

**The YODA Project
Research Proposal Review**

The following page contains the final YODA Project review
approving this proposal.

The YODA Project
Research Proposal Review - Final
(Protocol #: 2015-0500)

Reviewers:

- Nihar Desai
- Cary Gross
- Harlan Krumholz
- Richard Lehman
- Joseph Ross

Review Questions:

Decision:

- | | |
|---|----------------------------|
| 1. Is the scientific purpose of the research proposal clearly described? | Yes |
| 2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health? | Yes |
| 3. Can the proposed research be reasonably addressed using the requested data? | Yes, or it's highly likely |
| 4. Recommendation for this data request: | Approve |

Comments:

No additional comments.

**The YODA Project
Research Proposal Review**

Revisions were requested during review of this proposal.
The following pages contain the original YODA Project review and
the original submitted proposal.

The YODA Project
Research Proposal Review - Revisions Requested
(Protocol #: 2015-0500)

Reviewers:

- Nihar Desai
- Cary Gross
- Harlan Krumholz
- Richard Lehman
- Joseph Ross

Review Questions:

Decision:

- | | |
|---|----------------------------|
| 1. Is the scientific purpose of the research proposal clearly described? | No |
| 2. Will request create or materially enhance generalizable scientific and/or medical knowledge to inform science and public health? | Yes |
| 3. Can the proposed research be reasonably addressed using the requested data? | Yes, or it's highly likely |
| 4. Recommendation for this data request: | Not Approve |

Comments:

Please clarify in the Introduction whether the prior research that identified several drugs (dexamethasone, metoprolol, clopidogrel, oxycodone, and citalopram) used among CRPC patients that placed patients at risk for potentially risky DDI were because of each of the drugs interacting with Abiraterone or because the drugs interact with one another.

Six main outcome measures are discussed, but not all are clearly defined. In particular, how will adverse events be defined? The explanation given ("Postulated DDI are called if the patient experiences an adverse event grade ?2 (CTCAEv3.0) that was predicted by the DDI database screen.") is not clear as written.

It would be ideal if fewer abbreviations were used (for instance, why abbreviate Abiraterone as AA? Each is one word).

Principal Investigator

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SCOPUS ID: 6602635761

2015-0500

General Information

Key Personnel (in addition to PI): **First Name:** Liying
Last name: Zhang
Degree: PhD Biostatistics
Primary Affiliation: Sunnybrook Odette Cancer Centre
SCOPUS ID: 55913372100

First Name: Rehana
Last name: Jamani
Degree: MSc Candidate
Primary Affiliation: Sunnybrook Odette Cancer Centre
SCOPUS ID: N/A

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: Ride for Dad - Prostate Cancer Fight Foundation (Durham Chapter, ON, Canada)

 [coi_signed_all.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](#)

What type of data are you looking for?: Full CSR

Research Proposal

Project Title

Studying the Risk of Harmful Drug-Drug Interactions (DDI) in Patients with Castration-Resistant Prostate Cancer (CRPC) Treated with Abiraterone (AA)

Narrative Summary:

AA is inactivated via cytochrome P450 (CYP) 3A4, and inhibits various CYPs involved in the metabolism of other drugs commonly used in CRPC patients (pts). Thus, DDI may affect the activity or safety of both AA and co-medications. A retrospective review of 90 CRPC pts treated with AA revealed potential DDI in 95% of pts, but small sample size and lack of systematic documentation of adverse events (AE) amongst others did not allow definite conclusions about the risk of harmful DDI-related AE. Hence, we plan to study baseline and on-treatment medication histories, and AE of CRPC pts undergoing AA therapy within COU-AA-301 to identify the risk of harmful DDI.

Scientific Abstract:

BACKGROUND: While AA inhibits androgen biosynthesis by blocking CYP17, it also inhibits numerous other CYPs involved in the metabolism of widely used medications. Otherwise, AA inactivation depends on CYP3A4. Hence, there is presumably a high potential for DDI that can either diminish the efficacy of AA or of concurrent medications, or increase the risk of DDI-related AE. However, the frequency and nature of harmful DDI involving AA is poorly known. **OBJECTIVES:** To study the frequency, nature and severity of AA-associated DDI in CRPC pts treated with AA within COU-AA-301. **STUDY DESIGN AND PARTICIPANTS:** We will analyze baseline demographics, medication histories, on-treatment medication changes, and AE of pts that underwent AA therapy within COU-AA-301 (n=797). To screen for and grade the postulated risk of DDI, we will use two commercial databases (Lexicomp, Micromedex). **MAIN OUTCOME MEASURES:** Rate of CRPC pts starting AA considered at risk of significant DDI, most commonly used drugs/classes of drugs harboring potential risks for DDI with AA, documented DDI-related AE. **STATISTICAL ANALYSIS:** We will apply (1) descriptive analyses for continuous variables, and proportions for categorical variables, (2) a general linear mixed model (GLMM) for between- and within-subject variability of the percental change of medications from baseline to week 12, (3) univariate and multivariate GLMM analyses to identify significant relationships between demographic and disease covariates, and (4) generalized estimating equations to search for significant predictive factors.

Brief Project Background and Statement of Project Significance:

AA is a well-tolerated and patient-friendly oral agent that increases survival and delays symptomatic progression in pts with CRPC (1, 2). It impairs androgen biosynthesis by blocking CYP17, but also inhibits other CYPs involved in the metabolism of widely used medications (strong inhibition of CYP1A2, CYP2D6, and CYP2C8; moderate inhibition of CYP2C9, CYP2C19 and CYP3A4/5) (3). Hence, DDI may affect the activity or safety of both AA and certain co-medications. Whereas the frequency and clinical relevance of AA-related DDI is not well established, CRPC pts commonly use numerous medications for concurrent health conditions, including drugs with a narrow therapeutic range (4). The risk of clinically relevant DDI is further amplified in the often elderly and frail CRPC pts in which drug prescription is generally more challenging (5, 6).

We conducted a retrospective review of pharmacy records and medical charts of CRPC pts beginning AA treatment between January 2010 and April 2014 at Sunnybrook Odette Cancer Centre (Toronto, ON, Canada), to retrieve demographic information, individual drug histories and AE during AA therapy. Individual drug histories were analyzed for DDI using two commercial databases (Lexicomp, Micromedex). 90 informative pts were identified. Using Lexicomp, the most common drugs flagged for potential DDI of high clinical significance (i.e., "avoid combination", or "consider therapy modification") with AA were dexamethasone, metoprolol, clopidogrel, oxycodone, and citalopram. They were administered to 12 (13%), 10 (11%), 6 (7%), 4 (4%), and 4 (4%) pts respectively. Micromedex assigned a major risk of DDI to oxycodone and a moderate risk to metoprolol. At least 1 potentially significant DDI was found in 66/91 pts (75%) with Lexicomp, and in 38/91 pts (42%) with Micromedex. Most common AE were fluid retention seen in 19 pts (21%), fatigue in 15 (16%), liver-function test abnormalities in 13 (14%), hypertension in 13 (14%), and pain in 11 (12%), all corresponding to AE typically associated with the use of AA. We did not find unequivocal evidence for DDI-related AE, possibly due to widely applied DDI screening

before initiation of AA therapy, followed by according co-medication modifications. However, our study had a number of limitations, including the relatively small sample size, the retrospective nature of data collection, a lack of systematic collection of AE, and incomplete information on modifications of baseline co-medications (before starting AA, or during AA therapy). Thus, although the use of commercial DDI databases reveals a substantial risk of potentially DDI in CRPC pts undergoing AA therapy, the clinical relevance of these interactions is difficult to determine to date.

In COU-AA-301, drug histories (including treatment modifications) and AE were collected prospectively in 797 CRPC pts undergoing AA therapy. Using this dataset will enable us to study the frequency and relevance of potential interactions flagged by DDI database screen, and to formulate lists of drug combinations that should be avoided, or may be considered safe.

Specific Aims of the Project:

Hypothesis: When applying commercial DDI databases, many CRPC pts undergoing AA therapy are expected to use co-medications associated with the risk of potentially relevant DDI.

Primary endpoints: (1) to describe the rate of CRPC pts starting AA treatment considered at risk of significant DDI; (2) to identify the most commonly used drugs/classes of drugs harboring potential risks for DDI with AA.

Secondary endpoints: (3) to analyze medication changes between baseline, week 4 and week 12; (4) to identify the number of pts that suffered adverse events possibly related to DDI; (5) to identify drugs/classes of drugs involved in relevant DDI; (6) to determine if there are demographic covariates or disease characteristics that predict relevant DDI.

What is the purpose of the analysis being proposed? Please select all that apply. New research question to examine treatment safety

Research that confirms or validates previously conducted research on treatment safety

Preliminary research to be used as part of a grant proposal

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

We will include all patients randomized to the AA plus prednisone arm of COU-AA-301 (n=797) for which there are complete medications histories available at baseline and throughout the first 12 weeks of AA treatment.

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

Primary endpoints:

Patients at risk of significant DDI according to DDI database screen will be defined as follows: (1) Lexicomp database: DDI flagged as "avoid combination", or "consider therapy modification"; (2) Micromedex database: DDI flagged as "major" risk, or "moderate" risk. Because the identification of DDI differs between Lexicomp and Micromedex (based on our previous experience), we will calculate separate percentages of patients at risk for DDI according to Lexicomp and Micromedex, and separate percentages of patients using specific drugs/classes of drugs at risk of DDI.

Secondary endpoints:

We plan to analyze medication changes using the following categories: (1) cessation of medications considered at risk for DDI; (2) introduction of medications to possibly counteract predicted DDI; (3) other changes. Postulated DDI are called if the patient experiences an adverse event grade ≥2 (CTCAEv3.0) that was predicted by the DDI database screen.

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

To determine if there are demographic covariates or disease characteristics that predict relevant DDI, we will study the impact of the following variables on the aforementioned outcome measures: geographical origin of the patient (North America vs Europe vs Australia), age (<70, >70-80, >80), performance status (0-1 vs 2), number of co-medications at baseline (0 vs 1-5 vs >5), PSA as a marker of disease burden (below vs above the median PSA of 128.8 in the AA arm of COU-AA-301), and liver metastases (absent vs present; given the importance of the hepatic drug metabolism).

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

N/A

Statistical Analysis Plan:

Descriptive analyses will be conducted using mean, standard deviation, median and ranges for continuous variables, and proportions for categorical variables. For all pts and for subgroup of pts according to covariates of interest, we plan (i) to calculate the rate of CRPC individuals who are identified at risk of significant DDI, (ii) to estimate the proportions of drugs used harboring potential risks for DDI, and (iii) to calculate the proportions of pts that suffered AE possibly related to DDI. To investigate the percentual change of medications from baseline to week 12, a general linear mixed model (GLMM) will be applied to account for between- and within-subject variability. Univariate and multivariate GLMM analyses will be performed to search for significant relationship between medication changes and covariates of interest. For the endpoint of "any" risk of significant DDI during the study (yes vs no), univariate and multivariate logistic regression analyses will be conducted to see if there is significant association. To investigate the "proportion change" of pts with risk of significant DDI at baseline, at week 4, or at week 12, generalized estimating equations (GEEs) will be used to search for significant predictive factors. All analyses will be performed using Statistical Analysis Software (SAS), p-values < 0.05 will be considered as statistically significant.

Project Timeline:

Data collection/extraction: months 1-4.

Data analyses: months 5-8.

Manuscript preparation and submission: months 9-12.

Dissemination Plan:

We plan to present the data at 1-2 international meetings (eg ASCO GU, ASCO), and to submit an according manuscript to a urological oncology journal such as *European Urology* (Impact Factor 12.48). Based on our previous work there is also a keen interest for educational materials that facilitate the safe use of AA.

Bibliography:

1. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011;364:1995-2005.
2. Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*. 2013;368:138-48.
3. Hoy SM. Abiraterone acetate: a review of its use in patients with metastatic castration-resistant prostate cancer. *Drugs*. 2013;73:2077-91.
4. Droz JP, Balducci L, Bolla M, Emberton M, Fitzpatrick JM, Joniau S, et al. Background for the proposal of SIOG guidelines for the management of prostate cancer in senior adults. *Crit Rev Oncol Hematol*. 2010;73:68-91.
5. Shi S, Klotz U. Age-related changes in pharmacokinetics. *Current drug metabolism*. 2011;12:601-10.
6. Hubbard RE, O'Mahony MS, Woodhouse KW. Medication prescribing in frail older people. *Eur J Clin Pharmacol*. 2013;69:319-26.