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General Information

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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)
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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

Impact of statins on outcomes in patients with castration resistant prostate cancer treated with abiraterone

Narrative Summary:
Statins (inhibitors of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase) are a group of drugs used to treat lipid disorders and the most common drug worldwide use to prevent cardiovascular disease. Several studies have shown that statins inhibit growth of a tumor, invasion and metastasis formation (Chiang et al., 2015). Overall, the use of statins in prostate cancer after diagnosis has been associated with a decreased risk in mortality,Although the association of statins and prostate cancer has been widely study (Raval et al., 2016) the effectiveness of statins in patients with castration resistant prostate cancer (CRPC) treated with abiraterone has yet to be defined.

Scientific Abstract:
Background:Statins used to treat lipid disorders and to prevent cardiovascular disease. Several studies have shown that statins inhibit growth of a tumor, invasion and metastasis formation. Specifically in prostate cancer, in vitro-studies have shown statins could inhibit proliferation of castration-resistant prostate cancer (CRPC) cells. Although the association of statins and prostate cancer has been widely study the effectiveness of statins in patients with castration resistant prostate cancer (CRPC) treated with abiraterone has yet to be defined.
Primary Objective:
Evaluate the effect of statins on overall survival (OS) in patients with CRPC treated with abiraterone

Study Design
We will conduct a pooled retrospective analysis of patients with CRPC treated on trials with abiraterone, receiving or not statins. Patient inclusion criteria will include diagnosis of castration-resistant prostate cancer of any histological subtype, excluding patients who did not receive at least one dose of the study treatment or have no information about concomitant medication.

Participants
mCRPC treated with abiraterone in the clinical trials NCT00887198 and NCT00638690

Main Outcome Measure
OS will be defined as the time from initiation of therapy to death from any cause.

Analytical Methods
Variables will be summarized as number (%) of patients or median (range) of values. To identify imbalances between the groups, baseline characteristics will be compared between groups. Categorical variables will be compared using a Chi-square test and continuous variables will

Brief Project Background and Statement of Project Significance:
Background and Rationale:
Statins (inhibitors of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase) are a group of drugs used to treat lipid disorders and the most common drug worldwide use to prevent cardiovascular disease (Karmali et al., 2016). Several studies have shown that statins inhibit growth of a tumor, invasion and metastasis formation (Chiang et al., 2015). They block the production of isoprenoids, required for protein modifications. They also contribute to the reduction in the expression of vascular endothelial growth factor, sensitize tumor cells to NK cell activity, and modify the body inflammatory response (Bjarnadottir et al., 2015; Chan et al., 2003).
Currently, most information on the effects of statins on the risk of developing cancer is obtained from observational studies (Yu et al., 2014). The studies have different results depending on the location of cancer (Cardwell et al., 2014; Manthravadi et al., 2016). The protective effect of statins has been observed in different for different tumor types including prostate cancer, stomach cancer, or hepatocellular carcinoma (Manthravadi et al., 2016; Tan et al., 2016; Zhou et al., 2016)
Specifically in prostate cancer, in vitro-studies have shown statins could inhibit proliferation of castration-resistant prostate cancer (CRPC) cells (Furuya et al., 2016). There is persistence on these cells of intratumoral androgens originated from cholesterol by HMG-CoA. The inhibition of this enzyme results on decreased in vitro tumoral growth, limiting the endogenous supply of cholesterol. Additionally, simvastatin has been shown to inhibit prostate cancer micrometastases regulating various cellular functions (Liao and Laufs, 2005) such as the as the inhibition of integrin ?v?3 (prostate cancer cell integrin) activity or the suppression of interaction between ?v?3 with endothelial

ICAM-1 (Belal Al-Husein, 2013). A Danish study showed that long-term use of statins may help to reduce cancer-related mortality by 15% (Nielsen et al., 2012). A recent metaanalysis (Yang Meng, 2016) of 13 studies that enrolled 100,536 participants showed that prediagnostic and postdiagnostic statin use had a significantly lower risk of both all-cause mortality and prostate cancer-specific mortality (prediagnostic HR 0.56 and 0.53 respectively) (postdiagnostic HR 0.77 and 0.64 respectively). Overall, the use of statins in prostate cancer after diagnosis has been associated with a decreased risk in mortality, and the effect seems to be stronger in patients who used statins before diagnosis (Yu et al., 2014).
Although the association of statins and prostate cancer has been widely study (Raval et al., 2016) the effectiveness of statins in patients with castration resistant prostate cancer (CRPC) treated with abiraterone has yet to be defined.

Specific Aims of the Project:
Primary Objective:
1. Evaluate the effect of statins on overall survival (OS) in patients with CRPC treated with abiraterone
Secondary Objectives:
1. Evaluate the effect of statins on progressive free survival (PFS)
2. Evaluate the effect of statins on response rates defined by RECIST criteria
3. Evaluate the incidence of adverse effects between statins users and non-users
4. Evaluate the effect of statins on OS y PFS in different subgroups of patients:
- Patients without any cardiovascular risk factor
- Patients with 2 or more cardiovascular risk factors
- Patients with or without any cardiac event
Primary Endpoint:
1. OS will be defined as the time from initiation of therapy to death from any cause.
Secondary Endpoints:
1. PSA response rate (defined as the proportion of patients with a decrease of ?50% in the PSA concentration from the pretreatment baseline PSA value, which was confirmed after ?4 weeks by an additional PSA evaluation)
2. Radiographic evidence of progression-free survival according to Response Evaluation Criteria in Solid Tumors [RECIST]
a. Complete response
b. Partial response
c. Stable disease
d. Progressive disease
3. PFS will be defined as the time from initiation of therapy to date of progression or death from any cause

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
Participant-level data meta-analysis
Participant-level data meta-analysis uses only data from YODA Project

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
metastatic Castration resistant Prostate Cancer patients treated within clinicals trials NCT00638690 or NCT00887198

Main Outcome Measure and how it will be categorized/defined for your study:
OS will be defined as the time from initiation of therapy to death from any cause.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
Statins will be the main predictor. Will be categorized as dichotomous variable Yes/no
The main variable will be users versus non-users at baseline similar to other studies in cancer studying the association between statins and cancer (Mckay et al. European Journal of Cancer 52 (2016) 155e162)

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
age, sex, race, BMI, Hypertension, sites of metastasis, opioid use, statin use, statin dose, baseline PSA, best

response,

Statistical Analysis Plan:
Patient characteristics will be summarized descriptively. Variables will be summarized as number (%) of patients or median (range) of values. To identify imbalances between the groups, baseline characteristics will be compared between groups. Categorical variables will be compared using a Chi-square test and continuous variables will be compared using a two-sided t-test. Distributions of OS and PFS will be calculated using the Kaplan-Meier method. Median OS and PFS along with 95% confidence intervals will be reported. Associations between OS and PFS will be assessed using the log-rank test in univariate analysis or Wald-chi square test from Cox regression in multivariable analysis, adjusted for age, sex, race, BMI, , sites of metastasis, visceral metastases, gleason score, ASI use, statin use, baseline PSA

Project Timeline:
Start day 12/15/2016
Analysis 01/15/2017
Abstract 02/15/2017
Publication 06/15/2017

Dissemination Plan:
Target audience
Urologists, medical oncologists, radiotherapists, and scientists.
Study manuscript expected: Original paper to be published in a first quartile (Q1) journal such as European Urology or European Journal of Cancer.

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