACKGROUND

Clinical Need

- Recent data have demonstrated poor response to abiraterone and enzalutamide in the presence of a truncated form of the androgen receptor (AR) lacking the C-terminus[1-2]
- The prevalence of AR splice variants, of which AR-V7 is the most common, appears to be higher in patients following exposure to prior therapies **(Table 1)**

Table 1. Prevalence of AR-V7/C-Terminal Loss in Patients with Prostate Cancer in Clinical Trials

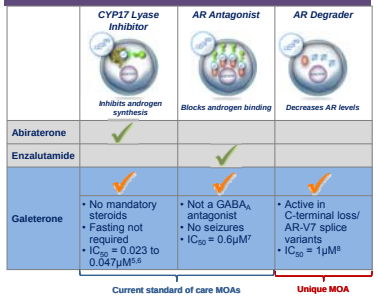
Stage of Disease	Prevalence*
M1 CRPC	12%[1] 23%[3] 26%[2]
Secondary Refractory/ Salvage	25% post-enzalutamide[1] 51% post-abiraterone[1] 67% post-enzalutamide+abiraterone[1] 59% post-secondary therapy[4]

*Prevalence reflects variable exposure to prior therapies.

Galeterone Mechanism of Action

- Galeterone is a selective, multitargeted, small molecule that disrupts androgen signaling at multiple points in the pathway **(Figure 1)**

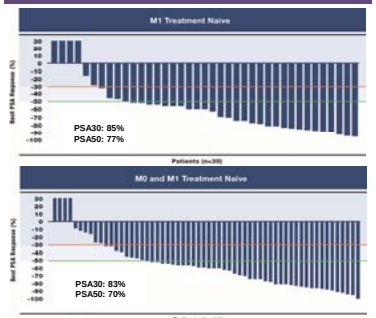
Figure 1. Mechanisms of action of galeterone vs abiraterone and enzalutamide



Androgen Receptor Modulation Optimized for Response–2 (ARMOR2)[5,9]

- Open-label, 2-part, phase 2 trial in mCRPC; M0-TN, M1-TN, M1-abiraterone or enzalutamide refractory; (N=107)
- ~90% of treatment emergent adverse events (AEs) were CTCAE Grade 1 or 2 (31Mar15 cut)
  - Most common (≥25%) related AEs: fatigue (37%), nausea (36%), pruritus (34%)
- Demonstrated clinically meaningful PSA reductions (**Figure 2**)

Figure 2. Maximal PSA reductions in ARMOR2 within 12 weeks[5,9]



M1: includes 39/39 patients who completed 12 weeks, reached PSA50, or terminated early. M0+M1: includes 80/81 patients that completed 12 weeks, reached PSA50, or terminated early. The one patient not included was non-evaluable (off treatment before Week 2). Data cut 31March2015. M0=non-metastatic disease; M1+metastatic disease; PSA=prostate specific antigen.

ARMOR3-SV Trial

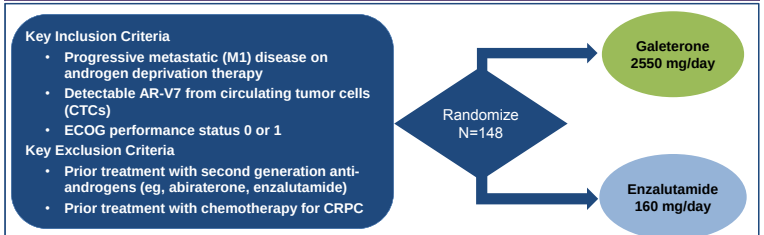
Overview

- ARMOR3-SV is a phase 3, randomized, open-label, multicenter, controlled clinical trial comparing galeterone with enzalutamide in men expressing AR splice variant-7 (AR-V7) mRNA mCRPC (**Figures 3 and 4**)
- Enrollment expected to begin in second quarter of 2015
- Independent Data Monitoring Committee planned
- Powered (90%) to detect an 82% increase in median rPFS, enrolling 148 patients

Steering Committee

- Emmanuel Antonarakis, MD; Sidney Kimmel Cancer Center/Johns Hopkins University (Committee Chair)
- Johann de Bono, MD, PhD; The Institute of Cancer Research and the Royal Marsden Hospital (EU Study Lead)
- Jun Luo, PhD; Johns Hopkins University (Companion Diagnostic Advisor)
- Mary-Ellen Taplin, MD; Dana-Farber Cancer Institute/Harvard Medical School (US Study Lead)

Figure 3. ARMOR3-SV study design



Primary Endpoint

- Radiographic progression free survival (rPFS)

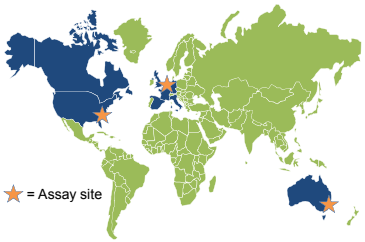
Secondary Endpoints

- Overall survival (OS)
- Time to cytotoxic therapy

Other Endpoints

- Symptomatic skeletal events
- Safety
- PSA50
- Time to PSA progression
- Time to ECOG deterioration
- Best overall response by RECIST 1.1

Figure 4. Planned ARMOR3-SV study sites and assay sites



Over 100 study sites in 9 countries

- Australia
- Belgium
- Canada
- France
- Germany
- Italy
- United States
- United Kingdom
- Spain

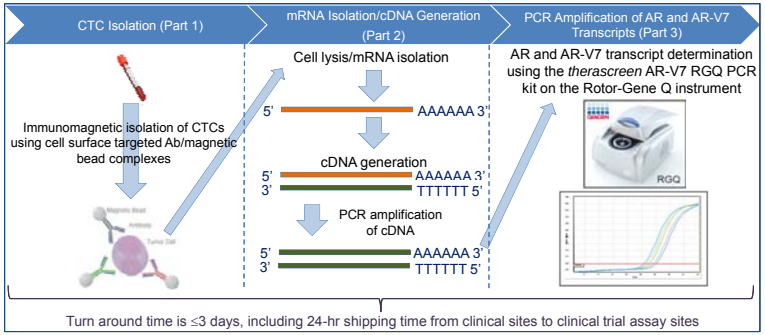
Assay Sites

- Research Triangle Park, NC, USA (assay parts 1-3 **[Figure 5]**)
- Melbourne, Australia (assay parts 1-3)
- Mechelen, Belgium (assay parts 1-2; part 3 completed in US until CE mark for the PCR kit is obtained)

Figure 5. CTC Collection and Evaluation

Companion Diagnostic Development

- Johns Hopkins University-discovered assay in development with Qiagen
- CTC isolation and RT-PCR (AR and AR-V7) determination
- PSA, PSMA, EGFR transcripts detected for prostate cancer CTC confirmation

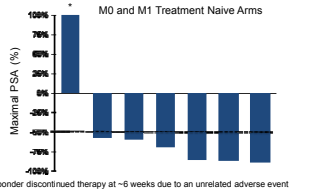


RATIONALE FOR GALETERONE IN AR-V7 POSITIVE mCRPC

Clinical Rationale

- In a retrospective analysis of patients from ARMOR2, 6 (86%) of 7 patients identified as having C-terminal loss, showed PSA50 response (**Figure 6**)[9]
- Time to PSA progression was 7.3 months (median, 31Mar2015 data cut)[5]

Figure 6. PSA50 Response in C-terminal loss patients in ARMOR2[9]

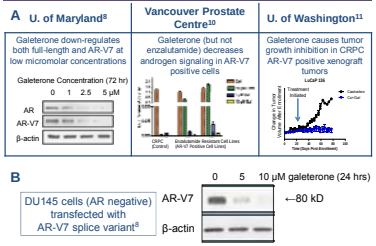


*Nonresponder discontinued therapy at ~6 weeks due to an unrelated adverse event

Preclinical Rationale

- Multiple preclinical studies have shown the activity of galeterone in AR-V7 expressing cells **(Figure 7A)**
- Galeterone decreases AR-V7 protein in cells lacking wild-type AR **(Figure 7B)**

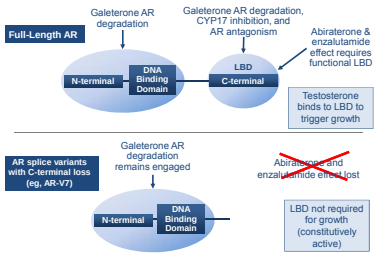
Figure 7. Key preclinical studies of galeterone



Mechanistic Rationale

- Galeterone mechanism of AR degradation does not require the presence of the ligand binding domain for activity **(Figure 8)**

Figure 8. Galeterone remains active against AR splice variants with C-terminal loss[5-8]



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