

# Bipolar Androgen Therapy (BAT) plus Olaparib in Men with Metastatic Castration-resistant Prostate Cancer (mCRPC)

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#### Background

BAT leads to a rapid fluctuation in testosterone (T) between nearcastrate and supraphysiologic levels and has shown promise in mCRPC. Its clinical effects may be mediated through induction of DNA damage, and preclinical studies suggest synergy in combination with the PARP inhibitor olaparib.

## **Materials and Methods**

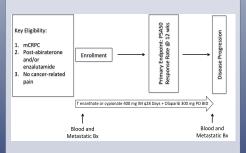
- This is a single center Phase 2 trial testing olaparib (300 mg PO BID) plus BAT.
- BAT entails intramuscular T cypionate/enanthate 400 mg every 28 days while continuing androgen deprivation to suppress endogenous T.
- Subjects were required to have no cancer-related pain and to have previously received abiraterone (abi) and/or enzalutamide (enza).
- The primary objective was to assess the PSA50 response rate (proportion with PSA decline ≥50%) following ≥12 weeks of therapy.
- The primary analysis was based on the entire study cohort; however, we also assessed outcomes stratified by DNA damage repair gene

  (DDP) mutational status.
- 50% of the study cohort were required to have at least one DDR gene alteration.

# **Objectives**

- Primary Objective: Determine the PSA 50 response rate (i.e. ≥50% decline in PSA from baseline)
- Key Secondary Objectives:
- Determine the radiographic response per RECIST 1.1 criteria
   Determine the radiographic progression free survival (PFS) using RECIST 1.1 criteria for soft tissue metastases and Prostate Cancer Working Group 3 (PCWG3) criteria for bone metastases
- Assess the incidence and severity of adverse events according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.
- Key Exploratory Objective: Evaluate differences in response and PFS in patients with/without mutations in genes involved in homologous recombination.

#### **Study Schematic**



## **Demographics**

- Thirty-six patients enrolled and 6 discontinued prior to response assessment, leaving 30 response evaluable patients.
- Patients discontinued early for progression (n=2), nausea (n=2), stroke (n=1) and myocardial infarction (MI) (n=1).

Table 1: Demographics. Safety cohort includes all patients that received treatment per protocol. The efficacy cohort includes those treated ≥12 weeks and who were evaluable for the primary endpoint.

Characteristic	Safety Cohort (N=36)	Efficacy Cohort (N=30)	
Median Age, Years (Range)	70.1 (51.8 - 87.8)	70.8 (51.8 - 87.8)	
Median PSA, ng/ml (Range)	25.6 (2.2 - 1409.7)	22.3 (2.2 - 435.9)	
Race, N (%)			
White	25 (69.4%)	21 (70.0%)	
Unknown	8 (22.2%)	6 (20.0%)	
Black	1 (2.8%)	1 (3.3%)	
Hawaiian or Pacific Islander	1 (2.8%)	1 (3.3%)	
Prior Treatment, N (%)			
Docetaxel	9 (25.0%)	7 (23.3%)	
Abiraterone	14 (38.9%)	12 (40.0%)	
Enzalutamide	7 (19.4%)	4 (13.3%)	
Abiraterone and Enzalutamide	11 (30.6%)	10 (33.3%)	
Radium-223	12 (33.3%)	8 (26.7%)	
Sipuleucel-t	13 (36.1%)	11 (36.7%)	

#### **Primary Analysis**

- PSA50 Response: 14 of 30 (47%) patients achieved a PSA50 response
- PSA50 response by DDR Status: 7/15 (47%) pts with and 7/15 (47%) pts without a DDR mutation achieved a PSA50 response

Figure 1: Best PSA Response. Orange bars represent patients with a mutation in a DNA damage response gene



## Secondary Analyses

- 13 patients were RECIST evaluable
- Objective responses were seen in 8 subjects (7 partial responses; 1 complete response).
- No difference in radiographic response were seen in patients with vs. without mutations in DDR genes.

**Figure 2:** Best Radiographic Response. Orange bars represent patients with a mutation in a DNA damage response gene

Note: one patient demonstrated a partial response by RECIST v1.1 criteria, while also demonstrating progressive bone metastases per PCWG3 criteria.

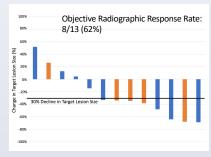


Figure 3: Radiographic Progression Free Survival

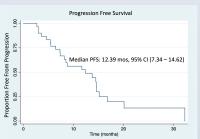
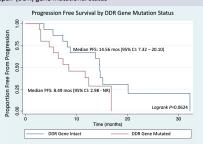


Figure 4: Radiographic Progression Free Survival by DNA damage repair (DDR) gene mutational status



#### **Secondary Analyses**

**Figure 5:** Distribution of mutations in DNA damage repair (DDR) genes. PSA response data for each individual patient (N=15) with a DDR gene alteration is also provided.

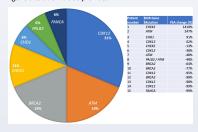


Table 2: Treatment related adverse events (AE). This includes all AEs felt to be at least possibly related to either study drug.

\*Grade 5 event

Anemia 7,19.4%) 1.12.8% 0.0% Constipation 7,19.4%) 0.0% Constipation 7,19.4%) 0.0% 0.0% 0.0% 0.0% 0.0% 0.0% 0.0% 0.	Adverse Event (AE)	All Grades, N (%)	Grade ≥3, N (%)
Breast tenderness         1 (2.8%)         0 (0%)           Constipation         7 (19.4%)         0 (0%)           Creatinine elevation         3 (8.3%)         0 (0%)           Decreased appetite         7 (19.4%)         (0%)           Diarriea         4 (11.13%)         1 (2.8%)           DVT         1 (2.8%)         0 (0%)           Dyspeusia         3 (8.3%)         0 (0%)           Dyspepsia         1 (2.8%)         0 (0%)           Patigue         20 (55.6%)         1 (2.8%)         0 (0%)           Headache         1 (2.8%)         0 (0%)         0 (0%)           Myclaridal Infarction         1 (2.8%)         0 (0%)         0 (0%)           Mycardial Infarction         1 (2.8%)         0 (0%)         0 (0%)           Nocturia         3 (8.3%)         0 (0%)         0 (0%)           Noturia         3 (8.3%)         0 (0%)         0 (0%)           Peripheral edema         1 (2.8%)         1 (2.8%)         1 (2.8%)           Peripheral edema         1 (2.8%)         0 (0%)         1 (2.8%)         0 (0%)           Rash         2 (5.6%)         0 (0%)         1 (2.8%)         1 (2.8%)         1 (2.8%)         1 (2.8%)         1 (2.8%)	Abdominal discomfort	2 (5.6%)	0 (0%)
Constipation         7 (19.4%)         0 (9%)           Creatinine elevation         3 (8.3%)         0 (9%)           Decreased appetite         7 (19.4%)         (9%)           Diarrhea         4 (11.1%)         1 (2.8%)           DVT         1 (2.8%)         0 (9%)           Dysgeusia         3 (8.3%)         0 (9%)           Pyspepsia         1 (2.8%)         0 (9%)           Fatigue         20 (55.6%)         1 (2.8%)           Insomnia         1 (2.8%)         0 (9%)           Insomnia         1 (2.8%)         0 (9%)           Myalgia         2 (5.6%)         0 (9%)           Myalgia         2 (5.6%)         0 (9%)           Myalgia         2 (5.6%)         0 (9%)           Nausea         18 (50.0%)         0 (9%)           Nocturia         3 (8.3%)         0 (9%)           Pain         5 (13.9%)         0 (9%)           Peripheral edema         1 (2.8%)         1 (2.8%)           Peripheral edema         1 (2.8%)         0 (9%)           Rash         2 (5.6%)         0 (9%)           Stroke         1 (2.8%)         1 (2.8%)           Nombout         2 (5.6%)         0 (9%)	Anemia	7 (19.4%)	1 (2.8%)
Creatinine elevation         3 (8.3%)         0 (9%)           Decreased appetite         7 (19.4%)         (9%)           Diarrhea         4 (11.1%)         1 (2.8%)         0 (9%)           DVT         1 (2.8%)         0 (9%)           Dyspepsia         3 (8.3%)         0 (9%)           Dyspepsia         1 (2.8%)         0 (9%)           Fatigue         20 (55.6%)         1 (2.8%)         0 (9%)           Headache         1 (2.8%)         0 (9%)           Headache         1 (2.8%)         0 (9%)           Mykapia         2 (5.6%)         0 (9%)           Mycardial Infarction         1 (2.8%)         0 (9%)           Nocturia         3 (8.3%)         0 (9%)           Nocturia         3 (8.3%)         0 (9%)           Pein         5 (3.39%)         0 (9%)           PE         1 (2.8%)         0 (9%)           PE ripriaral edema         1 (2.8%)         0 (9%)           Per pripheral edema         1 (2.8%)         0 (9%)           Rash         2 (5.6%)         0 (9%)           Stroke         1 (2.8%)         1 (2.8%)           Thrombocytopenia         2 (5.6%)         0 (9%)           Vomiting <t< td=""><td>Breast tenderness</td><td>1 (2.8%)</td><td>0 (0%)</td></t<>	Breast tenderness	1 (2.8%)	0 (0%)
Decreased appetite         7 (9.4%)         (0%)           Diarrhea         4 (11.1%)         1 (2.8%)         0 (0%)           DVT         1 (2.8%)         0 (0%)         0 (0%)           Dysgeusia         3 (8.3%)         0 (0%)           Dysgeusia         1 (2.8%)         0 (0%)           Patigue         20 (55.6%)         1 (2.8%)           Headache         1 (2.2%)         0 (0%)           Insomnia         1 (2.8%)         0 (0%)           Myalgia         2 (5.6%)         0 (0%)           Myalgia         2 (5.6%)         0 (0%)           Myocardial Infarction         1 (2.8%)         1 (2.8%)           Noucturia         3 (8.3%)         0 (0%)           Pain         5 (13.9%)         0 (0%)           Peripheral edema         1 (2.8%)         1 (2.8%)           Peripheral edema         1 (2.8%)         0 (0%)           Peripheral edema         1 (2.8%)         0 (0%)           Stroke         1 (2.8%)         0 (0%)           Vombing         5 (13.9%)         0 (0%)           Vomiting         5 (13.9%)         0 (0%)	Constipation	7 (19.4%)	0 (0%)
Dlarrhea         4 (11.1%)         1 (2.8%)           DVT         1 (2.8%)         0 (0%)           Dysgeusia         3 (8.3%)         0 (0%)           Dyspepsia         1 (2.8%)         0 (0%)           Dyspepsia         1 (2.8%)         1 (2.8%)           Headache         1 (2.8%)         0 (0%)           Insornia         1 (2.8%)         0 (0%)           Uightheadednes/Dizziness         2 (5.6%)         0 (0%)           Myolagia         2 (5.6%)         0 (0%)           Myolagia         1 (2.8%)         1 (2.8%)           Nocturia         3 (8.3%)         0 (0%)           Nocturia         3 (8.3%)         0 (0%)           Pein         5 (13.9%)         0 (0%)           Peripheral edema         1 (2.8%)         1 (2.8%)           Peripheral edema         1 (2.8%)         0 (0%)           Rash         2 (5.6%)         0 (0%)           Stroke         1 (2.8%)         1 (2.8%)           Thrombocytopenia         2 (5.6%)         0 (0%)           Vomiting         5 (13.9%)         0 (0%)	Creatinine elevation	3 (8.3%)	0 (0%)
DVT 1 (2.8%) 0 (9%) Dysgeusia 3 (8.3%) 0 (9%) Dysgeusia 3 (8.3%) 0 (9%) Dysgeusia 1 (2.8%) 0 (9%) Fatigue 20 (55.6%) 12.28%) Headache 1 (2.8%) 0 (9%) Insormia 1 (2.8%) 0 (9%) Insormia 1 (2.8%) 0 (9%) Myalgia 2 (5.6%) 0 (9%) Myalgia 2 (5.6%) 0 (9%) Myalgia 1 (5.6%) 1 (2.8%) 1 (2.8%) Nocturia 1 (2.8%) 1 (2.8%) Pain 5 (3.39%) 0 (9%) Peripheral edema 1 (2.8%) 1 (2.8%) Peripheral edema 1 (2.8%) 1 (2.8%) Peripheral edema 1 (2.8%) 0 (9%) Rash 2 (5.6%) 0 (9%) Rash 2 (5.6%) 0 (9%) Stroke 1 (2.8%) 1 (2.8%) Thrombocytopenia 2 (5.6%) 0 (9%) Thrombocytopenia 2 (5.6%) 0 (9%) Vomiting 5 (13.9%) 0 (9%)	Decreased appetite	7 (19.4%)	(0%)
Dysgeusia         3 (8.3%)         0 (0%)           Dyspepsia         1 (2.8%)         0 (0%)           Fatigue         20 (55.6%)         1 (2.8%)           Headache         1 (2.8%)         0 (0%)           Lightheadedness/Dizziness         2 (5.6%)         0 (0%)           Myolagia         2 (5.6%)         0 (0%)           Myocardial Infarction         1 (2.8%)         1 (2.8%)           Nocturia         3 (8.3%)         0 (0%)           Nocturia         3 (8.3%)         0 (0%)           Pain         5 (13.9%)         0 (0%)           PE         1 (2.8%)         1 (2.8%)           Pruritus         1 (2.8%)         0 (0%)           Pruritus         1 (2.8%)         0 (0%)           Rash         2 (5.6%)         0 (0%)           Strobe         1 (2.8%)         1 (2.8%)           Thrombocytopenia         2 (5.6%)         0 (0%)           Vomiting         5 (13.9%)         0 (0%)	Diarrhea	4 (11.1%)	1 (2.8%)
Dysopoja         1 (2.8%)         0 (9%)           Fatigue         20 (55.6%)         1 (2.8%)         0 (9%)           Headache         1 (2.8%)         0 (9%)         1 (2.8%)         0 (9%)           Lightheadedness/Dizziness         2 (5.6%)         0 (9%)         1 (2.8%)	DVT	1 (2.8%)	0 (0%)
Fatigue         20 (55.56%)         1 (2.8%)         0 (0%)           Headache         1 (2.8%)         0 (0%)           Insomnia         1 (2.8%)         0 (0%)           Lightheadedness/Dizziness         2 (5.6%)         0 (0%)           Myolagia         2 (5.6%)         0 (0%)           Myoardial Infarction         1 (2.8%)         0 (0%)           Nocturia         3 (8.3%)         0 (0%)           Nocturia         5 (3.3%)         0 (0%)           PE         1 (2.8%)         1 (2.8%)           Peripheral edema         1 (2.8%)         0 (0%)           Pruritus         1 (2.8%)         0 (0%)           Rash         2 (5.6%)         0 (0%)           Stroke         1 (2.8%)         1 (2.8%)           Thrombocytopenia         2 (5.6%)         0 (0%)           Vomiting         5 (13.9%)         0 (0%)	Dysgeusia	3 (8.3%)	0 (0%)
Headache	Dyspepsia	1 (2.8%)	0 (0%)
Insomnia	Fatigue	20 (55.6%)	1 (2.8%)
Lightheadedness/Dizziness         2 (5.6%)         0 (0%)           Myolagia         2 (5.6%)         0 (0%)           Myocardial Infarction         1 (2.8%)         1 (2.8%)           Nausea         18 (50.0%)         0 (0%)           Nocturia         3 (8.3%)         0 (0%)           Pain         5 (13.9%)         1 (2.8%)           Peripheral edema         1 (2.8%)         1 (2.8%)           Peripheral edema         1 (2.8%)         0 (0%)           Rash         2 (5.6%)         0 (0%)           Stroke         1 (2.8%)         1 (2.8%)         1 (2.8%)           Thrombocytopenia         2 (5.6%)         0 (0%)           Vomiting         5 (13.9%)         0 (0%)	Headache	1 (2.8%)	0 (0%)
Myalgia         2 (5.6%)         0 (0%)           Myocardial Infarction         1 (2.8%)         1 (2.8%)           Nususea         18 (500%)         0 (0%)           Nocturia         3 (8.3%)         0 (0%)           Pain         5 (13.3%)         0 (0%)           PE         1 (2.8%)         1 (2.8%)           Peripheral edema         1 (2.8%)         0 (0%)           Prurtus         1 (2.8%)         0 (0%)           Stroke         1 (2.8%)         1 (2.8%)           Thrombocytopenia         2 (5.6%)         0 (0%)           Vomiting         5 (13.9%)         0 (0%)	Insomnia	1 (2.8%)	0 (0%)
Myocardial Infarction         1 (2.8%)         1 (2.8%)           Nausce         18 (50.0%)         0 (0%)           Nocturia         3 (8.3%)         0 (0%)           Perin         5 (13.9%)         0 (0%)           PE         1 (2.8%)         1 (2.8%)           Peripheral edema         1 (2.8%)         0 (0%)           Rash         2 (5.6%)         0 (0%)           Rash         2 (5.6%)         1 (2.8%)         1 (2.8%)           Thrombocytopenia         2 (5.6%)         0 (0%)           Vomiting         5 (13.9%)         0 (0%)	Lightheadedness/Dizziness	2 (5.6%)	0 (0%)
Nausea         18 (50.0%)         0 (0%)           Nocturia         3 (8.3%)         0 (0%)           Pain         5 (13.9%)         0 (0%)           PE         1 (2.8%)         0 (0%)           Peripheral edema         1 (2.8%)         0 (0%)           Pruffus         1 (2.8%)         0 (0%)           Rash         2 (5.6%)         0 (0%)           Stroke         1 (2.8%)         1 (2.8%)           Thrombocytopenia         2 (5.6%)         0 (0%)           Vomiting         5 (13.9%)         0 (0%)	Myalgia	2 (5.6%)	0 (0%)
Nocturia         3 (8.3%)         0 (0%)           Per portina         5 (13.9%)         0 (0%)           PE         1 (2.8%)         1 (2.8%)           Peripheral edema         1 (2.8%)         0 (0%)           Peripheral edema         1 (2.8%)         0 (0%)           Rash         2 (5.6%)         0 (0%)           Stroke         1 (2.8%)         1 (2.8%)         1 (2.8%)           Thrombocytopenia         2 (5.6%)         0 (0%)           Vomiting         5 (13.9%)         0 (0%)	Myocardial Infarction	1 (2.8%)	1 (2.8%)*
Pain         5(13.9%)         0 (0%)           PE         1 (2.8%)         1 (2.8%)           Peripheral edema         1 (2.8%)         0 (0%)           Pruritus         1 (2.8%)         0 (0%)           Rash         2 (5.6%)         0 (0%)           Stroke         1 (2.8%)         1 (2.8%)           Thrombocytopenia         2 (5.6%)         0 (0%)           Vomiting         5 (13.9%)         0 (0%)	Nausea	18 (50.0%)	0 (0%)
PE 1 (2.8%) 1 (2.8%) 2 (2.8%) 1 (2.8%) 9 (2.8%) 9 (2.8%) 9 (2.8%) 9 (2.8%) 9 (2.8%) 9 (2.8%) 9 (2.8%) 1 (2.8%) 1 (2.8%) 1 (2.8%) 1 (2.8%) 1 (2.8%) 1 (2.8%) 1 (2.8%) 1 (2.8%) 1 (2.8%) 9 (2.8%)	Nocturia	3 (8.3%)	0 (0%)
Peripheral edema         1 (2.8%)         0 (0%)           Pruritus         1 (2.8%)         0 (0%)           Pruritus         2 (5.6%)         0 (0%)           Stoke         1 (2.8%)         1 (2.8%)           Stroke         1 (2.8%)         1 (2.8%)           Thrombocytopenia         2 (5.5,6%)         0 (0%)           Vomiting         5 (3.9%)         0 (0%)	Pain	5 (13.9%)	0 (0%)
Pruritus         1 (2.8%)         0 (3%)           Rash         2 (5.6%)         0 (3%)           Stroke         1 (2.8%)         1 (2.8%)           Thrombocytopenia         2 (5.6%)         0 (3%)           Vomiting         5 (13.9%)         0 (3%)	PE	1 (2.8%)	1 (2.8%)
Rash         2 (5.6%)         0 (0%)           Stroke         1 (2.8%)         1 (2.8%)           Thrombocytopenia         2 (5.6%)         0 (0%)           Vomiting         5 (13.9%)         0 (0%)	Peripheral edema	1 (2.8%)	0 (0%)
Stroke         1 (2.8%)         1 (2.8%)           Thrombocytopenia         2 (5.6%)         0 (0%)           Vomiting         5 (13.9%)         0 (0%)	Pruritus	1 (2.8%)	0 (0%)
Thrombocytopenia 2 (5.6%) 0 (0%) Vomiting 5 (13.9%) 0 (0%)	Rash	2 (5.6%)	0 (0%)
Vomiting 5 (13.9%) 0 (0%)	Stroke	1 (2.8%)	1 (2.8%)
	Thrombocytopenia	2 (5.6%)	0 (0%)
Weight loss 3 (8.3%) 0 (0%)	Vomiting	5 (13.9%)	0 (0%)
	Weight loss	3 (8.3%)	0 (0%)

## Conclusions

BAT plus olaparib is associated with high response rates and long PFS. Clinical benefit was observed regardless of DDR gene mutational status. Treatment was well tolerated, although caution should be taken in using this in men with a history of CV disease. Larger studies evaluating this regimen are warranted.

### <u>Acknowledgements</u>

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