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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?: No external grants or funds are being used to support this research.
How did you learn about the YODA Project?: Scientific Publication

Conflict of Interest

https://yoda.yale.edu/system/files/sv_6m4tghhxg7w7uxe-r_2f2754j4obsomou.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

1. NCT01715285 - 212082PCR3011 - A Randomized, Double-blind, Comparative Study of Abiraterone Acetate Plus Low-Dose Prednisone Plus Androgen Deprivation Therapy (ADT) Versus ADT Alone in Newly Diagnosed Subjects With High-Risk, Metastatic Hormone-naive Prostate Cancer (mHNPC)

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

Research Proposal

Project Title

Progression Free Survival and Mutation Landscape between Eastern and Western de novo Metastatic Prostate Cancer

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Narrative Summary:

Prostate cancer is a malignancy with huge difference in incidence and presentation globally. PSA screen significant influences the prevalence of de novo metastatic prostate cancer (dnmPC) with only 10% in the western countries but 2/3 in China. Whether PSA screen is associated with a more aggressive phenotype and genotype of dnmPC remains unknown. In the current project, we plan to evaluate the disease characteristics and treatment outcomes between Asian and Western participants from the LATTITUDE trial. Genomic landscape will also be compared using separate databases. Better understanding of the heterogeneity of dnmPC between the East and West may improve management globally.

Scientific Abstract:

Background
PSA screen significant influences the prevalence of de novo metastatic prostate cancer (dnmPC) with only 10% in the western countries but 2/3 in China. Retrospective study showed men on androgen deprivation therapy in Japan have less than half the adjusted cancer-specific mortality than those in the United States. We hypothesized that PSA screen may be associated with an aggressive phenotype and genotype of dnmPC which responds less favorable to systemic treatment.

Objective
Using individual patient data from LATTITUDE trial to perform geography-stratified (Asian vs. European/North American) analysis for radiographic progression free survival.

Study Design
A post-hoc analysis of LATTITUDE trial was performed to estimate the distribution of outcomes according to patients' geographic locations. Exploratory analysis includes comparisons of genomic alterations between Asian and Western dnmPC using separate cohorts.

Participants
Men enrolled in LATTITUDE trials. We also analyzed patients in institutional database from China and United states.

Main Outcome Measures
Radiographic progression free survival.

Statistical Analysis
The primary objective of this study is to estimate radiographic progression free survival distribution in Asian and Western patients, as determined by progression based on PCWG2 criteria or death from any cause. Propensity score methods is used to balance the baseline differences between Asian and Western patients.
Differences in genomic alteration between Asian and Western men with de novo metastatic prostate cancer will be performed in two separate cohorts.

Brief Project Background and Statement of Project Significance:

LATTITUDE trial provided level 1 evidence for the efficacy of abiraterone in de novo metastatic prostate cancer (dnmPC). The prevalence of dnmPC, however, is significantly influenced by PSA screen. The probability of dnmPC is only 10% in the United States[1] and nearly two-third in China[2]. Interestingly, men on androgen deprivation therapy in Japan have less than half the adjusted cancer-specific mortality than those in the United States[3]. Therefore, we hypothesized that PSA screen may be associated with an aggressive phenotype and genotype of dnmPC which responds less favorable to systemic treatment. To test the hypothesis, we will use individual patient data from LATTITUDE trial to perform continent-stratified (Asian vs. European/North American) analysis.
Propensity score matching is applied to estimate radiographic progression-free survival in Asian and Western men with dnmPC. Exploratory analysis includes comparisons of genomic alterations between Asian and Western dnmPC using separate cohorts.
Our study, although hypothesis generating, may advance our understanding the disparity of dnmPC between the East and West. The evaluation of genomic landscape of dnmPC across areas with distinct PSA screen pattern may

help to elucidate a biological heterogeneity of dnmPC. Therefore, our findings may complement currently risk stratification in dnmPC and provide a rational for Asian-specific treatment pattern.

Specific Aims of the Project:

Objectives: To explore the radiographic progression free survival and genomic landscape between Asian and Western de novo metastatic prostate cancer.
Hypotheses: PSA screen may be associated with a more aggressive phenotype and genotype of de novo metastatic prostate cancer. The heterogeneity may refine our understanding of de novo metastatic prostate cancer and subsequently improve individualized treatment approach.

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:

Patients enrolled in LATTITUDE trial and treatment outcomes.
Genomic data will be retrieved from Fudan University Shanghai Cancer Center (Chinese patients).

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

This geography-stratified (Asian vs. European/North American) will evaluate radiographic progression-free survival in Asian and Western men with de novo metastatic prostate cancer.
Secondary end points included PSA response, overall survival and safety.

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

Geographic location of participants (Asian vs. European/North American), Clinicopathological variables as age, body mass index, Gleason score, tumor stage, performance of status, site of metastases, PSA, medication, comorbidity, et al.

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

Race (White, African American, Asian, other)

Statistical Analysis Plan:

The primary objective of this study is to estimate radiographic progression free survival distribution in Asian and Western patients, as determined by progression based on PCWG2 criteria or death from any cause. Propensity score methods is used to balance the baseline differences between Asian and Western patients.
Differences in genomic alteration between Asian and Western men with de novo metastatic prostate cancer will be performed in two separate cohorts.
Software Used:
RStudio
Project Timeline:

We anticipated start the project by the end of this year, finish the analysis before 1 Jun 2022, and draft the manuscript for submission before 1 Dec 2022.

Dissemination Plan:

We plan to submit the project to well-known meetings (GU-ASCO, ESMO) and journals (European Urology, Annals of Oncology)

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Bibliography:

1 Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER Research Data, 9 Registries, Nov 2020 Sub (1975-2018) - Linked To County Attributes - Time Dependent (1990-2018) Income/Rurality, 1969-2019 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2021, based on the November 2020 submission.
2 Zhu, Y. et al. Epidemiology and genomics of prostate cancer in Asian men. Nature Reviews Urology 18, 282-301, doi:10.1038/s41585-021-00442-8 (2021).
3 Cooperberg, M. R., Hinotsu, S., Namiki, M., Carroll, P. R. & Akaza, H. Trans-Pacific variation in outcomes for men treated with primary androgen-deprivation therapy (ADT) for prostate cancer. BJU International 117, 102-109, doi:10.1111/bju.12937 (2016).

Supplementary Material:

https://yoda.yale.edu/sites/default/files/response_to_yoda.pdf

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