Principal Investigator

First Name: Daniel
Last Name: George
Degree: MD
Primary Affiliation: Duke University Hospital
E-mail: matthew.labriola@duke.edu
Phone number: Phone: 919-668-4615
Address: Duke University Medical Center Box 103861, Durham NC 27710 US

City: DURHAM
State or Province: NC
Zip or Postal Code: 27703-6505
Country: United States

General Information

Key Personnel (in addition to PI):
First Name: Matthew
Last name: Labriola
Degree: MD
Primary Affiliation: Duke University Hospital
SCOPUS ID: 57201468693

First Name: Daniel
Last name: George
Degree: MD
Primary Affiliation: Duke University Hospital
SCOPUS ID: 7201471436

First Name: Yuan
Last name: Wu
Degree: PhD
Primary Affiliation: Duke
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?: Data Holder (Company)

Conflict of Interest

https://yoda.yale.edu/system/files/coi_form_dg.pdf
https://yoda.yale.edu/system/files/coi_form_ml.pdf
https://yoda.yale.edu/system/files/coi_form_yw.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

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; }

1. NCT00638690 - COU-AA-301 - 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
2. NCT00887198 - COU-AA-302 - 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

Adverse Events of Special Interest (AESI) Predict Response to Abiraterone Acetate (AA): A Retrospective Analysis

Narrative Summary:

AESI, such as hypokalemia and hypomagnesemia, represent on target inhibitory effects of adrenal steroid metabolism by AA. One explanation for differences in AESI includes varying intracellular concentrations of AA in the adrenal gland, which may correlate with intracellular concentrations of AA in tumor cells. Therefore, AESI may correlate with greater tumor concentrations of AA and impact patient outcomes. In the AbiRace study, AESI were correlated with improved rPFS with a trend towards improved time to PSA progression. Notably, black men had higher rates of AESI than white men. We propose a retrospective analysis of COU-AA-301 and 302 to determine if AESI predict response to AA.

Scientific Abstract:

Background
Abiraterone acetate (AA) is a steroid that is transported into cells through solute carrier organic anions (SLCOs) and may vary in the population by intracellular concentration [1]. Adverse events of special interests (AESI), particularly hypokalemia and hypomagnesemia, represent on target inhibitory effects of adrenal steroid metabolism by AA. One potential explanation for differences in variations in AESI may be due to differences in intracellular concentrations of AA in the adrenal gland, which may also correlate with intracellular concentrations of AA within tumor cells. Therefore, AESI may correlate with greater tumor concentrations of abiraterone and impact patient outcomes. In the AbiRace study, AESI were correlated with improved radiographic progression free survival (rPFS) with a trend towards improved time to PSA progression and overall survival (OS) [2]. Black men were noted to have higher rates of AESI than white men in this study.

Objective
To determine if AESI predict response to AA

Study Design
A retrospective cohort study of patients treated with AA on the COU-AA-301 and COU-AA-302 trials.

Participants
All patients treated on the COU-AA-301 and COU-AA-302 trials.

Main Outcome Measures
Frequency of AESI
Severity of AESI
Response to AA (rPFS, time to PSA progression, OS)

Statistical Analysis

To determine if treatment with abiraterone is correlated with frequency and/or severity of AESI, we will use the Wilcoxon rank sum test to check whether the frequency or severity of AESI is same between two treatment groups. To investigate if the frequency and/or severity of AESI differ by race, we will use the Wilcoxon rank sum test to check whether the frequency or severity of AESI is same between two races. Lastly, to delineate if the presence of AESI correlates with response to AA (PSA progression, rPFS, OS), we will use the logrank test to check whether each time-to-event outcome is same between patients with AESI and patients without AESI. In addition, Kaplan-Meier curves will be plotted to visually compare two groups for these time-to-event outcomes.

Brief Project Background and Statement of Project Significance:

Abiraterone acetate (AA) is a steroid that is transported into cells through solute carrier organic anions (SLCOs) and may vary in the population by intracellular concentration.[1] Adverse events of special interests (AESI), particularly hypokalemia and hypomagnesemia, represent on target inhibitory effects of adrenal steroid metabolism by AA. One potential explanation for differences in variations in AESI may be due to differences in intracellular concentrations of AA in the adrenal gland, which may also correlate with intracellular concentrations of AA within tumor cells. Therefore, AESI may correlate with greater tumor concentrations of abiraterone and impact patient outcomes. In the AbiRace study, AESI were correlated with improved radiographic progression free survival (rPFS) with a trend towards improved time to PSA progression and overall survival (OS).[2] Black men were noted to have higher rates of AESI than white men in this study (34% vs 22%). We propose a retrospective analysis of the patients treated with AA in the COU-AA-301 and COU-AA-302 trials to determine if AESI predict response to AA. In addition, we would compare differences in AESI by race. This work could reveal that the presence of AESI may serve as a biomarker for response to AA, and if so, may predict which patients would benefit combination therapy to ensure disease control. This work would also further analyze differences in AESI by race.

Specific Aims of the Project:

Aim 1: Determine if treatment with abiraterone is correlated with frequency and/or severity of AESI
Aim 2: Determine if the frequency and/or severity of AESI differ by race
Aim 3: Determine if the presence of AESI correlates with response to abiraterone (PSA progression, rPFS, OS)

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
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:

Data source – COU-AA-301 and COU-AA-302 via the YODA Project

Inclusion/Exclusion Criteria
Inclusion: Patients treated in the COU-AA-301 and COU-AA-302 trials who have adverse events reported
Exclusion: As per the COU-AA-301 and COU-AA-302 trials

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

Correlation between AESI and response to AA with response defined in terms of radiograph progression free survival, time to PSA progression, and overall survival.

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

The presence of AESI – particularly, hypokalemia (K<3.5) and hypomagnesemia (Mg <1.7)

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

Self-reported race

Statistical Analysis Plan:

To determine if treatment with abiraterone is correlated with frequency and/or severity of AESI, we will use the Wilcoxon rank sum test to check whether the frequency or severity of AESI is same between two treatment groups. To investigate if the frequency and/or severity of AESI differ by race, we will use the Wilcoxon rank sum test to check whether the frequency or severity of AESI is same between two races. Lastly, to delineate if the presence of AESI correlates with response to AA (PSA progression, rPFS, OS), we will use the logrank test to check whether each time-to-event outcome is same between patients with AESI and patients without AESI. In addition, Kaplan-Meier curves will be plotted to visually compare two groups for these time-to-event outcomes.
Software Used:
Python

Project Timeline:

Project start date – Nov 31, 2021. Analysis of the data by Jan 20, 2021. Abstract completion by Feb 17, 2022 for submission to ASCO. Manuscript drafted and submitted for publication by June 30, 2022. Data results reported back to YODA Project by June 30, 2022.

Dissemination Plan:

Submission to ASCO 2022. Suitable journals including Journal of Clinical Oncology; Prostate Cancer and Prostatic Diseases; Clinical Genitourinary Cancer

Bibliography:

1. Mostaghel EA, Eunpi C, Zhang A, et al. Association of Tissue Abiraterone Levels and SLCO Genotype with Intraprostatic Steroids and Pathologic Response in Men with High-Risk Localized Prostate Cancer Clin Cancer Res; 23(16); 4592–601. 2017 AACR.
2. George DJ, Heath EI, Sartor AO, et al. Abi Race: A prospective, multicenter study of black (B) and white (W) patients (pts) with metastatic castrate resistant prostate cancer (mCRPC) treated with abiraterone acetate and prednisone (AAP). Journal of Clinical Oncology 36, no. 18_suppl

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; }