

## Principal Investigator

**First Name:** Benjamin  
**Last Name:** Teply  
**Degree:** MD  
**Primary Affiliation:** University of Nebraska Medical Center  
**E-mail:** [ben.teply@unmc.edu](mailto:ben.teply@unmc.edu)  
**Phone number:** 617-308-0744  
**Address:** 986840 Nebraska Medical Center

**City:** Omaha  
**State or Province:** NE  
**Zip or Postal Code:** 68198-6840  
**Country:** USA  
**SCOPUS ID:** 57185469800

## 2016-1057

### General Information

**Key Personnel (in addition to PI):** **First Name:** Samuel  
**Last name:** Denmeade  
**Degree:** MD  
**Primary Affiliation:** Johns Hopkins University  
**SCOPUS ID:**

**First Name:** Fang  
**Last name:** Qui  
**Degree:** MS  
**Primary Affiliation:** University of Nebraska Medical Center  
**SCOPUS ID:**

**Are external grants or funds being used to support this research?:** No external grants or funds are being used to support this research.

**How did you learn about the YODA Project?:** Internet Search

 [teplycoi.pdf](#)

 [denmeadecoi\\_yoda.pdf](#)

 [yoda\\_project\\_coi\\_form\\_for\\_data\\_requestors\\_fq.pdf](#)

### Certification

**Certification:** All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.

**Data Use Agreement Training:** As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

**Associated Trial(s):** [NCT00638690 - A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Abiraterone Acetate \(CB7630\) Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy](#)  
[NCT00887198 - A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate \(CB7630\) Plus Prednisone in Asymptomatic or Mildly Symptomatic Patients With Metastatic Castration-Resistant Prostate Cancer](#)

**What type of data are you looking for?:** Individual Participant-Level Data, which includes Full CSR and all supporting documentation

## Research Proposal

### Project Title

Incidence of visceral metastasis at time of progression on abiraterone for metastatic castration-resistant prostate cancer

#### Narrative Summary:

Treatments for prostate cancer can be effective whether patients have metastatic disease in bones, lymph nodes, or organs (lung or liver). However, the prognosis is poor for patients with organ metastases at the start of treatment. It is not known whether the location of metastases is changed after therapy for medications like abiraterone. Some patients may develop more aggressive disease after treatment. We will determine if organ metastases are increased at the time of progression by comparing the sites/sizes of metastasis before and after therapy. The data from this project is important to future studies, in particularly as these medicines are being trialed in early in the disease course.

#### Scientific Abstract:

**Background:** Abiraterone is a life-prolonging treatment for patients with metastatic castration-resistant prostate cancer (CRPC), yet at the time of progression the tumors are often rendered clinically resistant to further androgen-directed therapy. In some patients, these tumors may be driven to an aggressive phenotype, in-part characterized by the development of visceral metastatic disease. We hypothesize that visceral metastases are increased at the time of progression on abiraterone.

**Objective:** Our primary objective is to estimate the incidence of visceral metastatic disease at the time of progression on abiraterone. Secondary objectives include comparing incidence of visceral metastatic disease between subjects treated with abiraterone or placebo, calculate visceral metastasis-free survival, and identify factors associated with development of visceral metastatic disease.

**Study Design:** We will analyze the distribution of metastatic disease for subjects who participated in the COU-AA-301, comparing baseline distributions to distribution at time of progression for cohorts of patients treated with abiraterone and placebo.

**Participants:** Our analysis will include all subjects available in the dataset from COU-AA-301.

**Main Outcome Measure:** The primary endpoint is incidence of visceral metastatic disease, calculated by analysis of disease distribution at baseline versus at time of progression.

**Statistical Analysis:** The primary endpoint will be analyzed by comparing pre- and post-treatment proportions of site-specific metastasis using McNemar's test of paired proportions.

#### Brief Project Background and Statement of Project Significance:

Abiraterone is a life-prolonging treatment for patients with metastatic castration-resistant prostate cancer (CRPC), yet the potent antiandrogen activity of the drug often yields tumors that are clinically resistant to further androgen-directed therapy at the time of progression [1]. Anecdotally, we have observed more clinically aggressive CRPC upon progression on abiraterone in some patients, including the development of life-threatening liver metastases. In this study, we are analyzing differences in the distribution of metastatic disease at the time of initiation and progression on abiraterone, with a particular interest in whether visceral metastatic disease is increased.

The distribution of sites of metastatic disease is important for CRPC because the pattern of disease influences survival [2]. For example, in analyses of patients treated with chemotherapy, patients with node-only disease have superior survival to those with bone disease or visceral disease. Liver metastatic disease portends the worst prognosis [3, 4]. The negative prognostic implications of visceral metastases have been confirmed in meta-analyses of patients treated with chemotherapy or hormonal therapy [5].

There are currently no published data describing the change disease distribution at the time of radiographic progression on novel hormonal agents (including abiraterone) or cabazitaxel. Chemotherapy with docetaxel has been previously reported to not change the distribution of metastatic disease—namely, patients with bone disease progress in bone, patients with nodal disease progress in nodes, and patients with visceral disease progress in those viscera [6]. However, given the unique mechanism of action of abiraterone, it is possible that disease distribution is significantly altered after exposure to abiraterone and similar agents.

Based upon this understanding of abiraterone's mechanism of action and our clinical observations, we hypothesize that visceral metastases are increased at the time of radiographic disease progression on abiraterone compared to baseline. In order to test this hypothesis, we will study the patterns of metastatic disease progression after treatment with abiraterone. We also aim to compare the change in metastatic disease distribution at progression for abiraterone for patients treated with placebo (prednisone alone) as well as to a parallel analysis of patients treated with cabazitaxel, to determine if similar changes are seen in all cohorts. This work is significant, in-part, as potent novel hormonal agents are now frequently used in the first-line for CRPC, and trials are testing these agents earlier in the course of the disease. Yet, these agents may be fundamentally changing the overall disease course and inducing early visceral disease in some patients.

### **Specific Aims of the Project:**

We hypothesize that visceral metastases are increased at time of progression on abiraterone compared to baseline.

Primary specific aim / objective:

1. To estimate the incidence of visceral metastasis at time of radiographic progression on abiraterone.

Secondary specific aims / objectives:

1. To estimate the visceral metastasis-free survival for patients treated with abiraterone.
2. To determine clinical factors associated with the development of visceral metastatic disease.
3. To associate overall survival with disease distribution at baseline in comparison to at radiographic progression.
4. To compare incidence of new visceral metastatic disease at progression and visceral metastasis-free survival in patients treated with abiraterone or placebo therapy.

**What is the purpose of the analysis being proposed? Please select all that apply.** New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations  
New research question to examine treatment safety

## **Research Methods**

### **Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:**

We will employ a post-hoc analysis of the COU-AA-301 data to compare the distribution of metastatic disease at study entry versus at the time of radiographic progression. Our primary endpoint is the presence of visceral metastatic disease at the time of progression on abiraterone in order to estimate the incidence of visceral metastatic disease.

All patients treated on the COU-AA-301 trial will be eligible for this analysis. Requested Data:

Demographic information

- Age
  - Race
  - Gleason Score
  - Date of Diagnosis
  - Prior anti-cancer therapies
  - Prior prostatectomy and/or radiation therapy
  - Investigations (PSA, Hgb, Cr, AlkPhos, LDH)
  - Pain score
  - Performance Status
  - Cohort
  - #cycles
  - Mode of progression
-

- Best PSA response
- Date of initiation
- Date of PSA progression (PSA progression-free survival)
- Date of Radiographic PFS (Radiographic progression-free survival)
- Date of death (overall survival)
- CT and NM Bone scan description of metastatic disease at baselin (# bone, nodal, visceral)
- CT and NM Bone scan description of metastatic disease at progression (# bone, nodal, visceral)

**Main Outcome Measure and how it will be categorized/defined for your study:**

The primary endpoint is the incidence of visceral metastatic disease at the time of disease progression. Thus, the main outcome measure will be the distribution of metastatic disease at the time of progression, broken down by location and number of metastases, with a comparison by RECIST criteria to determine if lesions are new/progressed. This outcome will be calculated for patients regardless of reason for study therapy completion (toxicity, clinical progression or radiographic progression). The data regarding the CT and NM bone scans at initiation and progression will be utilized for the measure.

**Main Predictor/Independent Variable and how it will be categorized/defined for your study:**

The primary independent variable will be assigned study treatment (abiraterone versus placebo). It is assigned per study protocol.

**Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:**

- Age at study entry (years)
- Race (Am. Indian, Asian, Black , Native Hawaiian or Other Pacific Islander, White)
- Gleason Score (sum)
- Date of Diagnosis
- Prior anti-cancer therapies (number of prior hormonal therapies, prior ketoconazole, prior chemotherapies)
- Prior prostatectomy and/or radiation therapy (Y/N for each)
- Investigations (PSA, Hgb, Cr, AlkPhos, LDH)
- Pain score / presence of pain (binary Y/N)
- Performance Status (ECOG)
- Cohort (Abiraterone or Placebo)
- # cycles administered / duration of exposure to agent (in # of cycles)
- Mode of progression (clinical, radiographic, toxicity)
- Best PSA response (% reduction)
- Date of Abiraterone or Prednisone initiation
- Date of PSA progression (PSA progression-free survival)
- Date of Radiographic PFS (Radiographic progression-free survival)
- Number of bone mets at baseline
- Number of nodal mets at baseline
- Number of visceral mets (liver, lung, other) at baseline
- Number of bone mets at progression – and if progression in bone
- Number of nodal mets at progression – and if progression in node
- Number of visceral mets (liver, lung, other) at progression – and if progression in viscera

**Statistical Analysis Plan:**

Disease characteristics will be compared using descriptive statistics and t-tests. Pre- and post-treatment proportions of site-specific metastases will be compared using McNemar's test of paired proportions. Multivariate analyses will be performed to determine if other clinical characteristics or factors are associated with development of visceral metastatic disease. Kaplan-Meier analyses will be used to compare the time-to-event endpoints. Interaction tests will be used to compare the differences between cohorts.

**Project Timeline:**

- Project start date: 9/2016
- Analysis completion date: 11/2016
- Date manuscript drafted/submitted: 2/2017
- Results reported 5/2017

**Dissemination Plan:**

Anticipate presentation of data at GU ASCO 2017 or ASCO 2017, with manuscript publication in European Urology or similar journal.

**Bibliography:**

1. Azad AA, Eigel BJ, Murray RN, et al. Efficacy of enzalutamide following abiraterone acetate in chemotherapy-naive metastatic castration-resistant prostate cancer patients. *European urology*. 2015;67(1):23-9.
2. Pond GR, Sonpavde G, de Wit R, et al. The prognostic importance of metastatic site in men with metastatic castration-resistant prostate cancer. *European urology*. 2014;65(1):3-6.
3. Goodman OB, Jr., Flaig TW, Molina A, et al. Exploratory analysis of the visceral disease subgroup in a phase III study of abiraterone acetate in metastatic castration-resistant prostate cancer. *Prostate cancer and prostatic diseases*. 2014;17(1):34-9.
4. Evans CP, Higano CS, Keane T, et al. The PREVAIL Study: Primary Outcomes by Site and Extent of Baseline Disease for Enzalutamide-treated Men with Chemotherapy-naive Metastatic Castration-resistant Prostate Cancer. *European urology*. 2016.
5. Halabi S, Kelly WK, Ma H, et al. Meta-Analysis Evaluating the Impact of Site of Metastasis on Overall Survival in Men With Castration-Resistant Prostate Cancer. *J Clin Oncol*. 2016;34(14):1652-U191.
6. Sella A, Sternberg C, Kovel S, et al. Progression after docetaxel-based chemotherapy in androgen-independent prostate cancer. *BJU international*. 2007;100(3):533-5.