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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-terminus1-2
- · 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 <sup>1</sup> 51% post-abiraterone <sup>1</sup> 67% post- enzalutamide+abiraterone <sup>1</sup> 59% post-secondary therapy <sup>4</sup>	

#### 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				
	CYP17 Lyase Inhibitor  Inhibits androgen synthesis	AR Antagonist  Blocks androgen binding	AR Degrader  Decreases AR levels	
Abiraterone	<b>√</b>			
Enzalutamide		<b>✓</b>		
Galeterone	• No mandatory steroids • Fasting not required • IC <sub>50</sub> = 0.023 to 0.047µM <sup>5,6</sup>	• Not a GABA <sub>A</sub> antagonist • No seizures • IC <sub>50</sub> = 0.6µM <sup>7</sup>	• Active in C-terminal loss/ AR-V7 splice variants • IC <sub>50</sub> = 1µM <sup>8</sup>	

### Current standard of care MOAs

# Androgen Receptor Modulation Optimized for Response–2 (ARMOR2)<sup>5,9</sup>

- 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. Maximal PSA reductions in ARMOR2 within 12 weeks<sup>5,9</sup>



M1: includes 39/39 patients who completed 12 Weeks, reached PSA50, or terminated early. M0 ·M1: includes 60/61 patients that completed 12 weeks, reached PSA50, or terminated early. The one patient not included was non-evaluable (off treatment before Week 2). Data out/ 3/March2015. M0-non-metastatic disease, M1 metastatic desse; PSA\*-prostate specific

## **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 Key Inclusion Criteria Progressive metastatic (M1) disease on 2550 mg/day androgen deprivation therapy Detectable AR-V7 from circulating tumor cells (CTCs) Randomize ECOG performance status 0 or 1 N=148 **Key Exclusion Criteria** Prior treatment with second generation antiandrogens (eg, abiraterone, enzalutamide) Enzalutamide 160 mg/day Prior treatment with chemotherapy for CRPC

## 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

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



Figure 5. CTC Collection and Evaluation

Companion Diagnostic Development

#### Over 100 study sites in 9 countries

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

## Assay Sites

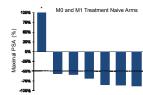
- · Research Triangle Park, NC, USA
- (assay parts 1-3 [Figure 5]) Melbourne, Australia (assay parts 1-3)
- · Mechelen, Belgium (assay parts 1-2; part 3 completed in US until CE mark for the PCR kit is obtained)

## **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<sup>9</sup>



r discontinued therapy at ~6 weeks due to an unrelated adverse even

#### 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

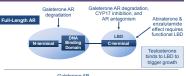
A U. of Maryland®	Vancouver Prostate Centre <sup>10</sup>	U. of Washington <sup>11</sup>
Galeterone down-regulates both full-length and AR-VF at low micromolar concentrations Galeterone Concentration (72 hr) 0.1 2.5 5 μM AR-VF	Galeterone (but not enzalutamide) decreases androgen signaling in AR-V7 positive cells	Galeterone causes tumor growth inhibition in CRPC AR-V7 positive xenograft tumors tumors tumors and tumors tumors are selected to the selected tumors are selected tumors and tumors are selected tumors are selected tumors and tumors are selected tumors and tumors are selected tumors a



### 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<sup>5-8</sup>





## CONTACT INFORMATION

- For additional information please contact
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## REFERENCES

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### mRNA Isolation/cDNA Generation PCR Amplification of AR and AR-V7 AR and AR-V7 transcript determination Cell lysis/mRNA isolation using the therascreen AR-V7 RGQ PCR kit on the Rotor-Gene Q instrument AAAAAA 3' Immunomagnetic isolation of CTCs 0 using cell surface targeted Ab/magnetic bead complexes cDNA generation AAAAA 3 TTTTTT 5' PCR amplification of cDNA AAAAAA 3 TTTTTT 5 Turn around time is ≤3 days, including 24-hr shipping time from clinical sites to clinical trial assay sites