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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)

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_2022_ashley_hopkins.pdf
https://yoda.yale.edu/system/files/coi_form_ms.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. 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
3. NCT01343277 - ET743-SAR-3007 - A Study of Trabectedin or Dacarbazine for the Treatment of Patients With Advanced Liposarcoma or Leiomyosarcoma
4. 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

Summarising the therapeutic and adverse effects of anticancer medicines according to race and sex: pooled analysis of clinical trials

Narrative Summary:

Over the last decade there has been substantial advancement in the treatment of solid tumours, including the introduction of immune checkpoint inhibitors, targeted therapies, and novel chemotherapies. However, response and toxicity to many of these medicines remains highly unpredictable. Two factors urgently requiring investigation are potential differences in therapeutic and adverse effects of contemporary anticancer medicines according to race and sex.

Scientific Abstract:

Background:
Two factors urgently requiring investigation are potential differences in therapeutic and adverse effects of contemporary anticancer medicines according to race and sex.
Objectives:
This study aims to summarise the key adverse effects and therapeutic outcomes of anticancer medicines registered by the FDA in the past decade according to race and sex.
Study Design and Participants:
Our research team has systematically collated information on anticancer medicines registered by the United States, Food and Drug Administration (FDA) in the past decade for the treatment of solid tumours. The key clinical trials which backbone the registration of these medicines was then collated from the product information sheets prepared by the sponsoring pharmaceutical company. The eligibility for individual participant data sharing of these clinical trials was then established with the sponsoring pharmaceutical company via email.
This study will pool available individual participant data from eligible for sharing phase 2 and 3 clinical trials to characterize the adverse event and therapeutic response profiles of contemporary treatment options for solid tumours according to race and sex. Analyses will utilise per-protocol populations and all study arms transparently shared. Summaries of trial sponsors not willing to participate individual participant data to this study will be published.
Main Outcome Measure:
Individual participant data are required for adverse event and therapeutic outcomes including clinician/patient reported adverse effects, and response, progression-free survival/ disease-free survival, and where available overall survival. The coprimary predictors of adverse event and therapeutic outcomes to be evaluated in this study will be race and sex.
Statistical Analysis:
Crude associations for adverse event will be reported based cohort frequencies of treatment induced grade ? 1, grade ? 3, and sentinel (e.g., drug cessation, hospitalisation, or death) adverse events according to race and sex. Crude associations for therapeutic outcomes will be reported based upon Kaplan Meier estimates of median time to events (e.g., median time to progression-free survival, disease-free survival, and overall survival) according to race and sex. Cox proportional hazard analysis will be used to assess the association between race/sex and the time to

adverse events/ survival time. Associations will be reported as hazard ratios with 95% confidence intervals.

Brief Project Background and Statement of Project Significance:

Over the last decade there has been substantial advancement in the treatment of solid tumours, including the introduction of immune checkpoint inhibitors, targeted therapies, and novel chemotherapies. However, response and toxicity to many of these medicines remains highly unpredictable. Two factors urgently requiring investigation are potential differences in therapeutic and adverse effects of contemporary anticancer medicines according to race and sex [1, 2].

Race differences are associated with a significant health disparity gap. For many common malignancies there are substantial differences in incidences according to race, while race is a phenotype for differences in genetic and tumour biology factors. Further there are inequities in drug development processes (e.g., in reporting and representation) and it is unclear if this is resulting in systematic disparities in anticancer treatment therapeutic and adverse effects [1, 3-10]. Science is also becoming increasingly aware that sex is an important modifier of health, disease and medicine efficacy [11]; however, the availability of quality information to inform sex (or gender) differences in outcomes from anticancer medicines are currently limited [2, 12]. This project will bring together individual participant data from key clinical trials to summarise the therapeutic and adverse effects of contemporary anticancer medicines according to race and sex. Being able to appraise the expected response and adverse effect profile of anticancer treatments according to racial and sex differences will enable patients and clinicians to make better patient-centred decisions.

Specifically, this project will utilise data available via Janssen's data sharing policy and the data sharing policy of other pharmaceutical companies to summarise the therapeutic and adverse effects of contemporary anticancer medicines according to race and sex. Our research team has systematically collated information on anticancer medicines registered by the United States, Food and Drug Administration (FDA) in the past decade for the treatment of solid tumours. The key clinical trials which backbone the registration of these medicines was then collated from the product information sheets prepared by the sponsoring pharmaceutical company. The eligibility for individual participant data sharing of these clinical trials was then established with the sponsoring pharmaceutical company via email. This study will pool individual participant data from eligible for sharing phase 2 and 3 clinical trials to characterize the adverse event and therapeutic response profiles of contemporary treatment options for solid tumours according to race and sex. Summaries of trial sponsors not willing to participate individual participant data to this study will be published (noting all data requested in the study has previously been indicated as eligible for sharing).

Specific Aims of the Project:

The hypothesis of this research is that if the pharmaceutical industry has functioning and timely data transparency policy, then it will be leverageable to provide information summarising the therapeutic and adverse effects of contemporary anticancer medicines according to race and sex.
Specifically, this study aims to:
1. Summarise the key adverse effects of anticancer medicines registered by the FDA in the past decade according to race and sex.
2. Summarise the key therapeutic outcomes of anticancer medicine registered by the FDA in the past decade according to race and sex.

What is the purpose of the analysis being proposed? Please select all that apply.
Participant-level data meta-analysis
Participant-level data meta-analysis pooling data from YODA Project with other additional data sources

Research Methods

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

The research team has systematically collated information on anticancer medicines registered by the FDA in the past decade for the treatment of solid tumours. The key clinical trials which backbone the registration of these medicines was then collated from the product information sheets prepared by the sponsoring pharmaceutical company. The eligibility for individual participant data sharing of these clinical trials was then established with the

sponsoring pharmaceutical company via email. This study will pool individual participant data from eligible for sharing phase 2 and 3 clinical trials to characterize the adverse event and therapeutic response profiles of contemporary treatment options for solid tumours according to race and sex. Analyses will utilise per-protocol populations and all study arms transparently shared. Information on clinical trials which are not transparently shared by the industry sponsor will be highlighted prior to analysis.

Please see supplementary file 1 for more details.

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

Individual participant data are required for adverse event and therapeutic outcomes including clinician/patient reported adverse effects according to grade or sentinel events, and response, progression-free survival/ disease-free survival, and where available overall survival. Event flag, censoring and time after treatment initiation data will be calculated for these outcomes.

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

The coprimary predictors of adverse event and therapeutic outcomes to be evaluated in this study will be race and sex. Race is commonly collected within clinical oncology trials, often categorised within individual participant data as white, Asian, black, and other. Sex data is most commonly within clinical oncology trials as male versus female. This study will provide summarisation of race, sex and gender data which has been recorded during trial execution.

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

Where available summaries of available ethnicity, socioeconomic, geographical region, patient reported financial statuses, patient-reported outcomes, concomitant medicine, and medical history data according to race and sex will be reported. Exploratory analyses adjusted for age, weight, performance status, cancer type, stage of disease, and line of therapy will be conducted – missing data will be summarised. Individual participant data on the above outcome, covariate and adjustment data will be required.

Statistical Analysis Plan:

Primary and Secondary Endpoints:
1. Summarise the key adverse effects of anticancer medicine registered by the FDA in the past decade according to race and sex. Data are required on clinician/patient reported adverse effects according to grade or sentinel events.
2. Summarise the key therapeutic outcomes of anticancer medicine registered by the FDA in the past decade according to race and sex. Data are required for progression-free survival/ disease-free survival, and where available overall survival.

Primary predictor and sensitivity analyses:
The coprimary predictors of adverse event and therapeutic outcomes to be evaluated in this study will be race and sex. Race is commonly collected within clinical oncology trials, often categorised within individual participant data as white, Asian, black, and other. Sex data is most commonly within clinical oncology trials as male versus female. This study will provide summarisation of race, sex and gender data which has been recorded during trial execution. Where available summaries of available ethnicity, socioeconomic, geographical region, patient reported financial statuses, patient-reported outcomes, concomitant medicine, and medical history data according to race and sex will be reported. Exploratory analyses adjusted for age, weight, performance status, cancer type, stage of disease, and line of therapy will be conducted – missing data will be summarised.

Statistical analysis:
Crude associations for adverse event will be reported based cohort frequencies of treatment induced grade ? 1, grade ? 3, and sentinel (e.g., drug cessation, hospitalisation, or death) adverse events according to race and sex. Crude associations for therapeutic outcomes will be reported based upon Kaplan Meier estimates of median time to events (e.g., median time to progression-free survival, disease-free survival, and overall survival) according to race and sex.
Cox proportional hazard analysis will be used to assess the association between race/sex and the time to adverse events/ survival time. Associations will be reported as hazard ratios with 95% confidence intervals (CI). Adjusting

for between treatment and trial differences, this study will utilise a 2-stage individual-participant data meta-analysis approach. Whereby HRs and 95% CIs will initially be estimated individually for each trial arm. HRs and 95%CI will then be pooled and presented in forest plot according to conventional meta-analysis techniques. P values <0.05 will be considered statistically significant. Analyses based upon therapeutic classes will also be conducted to enable a better understanding of whether the relationships identified are specific to certain classes of treatment or are common to contemporary treatment options. As this analysis is primarily hypothesis generating and will require subsequent validation of any findings, no formal adjustment for multiple testing is intended. However, this limitation will be clearly stated in any publications of results. As it is expected that < 5% of race and sex data will be missing, a complete case analysis is planned. Exploratory analyses adjusted for available age, weight, performance status, cancer type, stage of disease, and line of therapy data will be conducted. Summary statistics of available ethnicity, socioeconomic, geographical region, patient reported financial statuses, patient-reported outcomes, concomitant medicine, and medical history data according to race and sex will also be reported.

Power:
Based upon a 30% incidence of toxicity, a sample size of approximately 600 is required to detect a predictor (with a 10% frequency within the population) associated with a two-fold risk (?=0.05 with 80% power). Based upon an event rate of 40% during trial follow-up (e.g. for progression), approximately 450 participants are required for 80% power to detect a predictor (with a 10% frequency within the population) associated with a two-fold hazard of the event (?=0.05).
Software Used:
R

Project Timeline:

Target Analysis Start Date: 7/1/22
Estimated Analysis Completion Date: 7/1/23
Manuscript Submission: 9/1/23
Reported back to YODA: 1/1/24

Dissemination Plan:

A summary of the proposed research plan will be posted publicly immediately following acceptance of the research proposal. Results of all completed analyses will be published in peer-reviewed international publications and where possible presented at scientific meetings. Manuscript(s) will be targeted primarily to international oncology journals (e.g., British Journal of Cancer, International Journal of Cancer) and will be submitted as soon as possible following completion of the requisite analyses. As a related perspective piece to the scientific community (independent on the planned meta-analyses): At 9-months from initial proposal submission, summaries of trial sponsors not willing (or unable) to participate individual participant data to this study will collated with the aim to publish at 12-months (noting all data requested in the study has previously been indicated as within scope for sharing and would be considered for sharing upon receipt of a full proposal). The time from proposal submission to data access will be included in the publication, as well as a summary of the scope of data provided by each sponsor.

Bibliography:

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Supplementary Material:

https://yoda.yale.edu/sites/default/files/supplementary_file_1.pdf
https://yoda.yale.edu/sites/default/files/quality_control_yoda.pdf

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