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Galeterone in Four Castrate Resistant Prostate Cancer (CRPC) Populations: Results from ARMOR2

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- Consulting: Cowan, Guide Point Global

Castration-Resistant Prostate Cancer: Background

- Prostate cancer is the most commonly diagnosed cancer and the 3rd most common cause of cancer-related death in men in the EU[1]
  - 10%–20% of men with prostate cancer will advance to CRPC[2]
- Treatment of CRPC typically targets the AR, supported by the efficacy of newer AR-directed therapies in this setting[1,3]
  - Androgen synthesis inhibitors
  - AR-signaling inhibitors
- Mechanisms of response and resistance to AR-directed agents is of great interest and still to be defined

AR=androgen receptor; CRPC=castration-resistant prostate cancer.

1. Horwich A et al. *Ann Oncol*. 2013; 24(suppl 6):vi106-14. 2. Kirby M et al. *Int J Clin Pract*. 2011;65:1180-92. 3.Heidereich A et al. EAU Guidelines on Prostate Cancer. Available at: http://www.uroweb.org/gls/pdf/09_Prostate_Cancer_LR.pdf. Accessed August 11, 2014.

AR Splice Variants as a Resistance Mechanism

- Emerging data indicate AR-Vs (eg, AR-V7, AR^{v567es}) may be drivers of resistance in CRPC[1,2]
- Expression of AR-Vs has been shown to correlate with disease progression and shortened survival[3,4]
- AR-V7 is most abundant in CRPC specimens[5]
- Truncated ARs with C-terminal loss (splice variants) lack a functional LBD and are constitutively active[5]
- The biology of ARVs may differ depending on prior therapy and associated pathway abnormalities
- C-terminal AR-directed therapies may not be effective if ARV7 are biologically relevant[6-8]
- Novel agents are needed that target mutated ARs including ARVs

AR=androgen receptor; AR-V=AR splice variants; CRPC=castration-resistant prostate cancer; LBD=ligand binding domain.

1. Sprenger CT et al. *Horm Canc*. 2014;5:207-17. 2. Nakazawa M et al. *Horm Cancer*. 2014. DOI 10.1007/s12672-014-0190-1. 3. Hornberg E et al. *PLoS*. 2011;6(4):e19059. 4. Hu R et al. Cancer Res. 2009;69:16-22. 5. Guo Z et al. *Cancer Res*. 2009;69:2305-13. 6. Antonarakis E. AACR 2014. 7. Antonarakis ES et al. NEJM. 201410.1056/NEJMoa1315815. 8. Li Y et al. *Cancer Res*. 2013;73:483-9.

Lack of Response Associated with AR C-Terminal Loss/AR-V7 (MD Anderson)

- Phase 2 study that assessed expression of molecular components of AR signaling in bone marrow biopsy samples from patients with CRPC[1]
  - Patients with AR-V7 showed poor response to enzalutamide
- Sequential combination regimen of abiraterone and enzalutamide in CRPC patients (ASCO 2014)[2]
  - Patients with AR-V7 or C-terminal loss showed no benefit

Enzalutamide[1]				
	N	Primary Resistance[a]	Benefit	
			Moderate[b]	Prolonged[c]
AR-V7 Positive	7	86%	14%	0%
AR-V7 Negative	16	38%	31%	31%

Sequential Combination Abiraterone and Enzalutamide[2]			
	N	Primary Resistance	Benefit
AR-V7 Positive	2	100%	0%
C-terminal loss	2	100%	0%
No AR-V7 or C-terminal loss	11	18%	82%

[a]Primary resistance: <4 mos on therapy. [b]Moderate benefit: 4-6 mos on therapy. [c]Prolonged benefit: >6 mos on therapy.
AR=androgen receptor; AR-V=AR splice variant; CRPC=castration-resistant prostate cancer.
1. Efstathiou E et al. *Eur Urol*. 2014 May 29. pii: S0302-2838(14)00415-1. doi: 10.1016/j.eururo.2014.05.005. 2. Efstathiou E et al. ASCO 2014.

Lack of Response Associated with AR-V7 (Johns Hopkins University)

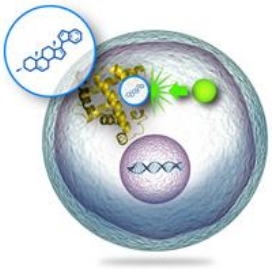
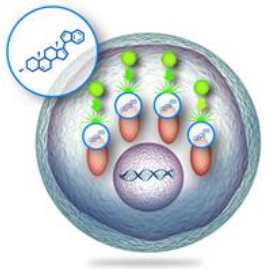
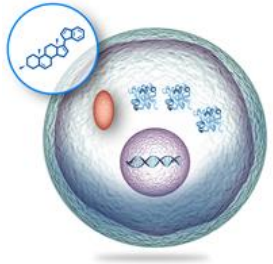
- Prospective study of M1 CRPC patients eligible for abiraterone (N=31) and enzalutamide (N=31) treatment; AR-V7 identified in CTC samples pretreatment
- None (0/18) of the AR-V7 positive patients achieved a PSA50
  - Only 1 AR-V7 positive patient showed any PSA reduction (enzalutamide)
- AR-V7 prevalence increased post additional treatments

Treatment[1]	Baseline AR-V7+	Response						
		AR-V7 status	PSA50	P- value	rPFS	P- value	OS (95% CI)	P value
Abiraterone (N=31)	19% (6/31)	+	0% (0/6)	.004	2.3 mos	<.001	10.6 mos (8.5–NR)	.002
		–	68% (17/25)		>6.3 mos		>11.9 mos (11.9–NR)	
Enzalutamide (N=31)	39% (12/31)	+	0% (0/12)	.004	2.1 mos	<.001	5.5 mos (3.9–NR)	.006
		–	53% (10/19)		6.1 mos		NR (NR–NR)	

Patient Treatment Status[2]	Before enzalutamide or abiraterone	Post enzalutamide	Post abiraterone	Post abiraterone & enzalutamide
AR-V7 Prevalence	12%	25%	51%	67%

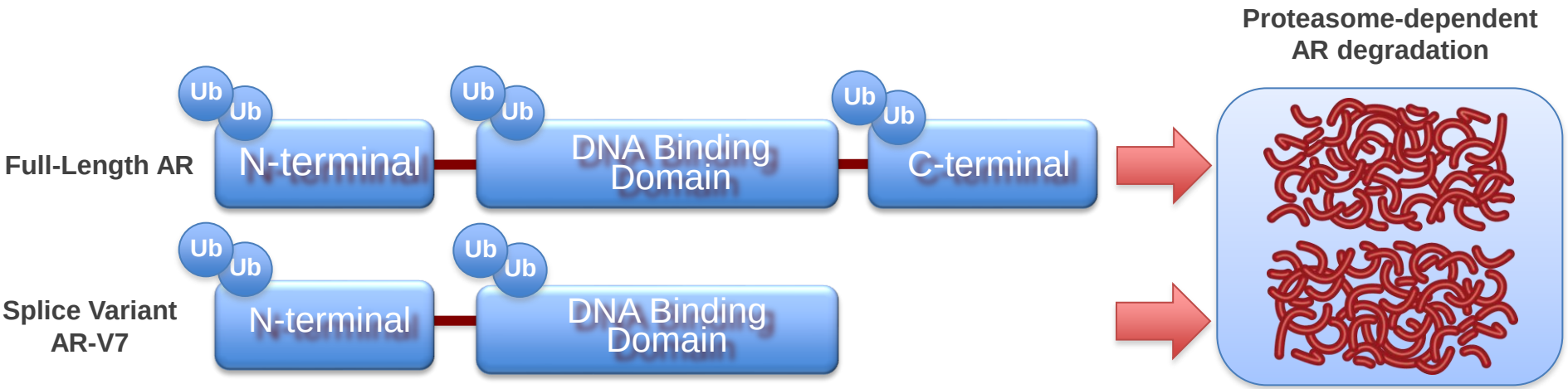
CRPC=castration-resistant prostate cancer; CTC=circulating tumor cell; M1=metastatic disease; NR=not reached; OS=overall survival; PSA=prostate specific antigen; rPFS=radiographic progression-free survival. 1. Antonarakis ES et al. NEJM. 201410.1056/NEJMoa1315815. 2.. Antonarakis ES et al. ASCO 2014

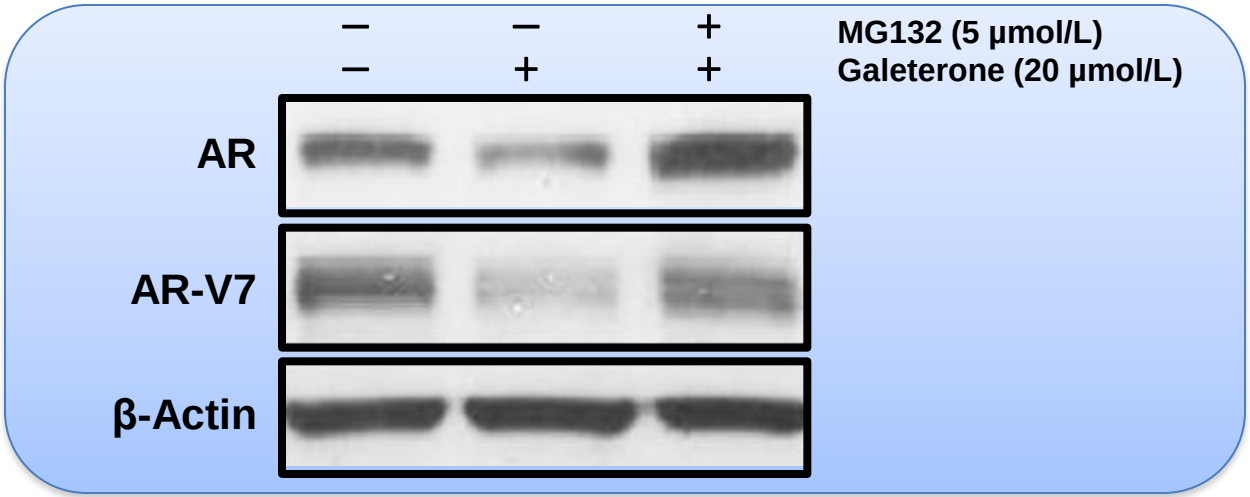
Galeterone: Selective, Multi-targeted, Small Molecule for Treatment of CRPC

	CYP17 Lyase Inhibitor	*AR Antagonist*	*AR Degrader*
	 *Inhibits androgen synthesis*	 *Blocks androgen binding*	 *Decreases AR levels*
Abiraterone	✓		
Enzalutamide		✓	
Galeterone	✓	✓	✓
	• *No mandatory steroids* • *Fasting not required* • *Preclinical activity in mutation T878A*	• *Not a $GABA_A$ antagonist* • *No seizures* • *Preclinical activity in mutation F876L*	• *Active in C-terminal loss AR splice variants*

In-licensed from the University of Maryland, Baltimore

Galeterone: Potentially Enhances AR Degradation Within the Proteasome





AR=androgen receptor; Ub=ubiquitination.

1. Lin H-K et al. *EMBO J*. 2002;21:4037-48. 2. Njar VC and AK Kweigyir-Afful. Unpublished data, used with permission.

Androgen Receptor Modulation Optimized for Response (ARMOR): Program Background

Trial Name	Objective	CRPC Population	Formulation	Results
ARMOR1	Dose-escalation, safety/efficacy	• TN, M0/M1 (N=49)	Capsule	At top dose: • 75% PSA30, 43% PSA50 • 60% tumor reduction (3/5 evaluable, 2 PRs) • Well tolerated
ARMOR2 Part 1	Dose confirmation, safety/efficacy	• TN, M0/M1 (n=25) • Abiraterone refractory (n=3)	SDD tablet[a]	• Tablet formulation eliminated food effect • 2,550 mg tablet confirmed as optimal dose • PSA efficacy at 2,550 mg (n=10) TN: 60% PSA50 and 80% PSA30 • Well tolerated
ARMOR2 Part 2	4 treatment groups explored at optimal dose of 2,550 mg/day	• TN, M0/M1 • Abiraterone refractory • Enzalutamide refractory	SDD tablet	• Study is ongoing

[a]SDD tablet was found to have similar exposure to highest dose of capsule formulation used in ARMOR1 without food effect (ie, similar exposure in fed or fasted conditions).

M0=non-metastatic disease; M1=metastatic disease; PR=partial response; PSA=prostate specific antigen; PK=pharmacokinetic; SDD=spray dry dispersion; TN=treatment naïve.

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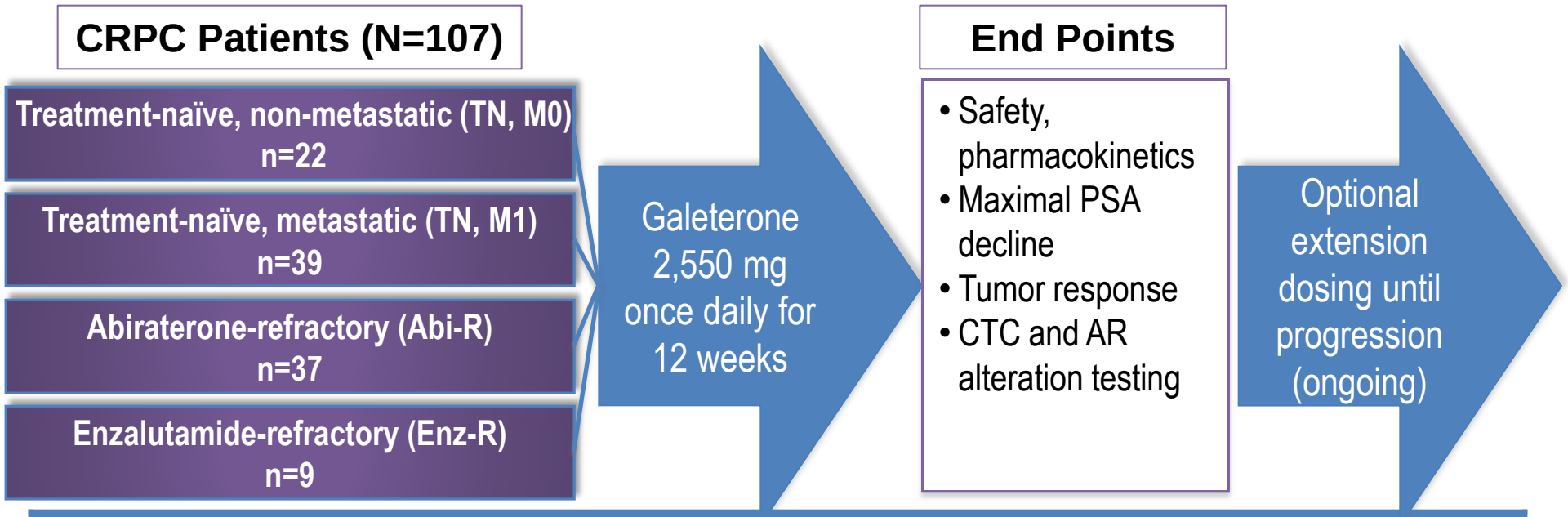
ARMOR2: Study Design



Selected Inclusion Criteria

- Pathologically-confirmed adenocarcinoma of the prostate, ongoing androgen blockade and serum testosterone <50 ng/dL
- Demonstration of progression by PCWG2 guidelines
- ECOG performance status ≤2
- Treatment-naïve: excluded prior treatment with CYP17 inhibitors or 2nd generation AR antagonists
- Abiraterone-refractory: failed abiraterone therapy after initial response; excluded prior treatment with other CYP17 inhibitors, 2nd generation AR antagonists, or chemotherapy
- Enzalutamide-refractory: failed enzalutamide therapy after initial response; excluded other prior treatment with CYP17 inhibitors or other 2nd generation AR antagonists

ARMOR2: Baseline Patient and Disease Characteristics

Patient and Tumor Characteristics (N=107)	
Age, median (range), y	71 (48–94)
Metastatic disease (M1) at screening, n (%)	82 (76.6)
ECOG Status, n (%) 0 1 2	 68 (63.6) 36 (33.6) 3 (2.8)
Prior therapies, n (%) Immunotherapy Radiation therapy Surgery Chemotherapy	 10 (9.3) 72 (67.3) 53 (49.5) 8 (7.5)
PSA, median (range), ng/dL	24.1(2.0–1114)
Gleason score at diagnosis, n (%) 6 7 8–10 Missing data	 8 (7.5) 38 (35.5) 52 (48.6) 9 (8.4)

Interim data cut (15Aug2014); data entry ongoing.

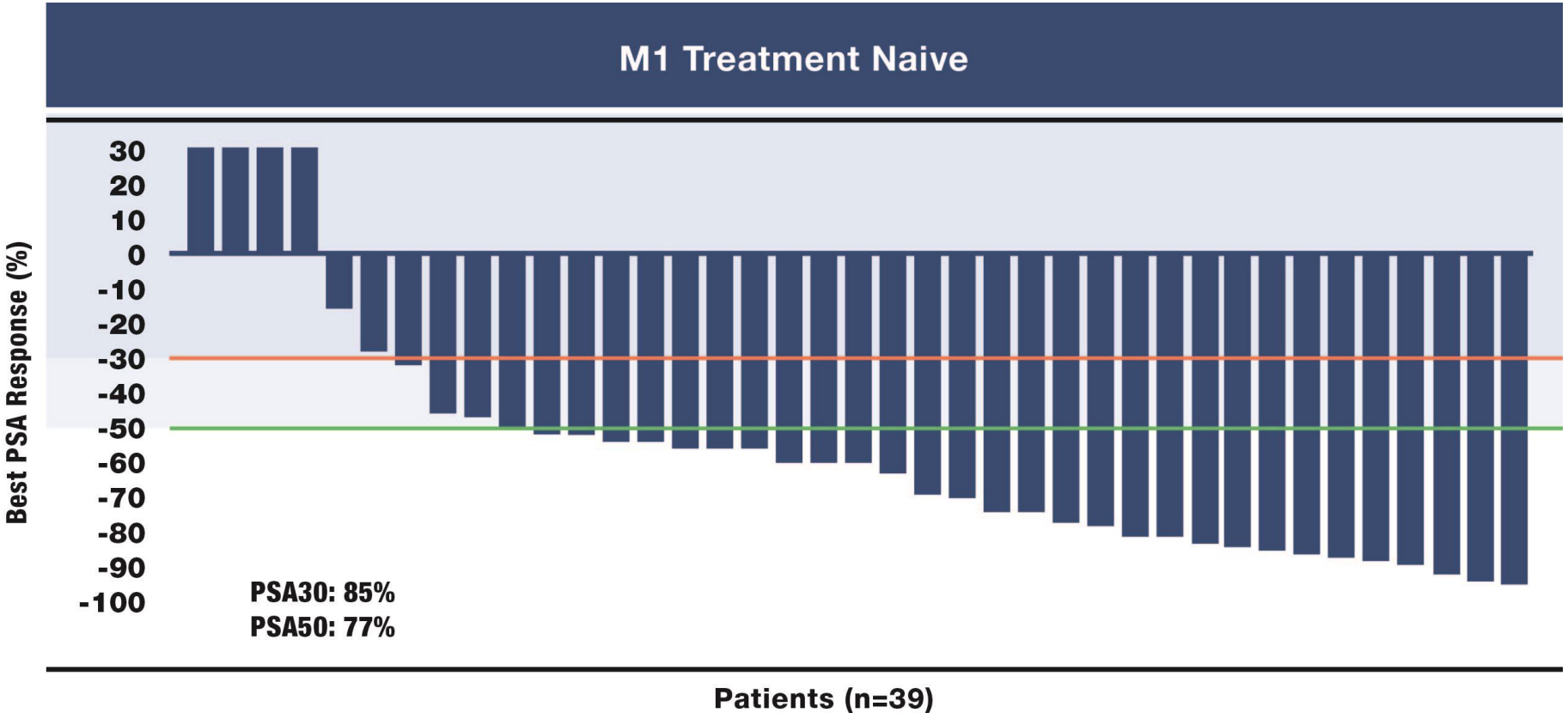
ARMOR2: Efficacy

Cohort	No.[a]	Any PSA Decline n (%)	Best Response by RECIST 1.1 (Soft Tissue/Visceral)[b] n (%)	Best Response by PCWG2 (Bone)[b] n (%)
M0, TN	21	21 (100)	No evidence of M1 at 12 weeks	No evidence of M1 at 12 weeks
M1, TN	39	35 (90)	PR 3/18 (17) SD 13/18 (72)	SD 27/36 (75)[c]
Abi-R	30	11 (37)[d]	SD 4/11 (36)	SD 13/28 (47)
Enz-R	9[e]	4 (44)	NA	SD 4/7 (57)

- Assessment of refractory patients underway
  - Demographics reflect poor prognostic factors (↑ Gleason, ↑ECOG, ↑baseline PSA)
  - CTC characteristic analysis for resistance mechanisms in progress (Epic Sciences)
  - Median number of months on prior therapy qualify as prolonged benefit (>6 months)
    - Abi-R: 10.9 months on abiraterone
    - Enz-R: 9.1 months on enzalutamide
- Findings of prolonged benefit support these patients were unlikely to be de-novo splice variant positive at the time of treatment

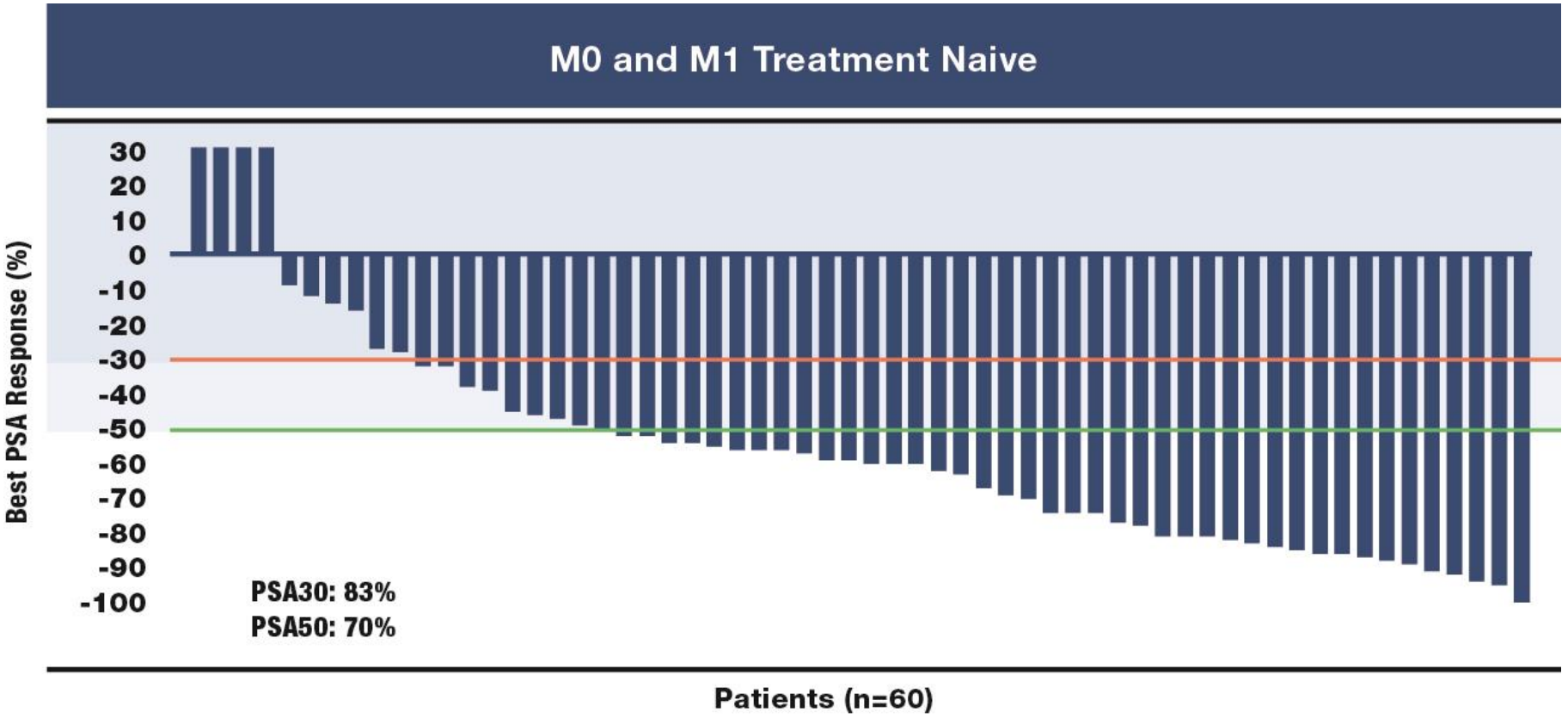
[a]Number of patients completing 12 weeks, reached PSA50, or terminated early. [b]Investigator assessed response (interim data) at 12 weeks in evaluable patients. [c]Includes 1 patient that was improved on bone scan. [d]PSA 30 for Abi-R is 3/30 or 10%, [e]One patient has not reached 12 weeks or early termination, Interim data cut (15Aug2014). PCWG2=Prostate Cancer Working Group 2, RECIST=Response Evaluation Criteria In Solid Tumors, PR=partial response, SD=stable disease.

ARMOR2: Efficacy
Maximal PSA Response Within 12 Weeks[a]



[a]39 evaluable patients of 39 enrolled included in graph. Evaluable defined as patients who (1) completed 12 weeks, (2) terminated prior to 12 weeks, or (3) achieved PSA50 prior to 12 weeks. Interim data cut (15Aug2014).

ARMOR2: Efficacy
Maximal PSA Response Within 12 Weeks[a]



[a]60 evaluable patients of 61 enrolled included in graph. Evaluable defined as patients who (1) completed 12 weeks, (2) terminated prior to 12 weeks, or (3) achieved PSA50 prior to 12 weeks. The 1 patient not included above was non-evaluable (off treatment before Week 2). Interim data cut (15Aug2014).

ARMOR2: Adverse Events

- Overall, ~90% of treatment emergent AEs were CTCAE Grade 1 or 2 in severity
- Most common treatment-emergent, related AEs were nausea, fatigue, pruritus, decreased appetite, diarrhea, hypokalemia[a], and vomiting

[a]Hypokalemia was more common in Enz-R and Abi-R compared with TN cohorts (TN=9.8%, Abi-R= 16.2%, Enz-R= 33%). Interim data cut (15Aug2014). AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events.

Treatment-Emergent Related AEs in ≥10% of Patients or Any CTCAE Grade 3/4 (N=107)		
	CTCAE All Grades, n (%)	CTCAE Grade 3/4, n (%)
Nausea	36 (33.6)	1 (<1)
Fatigue	35 (32.7)	3 (2.8)
Pruritus	28 (26.2)	4 (3.7)
Decreased appetite	22 (20.6)	0
Diarrhea	17 (15.9)	1 (<1)
Hypokalemia	15 (14.0)	3 (2.8)
Vomiting	13 (12.1)	0
ALT increased	9 (8.4)	5 (4.7)
AST increased	9 (8.4)	2 (1.9)
Rash	8 (7.5)	1 (<1)
Bilirubin elevated	7 (6.5)	1 (<1)
Alkaline phosphatase increased	5 (4.7)	1 (<1)
Hypertension	4 (3.7)	2 (1.9)
Creatinine phosphokinase increased	2 (1.9)	1 (<1)
Dyspnea	2 (1.9)	1 (<1)
Transaminases increased	2 (1.9)	1 (<1)
Anemia	1 (<1)	1 (<1)
Angioedema	1 (<1)	1 (<1)
Fluid retention	1 (<1)	1 (<1)
Hyperparathyroidism	1 (<1)	1 (<1)
Hypocalcemia	1 (<1)	1 (<1)
Hyponatremia	1 (<1)	1 (<1)
Malaise	1 (<1)	1 (<1)
Syncope	1 (<1)	1 (<1)

ARMOR2: CTC Exploratory Analysis

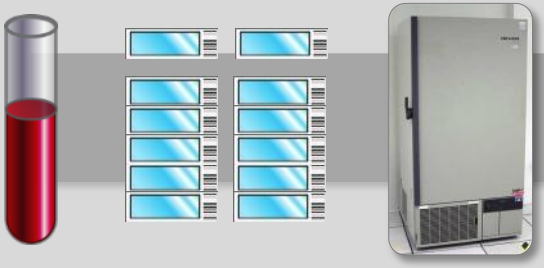
- Blood samples collected at baseline, Day 7, and Day 84 (Week 12) and sent to Epic Sciences for CTC analysis
- CTC enumeration determined for each sample
- In naïve patients with sufficient number of N-terminal AR+ CTCs C-terminal AR expression was evaluated to determine C-terminal loss; C-terminal loss accounts for splice variants affecting the C terminus (e.g. AR-V7)
- CTC evaluation of ABI/ENZA refractory patients is ongoing

CTC=circulating tumor cell.

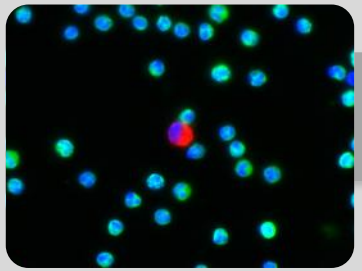
Epic Sciences CTC Identification & Characterization Process

Enrichment Free Approach

SLIDE PREPARATION

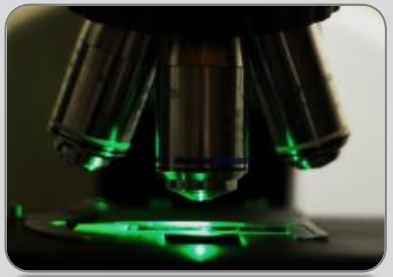


CELL STAINING

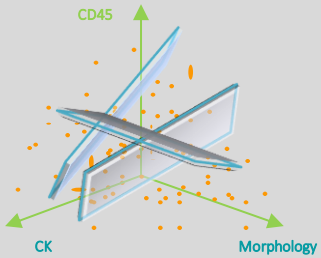


CK, CD45, DAPI, AR

SCANNING



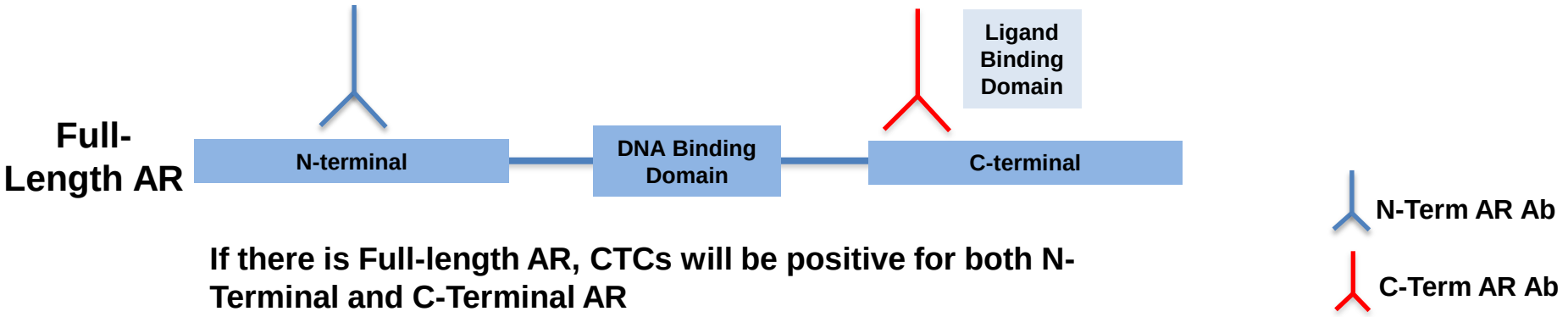
BIOMARKER ANALYSIS & CTC IDENTIFICATION



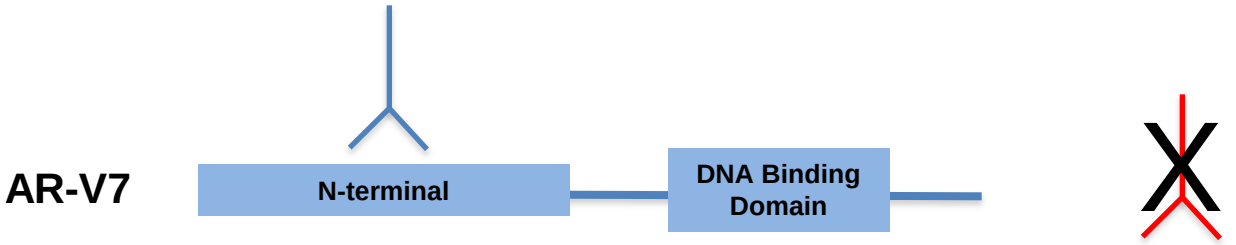
- Enumeration of CTCs
- Enumeration of AR+ CTCs (Both FL and C-Term Loss)

CTC=circulating tumor cell; FL=full length.

Antibody (Ab) Based Assays: C-Terminal Loss in AR Splice Variants



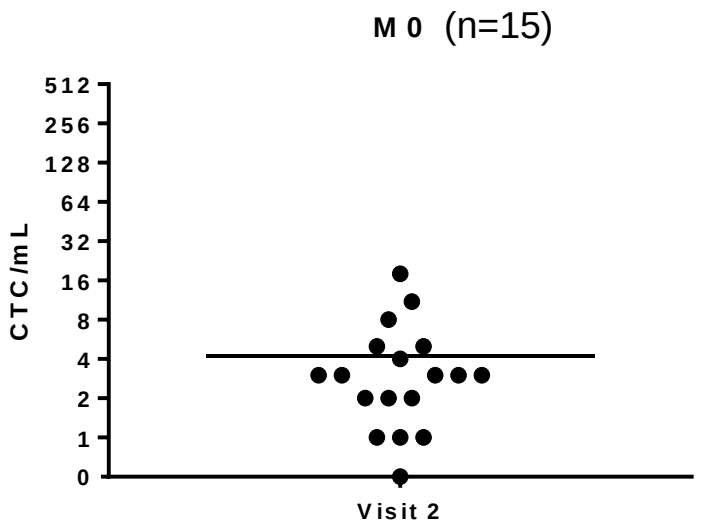
If there is Full-length AR, CTCs will be positive for both N-Terminal and C-Terminal AR

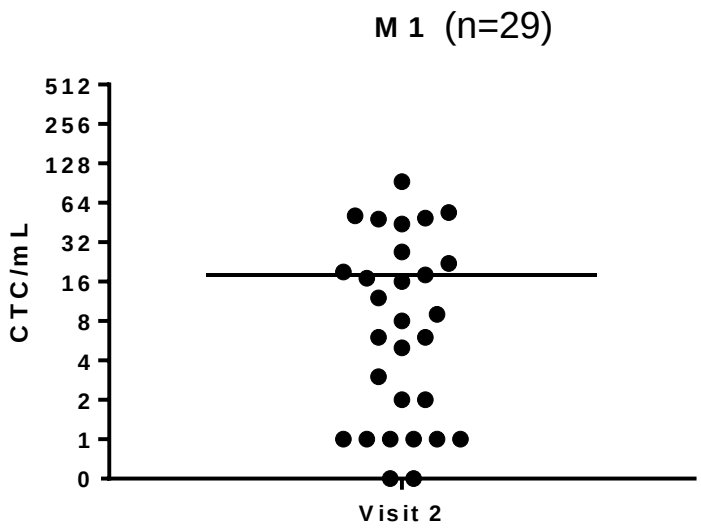


If there is AR-V7 or other variants, CTCs will be positive for N-Terminal AR but significantly reduced for C-Terminal AR

ARMOR2 Exploratory Analyses: CTC Results at Baseline

- 94% (44/47) samples had ≥1 CTC/mL
- Mean CTC count was higher in later-stage patients
- CTCs were higher (median= 30) in Abi-R and Enz-R cohorts compared with Abi/Enza naive cohort

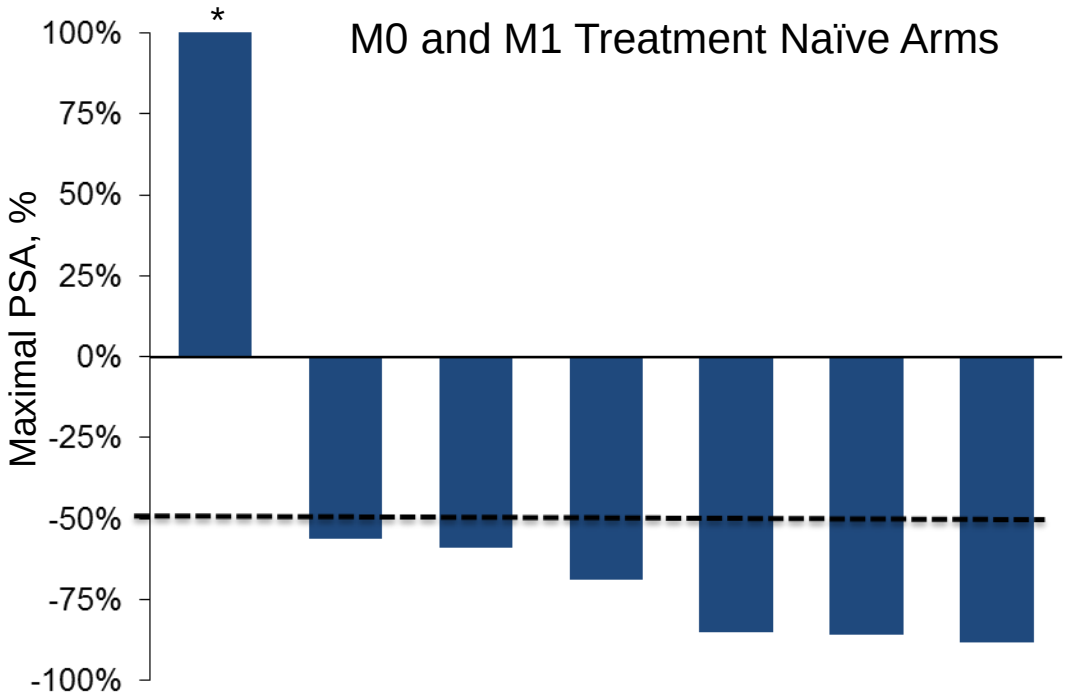




Interim data cut (15Aug2014)

ARMOR2: Galeterone Activity in Patients with AR C-terminal Loss

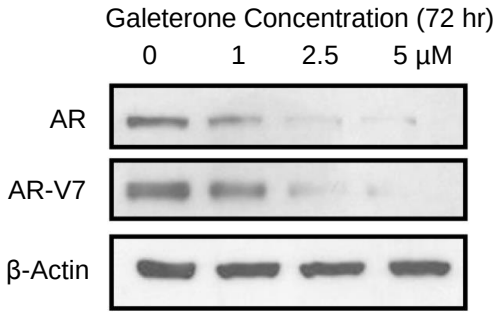
- 7 naïve patients showed C-terminal loss
- 6 of 7 with C-terminal loss had maximal >PSA50
- Of the 6 responders, all completed the primary study phase (12 weeks)
- 4 continued into optional extension phase
- Time on treatment for extension patients ranges from 155 to >274 days (ongoing)

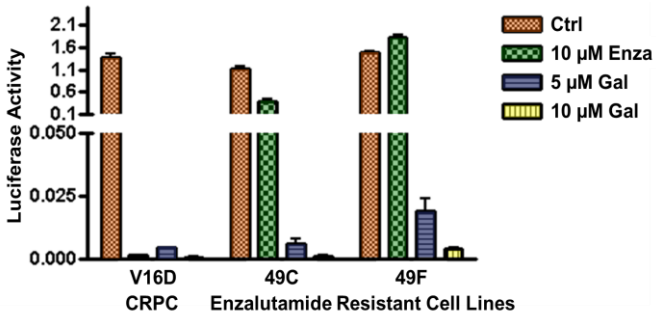


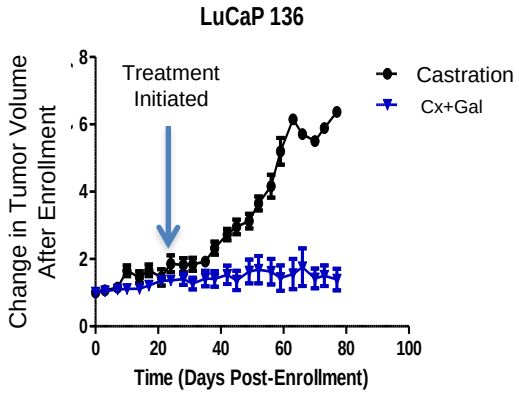
*The non-responder discontinued therapy due to an unrelated adverse event after ~6 weeks in the study and did not complete the primary study phase.
Interim data cut (15Aug2014)

Galeterone: Preclinical Data

University of Maryland[1]	*Vancouver Prostate Centre*[2]	*University of Washington*[3]
Galeterone down regulates both full-length and splice variant AR at low micromolar concentrations	Galeterone (but not enzalutamide) decreases androgen signaling in AR-V7 positive cells	Galeterone causes tumor growth inhibition in CRPC AR-V7 positive xenograft tumors







These preclinical data in cells expressing AR-V7 and additional studies support findings of clinical activity with galeterone in patients showing C-terminal loss

AR=androgen receptor; CRPC=castration-resistant prostate cancer.
1. Njar V. 2014 (Submitted). 2. Nakouzi NA et al. AACR NCI EORTC 2013. 3. Corey E et al. Unpublished data, used with permission.

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Conclusions

- Galeterone resulted in clinically meaningful PSA reductions and an acceptable safety profile in CRPC
  - Encouraging PSA response in abi/enza treatment-naïve patients with metastatic disease (TN M1): 85% PSA30, 77% PSA50
- Positive clinical data in patients with AR C-terminal loss
  - PSA50 response in 6 of 7 patients with AR C-terminal loss, suggests galeterone has activity in AR splice variants (e.g., AR-V7)
- Evidence of activity in CRPC harboring AR-Vs warrants further investigation of galeterone in a prospective, biomarker-based trial in CRPC patients with AR C-terminal loss
- ARMOR3 planning is underway