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

Michael T. Schweizer[1,2], Roman[3] Gulati, Todd Yezefski[1,2], Heather H. Cheng[1,2], Colin Sievers[1], Ruth Dumpit[4], Katerina Alexander[1], Nerina McDonald[1], Michael Lai[1], Katie Nega[1], Jeannette Hammond[1], Petros Grivas[1,2], Andrew Hsieh[1,4], Bruce Montgomery[1,2,5], Peter S. Nelson[1,4], Evan Y. Yu[1,2]

1. Department of Medicine, Division of Oncology, University of Washington, Seattle, WA; 2. Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA; 3. Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA; 4. Division of Human Biology, Fred Hutchinson Cancer Research Center, Seattle, WA; 5. VA Puget Sound Health Care System and PCF POPCAP network, Seattle, WA

## Background

BAT leads to a rapid fluctuation in testosterone (T) between near-castrate 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.

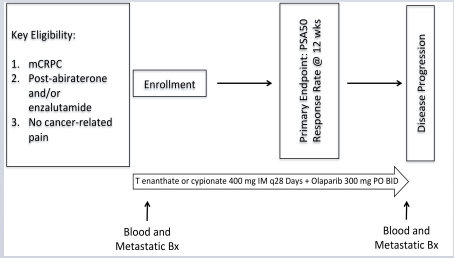
## Materials and Methods

- 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 (DDR) 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:
  1. Determine the radiographic response per RECIST 1.1 criteria
  2. 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
  3. 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).

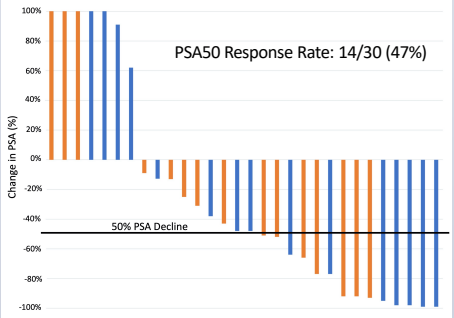
**Table 1:** Demographics. Safety cohort includes all patients that received treatment per protocol. The efficacy cohort includes those treated ≥12 weeks and who were evaluable for the primary endpoint.

| 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.

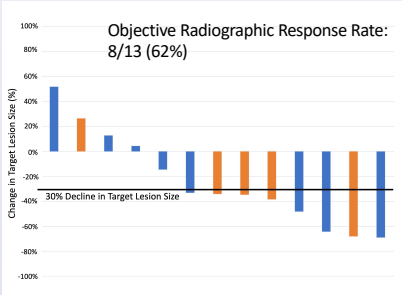



**Figure 3:** Radiographic Progression Free Survival

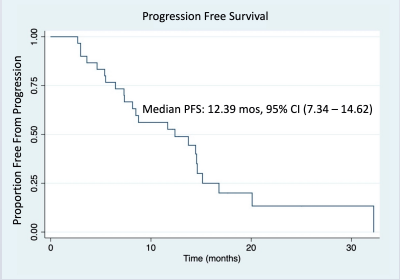
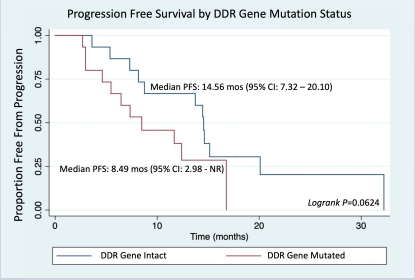
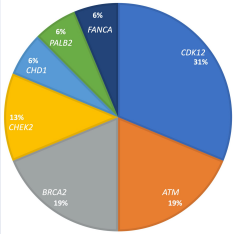



**Figure 4:** Radiographic Progression Free Survival by DNA damage repair (DDR) gene mutational status




## 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.




| Patient number | DDR Gene Mutation | PSA change (%) |
|---|---|---|
| 1 | *CHEK2* | 1410% |
| 2 | *ATM* | 247% |
| 3 | *CHD1* | 91% |
| 4 | *CDK12* | 62% |
| 5 | *CHEK2* | -13% |
| 6 | *CDK12* | -38% |
| 7 | *ATM* | -48% |
| 8 | *PALB2 / ATM* | -48% |
| 9 | *BRCA2* | -64% |
| 10 | *BRCA2* | -77% |
| 11 | *CDK12* | -95% |
| 12 | *BRCA2* | -98% |
| 13 | *CDK12* | -98% |
| 14 | *CDK12* | -99% |
| 15 | *FANCA* | -99% |

**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

| Adverse Event (AE) | All Grades, N (%) | Grade ≥3, N (%) |
|---|---|---|
| Abdominal discomfort | 2 (5.6%) | 0 (0%) |
| Anemia | 7 (19.4%) | 1 (2.8%) |
| 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%) |
| Diarrhea | 4 (11.1%) | 1 (2.8%) |
| DVT | 1 (2.8%) | 0 (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%) |
| Insomnia | 1 (2.8%) | 0 (0%) |
| Lightheadedness/Dizziness | 2 (5.6%) | 0 (0%) |
| Myalgia | 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%) | 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%) |
| 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.

## Acknowledgements

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