

## Principal Investigator

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## General Information

### Key Personnel (in addition to PI):

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**Are external grants or funds being used to support this research?:** External grants or funds are being used to support this research.

**Project Funding Source:** UAB (University of Alabama, Birmingham) support funds given to PI (Guru Sonpavde, MD)

## Conflict of Interest

[http://yoda.yale.edu/system/files/yoda\\_project\\_coi\\_form\\_for\\_data\\_requestors\\_sept\\_2014\\_0.pdf](http://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_sept_2014_0.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):**

1. [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](#)

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

## Research Proposal

### Project Title

RECIST response as a surrogate endpoint in metastatic castration-resistant prostate cancer: Retrospective analysis of COU-AA-302 and COU-AA-301

### Narrative Summary:

Advanced prostate cancer has been plagued by the lack of an optimal endpoint to rapidly assess the anti-tumor activity of new drugs due to the presence of mostly bone metastases. Unfortunately, bone metastases are not possible to accurately measure in contrast to measurable metastases in other organs like the lung, lymph nodes and liver. Since, current improved CT scan technology is more frequently detecting measurable tumors, we propose to study the COU-AA-301 dataset (and AA-302 trial when available) to validate the association between response of measurable tumors and survival. The validation of this association will expedite drug development and will represent an important advance.

### Scientific Abstract:

**Background:** Objective RECIST (Response Evaluation Criteria in Solid Tumors) criteria have not been generally applicable to metastatic castration-resistant prostate cancer (mCRPC) due to mostly non-measurable bone metastases. Given the more frequent detection of measurable disease with current CT imaging technology, the accrual of mCRPC patients with measurable tumors in phase II trials to assess RECIST changes may provide a more objective signal of efficacy of new drugs. The COU-AA-302 and COU-AA-301 phase III trials, which evaluated abiraterone, were both 'positive' for extension of overall survival (OS), and afford a unique opportunity to study the surrogacy of RECIST response to predict OS. The surrogacy of RECIST changes may then be examined across other agents to confirm universal applicability. Such a development will allow the objective determination of activity of agents in phase II trials and resources will be better utilized since the most suitable agents will be selected for phase III development.

**Objectives:** To study RECIST response as a surrogate for OS

**Study design and participants:** The COU-AA-302 will be employed as the discovery dataset and COU-AA-301 as the validation dataset.

**Outcome measures:** The association RECIST changes with OS will be studied.

**Statistical analysis:** Univariable and multivariable Cox regression analyses will evaluate the prognostic ability of RECIST changes. A landmark analysis will be performed using day 90 as the landmark time. RECIST changes will be evaluated as potential surrogates using the likelihood reduction factor.

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

Intermediate endpoints correlating with survival in men with mCRPC: mCRPC has been historically plagued by the lack of an optimal intermediate endpoint correlating with survival due to the presence of mostly bone metastases and lack of measurable disease [1-9]. PSA declines and radiographic progression are associated with survival, but are not validated across different drugs and have subjective components. Although circulating tumor cell (CTC) changes carry prognostic value, all patients do not have detectable CTCs and costs may be a barrier [10-13].

Objective measurable disease response:

Measurable disease response by WHO criteria was associated with OS in the setting of chemotherapy as shown in the TAX327 trial[14]. Partial responders demonstrated longer median OS (29.0 months) than patients with SD (22.1

months) or those with PD (10.8 months) or those who were not assessed (12.7 months). Radiologic response remained a significant but modest post-treatment prognostic factor for OS after adjusting for treatment, pain response, and  $\geq 30\%$  PSA decline ( $P = 0.009$ ), and remained significant based on landmark analyses. Recently, response by RECIST criteria was examined for association with OS in the VENICE dataset of patients receiving docetaxel-based chemotherapy (confidential; data submitted to GU ASCO symposium 2015)[15]. To briefly summarize the findings, 363 of 612 patients (59.3%) who received docetaxel-prednisone had measurable lesions. Objective changes in tumor size by RECIST within 90 days were robustly associated with OS in patients with mCRPC receiving first-line docetaxel-based chemotherapy.

COU-AA-302 and AA-301 trials:

The COU-AA-301 (N=1195) and AA-302 (N=1088) phase III trials are randomized trials that showed an extension of survival as well as multiple secondary endpoints (including RECIST response) with abiraterone + prednisone compared to placebo + prednisone in the post-docetaxel and pre-docetaxel settings, respectively [16, 17].

Statement of project significance:

Given the limitations of objectively measuring tumor burden in bone and more frequent detection of measurable disease with current imaging, the accrual of patients with measurable tumors in phase II trials to assess RECIST changes may provide a more robust and objective signal of efficacy of new drugs compared to currently used intermediate endpoints. The COU-AA-302 and AA-301 trial datasets offer the opportunity to validate the association between RECIST response and survival in the setting of abiraterone plus prednisone. It is proposed that COU-AA-302 be employed as the discovery dataset and AA-301 be employed as the validation dataset. If RECIST changes show at least moderate surrogacy for OS using these datasets, the surrogacy of RECIST changes may then be examined across other agents to confirm universal applicability. Such a development will allow the objective determination of activity of agents in phase II trials and resources will be better utilized since the most suitable agents will be selected for phase III development.

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

Given the limitations of objectively measuring tumor burden in bone in men with metastatic castration prostate cancer (mCRPC) and more frequent detection of measurable disease with current imaging, the accrual of men with measurable tumors in phase II trials to assess RECIST changes may be hypothesized to provide a more robust and objective signal of efficacy of new drugs compared to endpoints such as PSA response and radiographic progression-free survival.

1. To study the association of RECIST response with survival in docetaxel-naïve and post-docetaxel men with mCRPC receiving prednisone combined with placebo or abiraterone

Cox regression analyses of COU-AA-301 and COU-AA-302 trials will evaluate the prognostic ability of RECIST changes to predict survival after adjusting for previously reported baseline prognostic factors. The impact of RECIST changes independent of PSA response will be studied.

2. To evaluate RECIST response as a surrogate endpoint in docetaxel-naïve and post-docetaxel men with mCRPC receiving prednisone combined with placebo or abiraterone

RECIST changes will be evaluated as potential surrogates for OS using COU-AA-302 as the discovery dataset and COU-AA-301 as the validation dataset, using the likelihood reduction factor.

### **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

## **Research Methods**

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

Retrospective analyses of COU-AA-302 and AA-301 will be conducted to assess the association of RECIST changes with OS. The suitability of RECIST response as a surrogate endpoint will be assessed. COU-AA-302, the pre-docetaxel trial, will be employed as the discovery dataset and AA-301, the post-docetaxel trial, will be employed as the validation dataset. Clinical data (deidentified) will be requested from the COU-AA-302 and AA-301

trials. The following clinical and laboratory variables are requested:

1. Age
2. Therapy arm
3. Trial (AA-301 and AA-302)
4. ECOG-PS
5. Metastatic sites (PCWG2 subtype)
6. Pain
7. Hb
8. Alkaline phosphatase
9. PSA-DT
10. PSA
11. Testosterone level
12. Gleason score
13. Albumin
14. Date of therapy start
15. Date of protocol-defined progression on trial
16. Type of progression: Radiographic progression (measurable disease or bone scan), PSA progression, skeletal-related event, pain progression, and radiotherapy for symptoms or death
17. Date of last follow-up
18. Survival at last follow-up
19. Neutrophil count (baseline)
20. Lymphocyte count (baseline)
21. Measurable tumor
22. RECIST response status and % decline in RECIST dimension by day 90
23. PSA response

COU-AA-302 will be employed as the discovery dataset and AA-301 will be employed as the validation dataset. The AA-302 (NCT00887198) dataset has been requested and is expected to be available soon through the YODA project; however, in the event the NCT00887198 dataset is not available within 2-3 months, analysis and internal validation of the association of RECIST changes and OS will be conducted in the available NCT00638690 (AA-301) trial. Univariable and multivariable Cox regression analyses will evaluate the prognostic ability (with primary endpoint of overall survival and secondary endpoint of radiographic PFS) of RECIST changes (PR, SD, PD) and the previously reported prognostic factors (performance status, pain, visceral metastasis, anemia, PSA, alkaline phosphatase, neutrophil/lymphocyte ratio, PSA response) [17-24]. The impact of RECIST changes independent of PSA declines will be studied. Since there is the potential of a time-bias when using RECIST changes, a landmark analysis will be performed using day 90 as the landmark time. The Kaplan-Meier method will be used for to estimate OS within selected subgroups. Validation of factors hypothesized to be prognostic (performance status, pain, visceral metastasis, anemia, PSA, alkaline phosphatase, neutrophil/lymphocyte ratio, PSA response) will be initially examined in the discovery dataset, and then validated in the validation dataset. Results will be reported using a combination of hazard ratios, overall survival estimation, c-statistics, discrimination plots, tables, descriptive statistics and confidence intervals. RECIST changes will be evaluated as potential surrogates using the likelihood reduction factor [25]. All analyses will be two-sided and statistical significance will be defined at  $\alpha=0.05$  level.

**Project Timeline:**

1. Completion of contract- 11/2014
2. Obtain deidentified dataset-12/2014
3. Analysis and report submitted to YODA- 1/2014
4. Circulation of abstract targeting ASCO 2015 to YODA - 1/2014
5. Circulation of paper to YODA targeting JCO, Lancet Oncol or CCR- 2/2014

**Dissemination Plan:**

1. Circulation of abstract targeting ASCO 2015 - 1/2014
2. Circulation of paper targeting JCO, Lancet Oncol or CCR- 2/2014

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**Supplementary Material:**

 [cpc-recist-abiraterone-retrospective-concept.docx](#)