Abstract #5029

Galeterone in men with CRPC: results in four distinct patient populations from the ARMOR2 study

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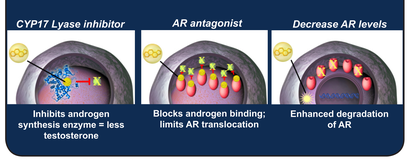
BACKGROUND

- Patients with advanced prostate cancer initially respond to androgen-deprivation therapy (ADT), but most develop progressive castration-resistant prostate cancer (CRPC) within 12–18 months,[1,2] and approximately 50% of prostate cancer patients have tumor recurrence after 5 years despite the use of ADT
- CRPC cells survive in an androgen-deprived environment via multiple compensatory pathways[3]
- Galeterone is a highly selective, multi-targeted, oral small molecule being developed for the treatment of CRPC, that disrupts the androgen receptor (AR) signaling pathway at multiple points (**Figure 1**):[3,4]
  - Selective inhibition of CYP17 lyase to prevent testosterone synthesis (mechanism of abiraterone)
  - Antagonism of androgen binding to AR (mechanism of enzalutamide)
  - Degradation of AR (unique mechanism)
- Despite advances in the treatment of metastatic CRPC (mCRPC), patients develop resistance and ultimately progress; an unmet medical need remains for therapies that may circumvent resistance, delay progression, and improve overall survival[5]
- Given the genetic heterogeneity of prostate cancer, molecular disease characterization may be helpful in the understanding of treatment resistance. It is also possible that predictive markers may be validated to guide rational treatment decisions[3]

Figure 1: Targets of galeterone



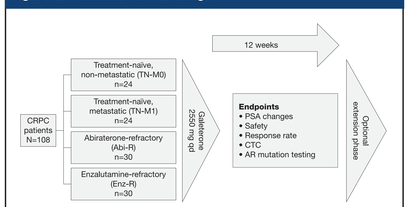
AR, androgen receptor; CYP, cytochrome P

- ARMOR2 is a two-part Phase II study being conducted in North America
  - Part 1 of the ARMOR2 trial was designed to confirm the dose of the spray dried dispersion (SDD) formulation; based on safety and PK and PSA response over 12 weeks in patients with CRPC, SDD galeterone 2550 mg once daily (qd) was selected[6–8]
  - Part 2 of ARMOR2 was designed to assess the safety and efficacy of SDD galeterone 2550 mg qd for 12 weeks in four distinct CRPC patient cohorts; the study included an optional extension phase

STUDY DESIGN

- Multiple treatment cohorts, open label for 12 weeks (**Figure 2**)
- The study included an optional extension

Figure 2: ARMOR2 Part 2 design*



* Protocol amendment will allow expanded assessment of galeterone activity, including AR mutation screening and the addition of Xofigo® combination and late-stage, post-chemotherapy patient cohorts

Table 1: ARMOR2 main inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Pathologically confirmed adenocarcinoma of the prostate • Ongoing androgen blockade with serum testosterone concentration <50 ng/dL • Demonstration of progression while on androgen blockade (two successive PSA increases at least 1 week apart, with the most recent PSA level >2 ng/mL) • Eastern Cooperative Oncology Group performance status ≤2	• Treatment-naïve: any prior treatment with CYP17 inhibitors or AR antagonists (e.g. abiraterone, TAK-700, ARN-509, ketoconazole, enzalutamide, galeterone) • Abiraterone-refractory (Abi-R): prior treatment with other CYP17 inhibitors (e.g. TAK-700, ketoconazole) or AR antagonists (e.g. enzalutamide, ARN-509), galeterone, or chemotherapy • Enzalutamide-refractory (Enz-R): prior treatment with CYP17 inhibitors (e.g. abiraterone, TAK-700, ketoconazole), other AR antagonists (e.g. ARN-509), or galeterone

ENDPOINTS

- Decreases in PSA
- Safety
- Response rate by modified Response Evaluation Criteria In Solid Tumors (RECIST) (v1.1) and Prostate Cancer Working Group 2 (PCWG2) criteria[9]
- CTC analysis
- AR mutation testing

RESULTS

Patient disposition and baseline characteristics

- The data presented here are interim (cut-off date of May 12, 2014) and include 87 CRPC patients treated with galeterone 2550 mg qd in 4 study cohorts (**Table 2**):
  - Non-metastatic treatment-naïve (TN-M0; n=17)
  - Metastatic treatment-naïve (TN-M1; n=39)
  - Abi-R (n=26)
  - Enz-R (n=5)

Table 2: Demographics and patient characteristics (all patients at 2550 mg qd)*

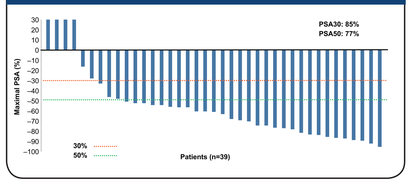
Patient Characteristics	TN-M0 (n=17)	TN-M1 (n=39)	Abi-R (n=26)†	Enz-R (n=5)†
Median age, years (range)	73.0 (54.0–86.0)	70.0 (52.0–89.0)	70.0 (48.0–89.0)	76.0 (55.0–79.0)
M Stage n (%)				
Non-Metastatic	17 (100)	0 (0)	1 (3.8)	0 (0)
Metastatic	0 (0)	38 (97.4)	24 (92.3)	5 (100)
Missing	0 (0)	1 (2.6)	1 (3.8)	0 (0)
Median PSA, ng/dL (range)	7.5 (2–63.7)	30.1 (3.4–634.1)	45.4 (4.5–1114.1)	71.5 (6.1–312.5)
Patients with metastatic disease*, n (%)				
Bone	0 (0)	22 (56.4)	10 (38.5)	3 (60.0)
Visceral	1 (5.9)	6 (15.4)	2 (7.7)	2 (40.0)
Soft Tissue	4 (23.5)	13 (33.3)	9 (34.6)	2 (40.0)
Other	0 (0)	5 (12.8)	0 (0)	0 (0)
ECOG status, n (%)				
ECOG 0	11 (64.7)	29 (74.4)	14 (53.8)	1 (20.0)
ECOG 1	6 (35.3)	8 (20.5)	11 (42.3)	3 (60.0)
ECOG 2	0 (0)	2 (5.1)	0 (0)	1 (20.0)
Missing	0 (0)	0 (0)	1 (3.8)	0 (0)
Gleason score				
≤7	11	18	9	3
8–10	6	17	15	2
Missing	0	4	2	0
Prior cancer therapies, n (%)				
Cancer surgery	7 (41.2)	16 (41.0)	13 (50.0)	3 (60.0)
Radiation therapy	12 (70.6)	22 (56.4)	20 (76.9)	3 (60.0)
Oncology treatment	17 (100)	32 (82.1)	21 (80.8)	5 (100)
Biologics	0 (0)	0 (0)	0 (0)	3 (60.0)
Chemotherapy	0 (0)	1 (3.1)	1 (4.8)	0 (0)
Hormone therapy	17 (100)	31 (96.9)	21 (100)	5 (100)
Immunotherapy	0 (0)	4 (12.5)	2 (9.5)	0 (0)
Other	0 (0)	3 (9.4)	4 (19.0)	2 (40.0)

*Demographics and safety data as of the May 12, 2014 interim data cutoff (clinical and laboratory databases); data entry ongoing. Because these are interim data, numbers may not add up to the total N.
†Abi-R and Enz-R patients exhibit severe disease status, characterized by high incidence of metastatic disease with higher median PSA at baseline, high percentage of patients with Gleason score ≥8, and high percentage of patients with ECOG PS ≥1.
ECOG PS, Eastern Cooperative Oncology Group performance status; PSA, prostate-specific antigen.

PSA response

- PSA response was assessed per PCWG2[9] (data cut-off May 12, 2014):
- PSA decreases of 30% and 50% in 39 treatment-naïve metastatic patients were reached in 85% and 77% of patients, respectively, after treatment with galeterone (**Figure 3**)

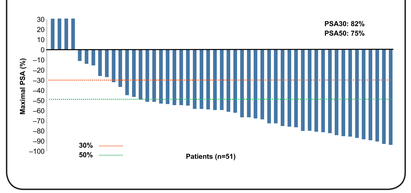
Figure 3: Maximal PSA response within 12 weeks in metastatic treatment-naïve patients (TN-M1) dosed with 2550 mg*



*All 39 enrolled included in graph.

- In 51 evaluable M0 and M1 treatment-naïve CRPC patients, PSA decreases of 30% and 50% were reached in 82% and 75% of patients, respectively, after treatment with galeterone (**Figure 4**)

Figure 4: Maximal PSA response within 12 weeks in treatment-naïve patients (TN-M0 and TN-M1) dosed with 2550 mg*



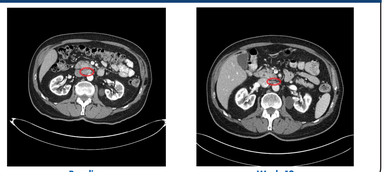
*51 evaluable patients of 56 enrolled included in graph. Evaluable is defined as patients who (i) completed 12 weeks, (ii) terminated prior to 12 weeks, or (iii) achieved PSA50 prior to 12 weeks. Of the 5 patients not included above, 3 have shown a maximal reduction of PSA30, 1 has shown a reduction less than PSA30, and 1 is non-evaluable.

- Abi-R is defined in the trial as PSA concentration increase ≥25% from nadir (sustained on two subsequent tests at least 1 week apart) or disease progression defined by modified RECIST (v1.1) and PCWG2[9] criteria in the Abi-R cohort: Abi-R patients exhibit severe disease status, characterized by high incidence of metastatic disease and high percentage of patients with higher median PSA at baseline, high percentage of patients with Gleason score ≥8, and high percentage of patients with ECOG PS ≥1
  - Median duration on prior abiraterone was 10.6 months (4.8, 22.8)
  - 27% (4/15) had any PSA decline, and 13% (2/15) have demonstrated a maximal PSA30
  - 35% (6/17) had stable (change <3) and 35% (6/17) had decreasing (≥3 count) circulating tumor cell (CTC) counts
- Data on Enz-R patients are included in the patient safety and disposition; however, PSA and tumor response data are too preliminary to report

Tumor response at Week 12

- Evaluable patients are defined as those with imaging data at baseline, 12 weeks, and follow-up scans as required per RECIST 1.1 and/or PCWG2. Response in soft tissue/viscera and bone is reported separately
  - TN-M0: Of the 2 patients with complete and evaluable RECIST data at Week 12, 1 patient demonstrated a partial response and 1 patient had stable disease. Of the 2 patients with complete and evaluable PCWG2 bone scan data, both showed stable disease at Week 12. Additional patients with evaluable disease at baseline had incomplete data at the time of data cut
  - TN-M1: Of the 23 patients with complete and evaluable RECIST data at Week 12, 2 patients demonstrated a partial response, 20 patients had stable disease and 1 patient demonstrated disease progression. Of the 28 patients with complete and evaluable PCWG2 bone scan data, 21 had stable disease and 7 had unconfirmed findings of flare or progression. Additional patients with evaluable disease at baseline had incomplete data at the time of data cut
  - Abi-R: Of the 8 patients with complete and evaluable RECIST data at Week 12, 5 patients had stable disease and 3 patients demonstrated disease progression. Of the 7 patients with complete and evaluable PCWG2 bone scan data, 4 had stable disease and 3 had unconfirmed findings of flare or progression. Additional patients with evaluable data at baseline had incomplete data at the time of data cut
- Of note, all radiographic interpretation was performed at the individual investigator sites. No centralized radiographic interpretation was reported

Figure 5: Pelvic CT scan in a treatment-naïve patient dosed at 2550 mg, with a PR per RECIST and a 94% reduction in PSA



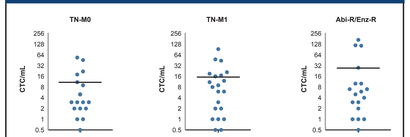
CTC evaluation

- Blood samples were collected at baseline, Week 1 (Day 7), and Week 12 (Day 84) and sent to Epic Sciences for enrichment-free CTC analysis. CTC enumeration was determined for each sample and N-terminal AR expression and localization was evaluated on each individual CTC from all time points. In addition, C-terminal AR expression was evaluated in relation to the N-terminal AR expression on a subset of patients to evaluate the presence of AR ligand binding domain (LBD) loss as a measure of functional inactivation through splice variants, rearrangements, mutations and/or deletions of the AR LBD

CTC enumeration

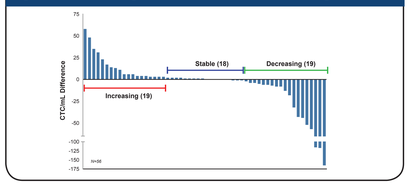
- CTC incidence at baseline was evaluated in each treatment cohort as shown in **Figure 6**. The mean CTC count was higher in later stage patients
  - 58 of the 63 (92%) baseline samples tested to date have at least 1 CTC/mL
  - Average CTC/mL for each cohort:
    - TN-M0: 10.9 CTC/mL (n=17)
    - TN-M1: 15.2 CTC/mL (n=21)
    - Abi-R/Enz-R: 25.6 CTC/mL (n=18)

Figure 6: CTC incidence at baseline (Visit 2)



- CTC/mL changes were observed within 1 week of treatment with galeterone as summarized in Figure 7 (baseline and Week 1)
  - 37 of 56 (66%) patients had stable (change <3 CTC/mL) or decreasing (≥3 CTC/mL) between baseline and Week 1
  - 12 of 18 (67%) evaluable Abi-R or Enz-R patients had stable (change <3 CTC/mL) or decreasing (≥3 CTC/mL) CTC between baseline and Week 1

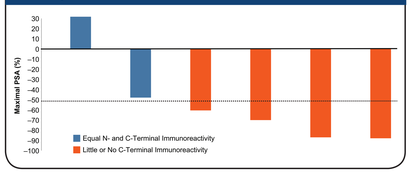
Figure 7: CTC changes observed within 1 week of galeterone



CTC characterization and AR C-terminal staining

- To identify patients who may have alterations to the LBD of AR, and identify patients with ligand-independent androgen signaling predicted to be resistant to other secondary hormonal therapies, analysis of CTC C-terminal AR loss in the presence of N-terminal AR positivity was evaluated on a subset of patients in the M0 and M1 treatment cohorts at 1 week, and is summarized in **Figure 8**
  - 4 of 4 patients with C-terminal loss had maximal PSA50, suggesting galeterone may have activity in patients with AR splice variant

Figure 8: All 4 treatment-naïve patients expressing little or no C-terminal receptor immunogenicity exhibit ≥50% maximal PSA response



Safety

- The most common adverse events were nausea, diarrhea, decreased appetite, fatigue, increased aminotransferase levels, and pruritus
- 75.9% of all patients treated with galeterone 2550 mg qd experienced at least one drug-related adverse event; in 74.2% of those patients, the maximum severity of the event was Grade 1 or 2 (**Table 3**)

Table 3: Number of patients with drug-related adverse events*

Event	All Grades n (%)*	Grade 3/4 n (%)*
Endocrine disorders		
Hyperparathyroidism	1 (1.5)	1 (1.5)
Gastrointestinal disorders		
Diarrhea	12 (18.2)	1 (1.5)
Constipation	8 (12.1)	0 (0)
Nausea	30 (45.5)	0 (0)
Vomiting	8 (12.1)	0 (0)
General and administration-site disorders		
Fatigue	23 (34.8)	2 (3.0)
Malaise	1 (1.5)	1 (1.5)
Investigations		
ALT elevation	6 (9.1)	3 (4.5)
AST elevation	7 (10.6)	1 (1.5)
Blood alkaline phosphatase elevation	4 (6.1)	1 (1.5)
Blood bilirubin elevation	4 (6.1)	1 (1.5)
Transaminases elevation	2 (3.0)	1 (1.5)
Metabolic and nutritional disorders		
Decreased appetite	15 (22.7)	0 (0)
Hypocalcemia	1 (1.5)	1 (1.5)
Hypokalemia	8 (12.1)	1 (1.5)
Hyponatremia	1 (1.5)	1 (1.5)
Nervous system disorders		
Syncope	1 (1.5)	1 (1.5)
Skin and subcutaneous tissue disorders		
Angioedema	1 (1.5)	1 (1.5)
Pruritus	21 (31.8)	4 (6.1)
Rash	7 (10.6)	1 (1.5)
Vascular disorders		
Hypertension	4 (6.1)	1 (1.5)

*66 of 87 patients dosed with 2550 mg are included in the May 12, 2014 data cut, and exhibited at least one drug-related adverse event. Percentages were calculated based on the reported events in these 66 patients. Adverse events ≥10% of the 66 patients or at least 1 Grade 3/4 are reported in this table.
ALT, alanine aminotransferase; AST, aspartate aminotransferase

- Unexpected serious adverse events considered possibly related to galeterone by the investigators were reported in 3 patients, as follows:
  - Syncope (Grade 3): the patient discontinued Galeterone 4 days prior to the event and had a significant history of nausea, diabetes and hypertension; the patient was receiving concomitant prochlorperazine (Compazine®) and insulin (Lantus®)
  - Hypocalcemia (Grade 4) and hyperparathyroidism (Grade 3): the patient had a significant history of hyperparathyroidism and calcium malabsorption due to bone lesions from prostate cancer. The patient was concomitantly on denosumab (Xgeva®) and calcium supplement
  - Angioedema (Grade 3): African-American patient had a history of hypertension. Galeterone was started 12 days prior to the event. The patient was concomitantly treated with the ACE inhibitor lisinopril, which may have caused the event

CONCLUSIONS

- **Galeterone is a small molecule for the treatment of prostate cancer, which disrupts the AR signaling pathway via multiple highly selective mechanisms of action**
- **Galeterone, at the recommended Phase II dose of 2550 mg/day, was safe and well tolerated in 87 patients with CRPC**
- **PSA response continues to be robust, including in the treatment-naïve metastatic cohort, with 85% of patients achieving PSA30 and 77% achieving PSA50**
- **Characterization of the Abi-R cohort is ongoing but early data suggest that galeterone is well tolerated and may be active in ARMOR2**
- **Preclinically, galeterone has been shown to have activity against multiple AR mutations, including AR-V7, AR-T878A, and AR-F876L**
- **CTC data with the reduction in C-terminal immunoreactivity are intriguing; galeterone showed significant PSA response in 4 of 4 patients**
- **Protocol amendment will allow expanded assessment of galeterone activity, including AR mutation screening and the addition of Xofigo® combination and in late-stage, post-chemotherapy patient cohorts**

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