Phase II Trial of Abiraterone Acetate Plus Prednisone in Black Men With Metastatic Prostate Cancer

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TRIAL INFORMATION

- **ClinicalTrials.gov Identifier:** NCT01735396
- **Sponsor:** Janssen Biotech
- **Principal Investigator:** Matthew David Galsky
- **IRB Approved:** Yes

LESSONS LEARNED

- The safety and activity findings of abiraterone acetate plus prednisone treatment in black men with mCRPC were similar to results from previously conducted studies with largely white populations.
- Poor trial accrual continues to be a challenge in black men with mCRPC and further efforts are needed to address such underrepresentation.

ABSTRACT

**Background.** Self-identified black men have higher incidence and mortality from prostate cancer in the United States compared with white men but are dramatically underrepresented in clinical trials exploring novel therapies for metastatic castration-resistant prostate cancer (mCRPC).

**Methods.** Black men with mCRPC were treated with abiraterone acetate (AA), 1,000 mg daily, and prednisone (P), 5 mg twice daily. The primary objective was to determine antitumor activity (defined by a ≥30% decline in prostate-specific antigen [PSA] level) and to correlate germline polymorphisms in androgen metabolism genes with antitumor activity. Secondary objectives included determining safety, post-treatment changes in measurable disease, and time to disease progression.

**Results.** From April 2013 to March 2016, a total of 11 black men were enrolled and received AA plus P (AA+P); 7 of 10 evaluable patients were docetaxel naive. Post-treatment declines in PSA level of ≥30% were achieved in 90% of patients. The side effect profile was consistent with prior clinical trials exploring AA+Pi in mCRPC. Due to poor accrual, the study was closed prematurely with insufficient sample size for the planned pharmacogenetic analyses.

**Conclusion.** In this small prospective study terminated for poor accrual, the safety and activity of AA+P in black men with mCRPC was similar to that reported in prior studies exploring AA in largely white populations. Further efforts are needed to address underrepresentation of black men in mCRPC trials.

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DISCUSSION

AA is a steroidal inhibitor of 17α hydroxylase/C17,20-lyase (CYP17), which, in combination with prednisone, is approved for the treatment of mCRPC, based on the results of two randomized phase III trials demonstrating improvements in survival [1, 2]; but black men were largely underrepresented in both. Although poor access to health care is related to inferior outcomes in black men with prostate cancer, at least in part, differences in disease biology may also impact treatment response and survival. Indeed, germline polymorphisms in androgen metabolism genes (AMGs) have been correlated with response to androgen deprivation therapy [3, 4], and several AMG polymorphisms have been demonstrated to be more common in black patients, including polymorphisms in CYP17 [5].

This investigation was designed as a pilot study with a primary objective of determining whether there is a correlation between inherited genetic polymorphisms and antitumor activity (as defined by a decline in PSA level of ≥30%) in black patients with mCRPC treated with abiraterone acetate. Specifically, germline polymorphisms (as determined from baseline peripheral blood samples) in CYP17 and other genes involved in androgen metabolism were to be evaluated. Because this was the first prospective study, to our knowledge, to explore the relationship of germline polymorphisms in androgen pathway genes with response to hormonal therapy...
in a prospective cohort of black patients with CRPC, the study was designed to be exploratory, hypothesis generating, and to inform the design of larger, more definitive studies.

The primary endpoint of the study was to correlate germline polymorphisms in AMGs to a post-treatment decline in PSA level of $\geq 30\%$. Unfortunately, the study was prematurely terminated due to poor accrual, precluding the planned pharmacogenetic analyses. Of 10 evaluable patients treated, 9 had a $\geq 30\%$ decline in PSA level. Treatment was generally well tolerated, with no subjects discontinuing treatment because of adverse effects. Treatment was generally well tolerated, with no subjects discontinuing treatment because of adverse effects, although incidence of some common adverse effects may have been higher than expected due to small sample size (e.g., fatigue).

To our knowledge, this is the first prospective interventional study exploring a treatment for mCRPC specifically enrolling black men; the study highlights several important lessons. Poor enrollment of black men in prostate cancer clinical trials is likely multifactorial: Black men are more often deemed ineligible for cancer clinical trials and are more likely to refuse participation when eligible [6, 7]. Despite opening our study at two centers with catchment areas made up of a large black population, these factors likely contributed to the poor accrual. Although it did not impact our study, increased use of multinational sites with very small black populations in phase III trials has further exacerbated disparities. Potential solutions include large multicenter postmarketing registries, patient navigation and community education, and dedicated clinical trials enrolling black patients [6, 8]. Although funding for multicenter investigator-initiated studies is often prohibitive, the National Cancer Institute cooperative group system may be an appropriate venue for such studies.

| Trial Information | Disease | Prostate cancer |
|-------------------|---------|----------------|
| Stage of disease/treatment | Metastatic/advanced |
| Prior therapy | No designated number of regimens |
| Type of study - 1 | Phase II |
| Type of study - 2 | Single Arm |
| Primary Endpoint | Overall response rate |
| Secondary Endpoint | Efficacy |
| Secondary Endpoint | Correlative endpoint |
| Secondary Endpoint | Safety |
| Additional Details of Endpoints or Study Design | The primary objective of this study was to determine a correlation between inherited genetic polymorphisms and antitumor activity (as defined by a decline in PSA of $\geq 30\%$) in black patients with castration-resistant prostate cancer treated with abiraterone acetate. Specifically, germline polymorphisms (as determined from baseline peripheral blood samples) in CYP17 and other genes involved in androgen metabolism will be evaluated—a total of approximately 120 polymorphisms tagging all known, common variations across 20 genes of interest. Unfortunately, the study was prematurely terminated due to poor accrual, precluding the planned pharmacogenetic analyses. Of 10 evaluable patients treated, 9 had a $\geq 30\%$ PSA decline. |

| Investigator’s Analysis | Active but results overtaken by other developments |

| Drug Information | Drug 1 | Abiraterone acetate |
|------------------|--------|---------------------|
| Generic/Working name | Abiraterone acetate |
| Trade name | Zytiga |
| Company name | Janssen Biotech |
| Drug type | Biological |
| Drug class | Androgen receptor |
| Dose | 1,000 mg per flat dose |
| Route | Oral |
| Schedule of Administration | Take 1,000 mg every morning on an empty stomach |
| Drug 2 | Prednisone |
| Drug class | Corticosteroid |
| Dose | 5 mg, twice daily, per flat dose |
| Route | Oral |

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# Patient Characteristics

| Characteristic                          | Value                                           |
|-----------------------------------------|-------------------------------------------------|
| Number of patients, male                | 11                                              |
| Number of patients, female              | 0                                               |
| Stage                                   | Stage IV, castration-resistant prostate cancer  |
| Age                                     | Median (range): 66 (54–78)                      |
| Number of prior systemic therapies      | Median (range): 3 (1–4)                         |
| Performance Status: ECOG                | 0 — 8, 1 — 3, 2 — 3, Unknown —                 |
| Cancer Types or Histologic Subtypes     | Adenocarcinoma of the prostate 11               |

## Primary Assessment Method

### Control Arm: Adenocarcinoma of the Prostate

| Category                              | Value                                           |
|---------------------------------------|-------------------------------------------------|
| Number of patients screened           | 11                                              |
| Number of patients enrolled           | 11                                              |
| Number of patients evaluable for toxicity | 10                                          |
| Number of patients evaluated for efficacy | 10                                          |
| Response assessment PR                | n = 9 (90)                                      |
| Response assessment SD                | n = 1 (10)                                      |

### Control Arm: Total Patient Population

| Category                              | Value                                           |
|---------------------------------------|-------------------------------------------------|
| Number of patients screened           | 11                                              |
| Number of patients enrolled           | 11                                              |
| Number of patients evaluable for toxicity | 10                                          |
| Number of patients evaluated for efficacy | 10                                          |
| Response assessment PR                | n = 9 (90)                                      |
| Response assessment SD                | n = 1 (10)                                      |

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**Figure 1.** Waterfall plot of maximum post-treatment declines in prostate-specific antigen levels.
### Adverse Events

| Name                          | All Cycles |
|-------------------------------|------------|
|                               | *NC/NA 1 2 3 4 5 All Grades |
| Fatigue                       |            |
|                               | 30% 40% 30% 0% 0% 0% 70% |
| Hot flashes                   |            |
|                               | 60% 30% 10% 0% 0% 0% 40% |
| Nausea                        |            |
|                               | 60% 40% 0% 0% 0% 0% 40% |
| Vomiting                      |            |
|                               | 60% 40% 0% 0% 0% 0% 40% |
| Hypocalcemia                  |            |
|                               | 80% 0% 10% 10% 0% 0% 20% |
| Hypokalemia                   |            |
|                               | 80% 0% 10% 10% 0% 0% 20% |
| Cough                         |            |
|                               | 70% 30% 0% 0% 0% 0% 30% |
| Alkaline phosphatase increased|            |
|                               | 30% 50% 10% 10% 0% 0% 30% |
| Hypophosphatemia              |            |
|                               | 60% 10% 20% 10% 0% 0% 40% |
| Urinary incontinence          |            |
|                               | 70% 20% 10% 0% 0% 0% 30% |
| Platelet count decreased      |            |
|                               | 80% 20% 0% 0% 0% 0% 20% |
| Hyperglycemia                 |            |
|                               | 50% 40% 10% 0% 0% 0% 50% |
| Diarrhea                      |            |
|                               | 80% 20% 0% 0% 0% 0% 20% |
| Lymphocyte count decreased    |            |
|                               | 60% 10% 20% 10% 0% 0% 40% |
| Anorexia                      |            |
|                               | 70% 10% 20% 0% 0% 0% 30% |
| Muscle weakness in lower limb |            |
|                               | 80% 10% 0% 10% 0% 0% 20% |
| Hypoalbuminemia               |            |
|                               | 80% 0% 20% 0% 0% 0% 20% |
| Aspartate aminotransferase level increased |          |
|                               | 70% 30% 0% 0% 0% 0% 30% |
| Alanine aminotransferase level increased |          |
|                               | 80% 20% 0% 0% 0% 0% 20% |
| Back pain                     |            |
|                               | 70% 30% 0% 0% 0% 0% 30% |

**Adverse Events Legend**

- >1 occurrence in any individual patient.
- *No Change from Baseline/No Adverse Event.

### Assessment, Analysis, and Discussion

**Completion**

Study terminated before completion

**Terminated reason**

Did not fully accrue

**Pharmacokinetics/Pharmacodynamics**

Not collected

**Investigator’s Assessment**

Endpoint not met because study closed early due to poor accrual.

Abiraterone acetate (AA) is a steroidal inhibitor of 17α-hydroxylase/C17,20-lyase (CYP17), which, in combination with prednisone, is approved for the treatment of metastatic castration-resistant prostate cancer (mCRPC), based on the results of 2 randomized phase III trials demonstrating improvements in survival [1, 2]; but black men were largely underrepresented in both. Although poor access to health care is related to inferior outcomes in black men with prostate cancer, at least in part, differences in disease biology may also impact treatment response and survival. Indeed, germline polymorphisms in androgen metabolism genes (AMGs) have been correlated with response to androgen deprivation therapy [3, 4], and several AMG polymorphisms have been demonstrated to be more common in black patients, including polymorphisms in CYP17 [5].

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DISCLOSURES

Che-Kai Tsao: Dendreon (C/A, RF); Bobby Liaw: Bayer (C/A); William Kyu Oh: Janssen (C/A); Matthew David Galsky: Genentech, AstraZeneca, Astellas (C/A), Bristol-Myers Squibb, Merck, Dendreon (RF), Dual Therapeutics (OI). The other authors indicated no financial relationships. (C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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