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How did you learn about the YODA Project?: Data Holder (Company)

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_coi_forms_0.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

Systematic review and individual participant data meta-analyses of systemic treatments for hormone-sensitive metastatic prostate cancer

Narrative Summary:

Treatment for men with metastatic, hormone-sensitive prostate cancer had been hormone therapy alone; recent clinical trials began testing promising treatments. We will bring together information from these trials to quickly and reliably evaluate which treatments work best for which men. We will use information from relevant trials as part of a collaborative, worldwide data-sharing effort, which we will update regularly to keep results current. We aim to find out which treatment(s) improve survival and identify those men who benefit more (or less) from the individual treatments.

Scientific Abstract:

Background For decades, standard care for men with metastatic, hormone-sensitive prostate cancer (mHSPC) has been hormone therapy. Addition of docetaxel has been shown to improve survival and recently our systematic review and network meta-analysis (NMA) using aggregate data suggested that abiraterone plus androgen deprivation therapy (ADT) was the optimal treatment for mHSPC, however, some uncertainties remain.
Objective We aim to determine the effect of 1) docetaxel, 2) abiraterone acetate plus prednisolone/prednisone, 3) zoledronic acid plus ADT versus ADT alone, and examine if the effect differs depending on men's characteristics (e.g. volume of disease, risk group, etc.). Secondly, we will evaluate the relative effectiveness of available systemic treatments plus ADT and ADT alone.
Study Design Individual Participant Data meta-analysis and NMA.
Participants Men with mHSPC.
Main Outcome Measure(s) Overall survival, Prostate cancer-specific survival
Statistical Analysis The analyses will be performed on an intention-to-treat basis. For time-to-event data, a hazard ratio with corresponding 95% confidence intervals will be calculated for each trial individually and combined across all using the fixed-effect inverse-variance meta-analysis; random-effects models will be fitted as sensitivity analyses. Statistical heterogeneity will be assessed using $?^2$ tests and I^2 statistic. Relative effectiveness of included treatments will be formally compared in NMA (frequentist and Bayesian approaches). All analyses will be performed using Stata software (version 15.1).

Brief Project Background and Statement of Project Significance:

Prostate cancer is a major health problem worldwide and is the second most common cancer in men. For decades, standard of care for men with locally advanced or metastatic hormone-sensitive prostate cancer (mHSPC) has been androgen deprivation therapy (ADT). However, recent data from the STAMPEDE trial indicated that the median failure-free survival time following ADT is in the region of 11 months. Although the vast majority of men respond to ADT it is not curative, and disease recurs in virtually all patients (1). Therefore, a number of randomised controlled trials (RCTs) have evaluated, or are currently evaluating, a variety of systemic therapies, including bisphosphonates (2), cytotoxic chemotherapy (3), radium-223 and new hormone therapies (4), including abiraterone and enzalutamide.
Given that not all trials have or will produce definitive results, there is a clear need for synthesis. Therefore, we are

conducting a series of systematic reviews and meta-analyses following the Framework for Adaptive Meta-analysis (FAME), a prospective approach taking all relevant trials into account. We have already reported syntheses of the effects of docetaxel, bisphosphonates and abiraterone in mHSPC (5, 6). These separate, pairwise meta-analyses, using aggregate data, demonstrated improved survival and progression outcomes when either docetaxel or abiraterone, but not bisphosphonates, were added to standard of care.
Few trials have set out to directly compare the different treatments. In particular, since results of trials and systematic reviews of docetaxel and abiraterone reported survival benefits of each treatment, there has been a clear need to reliably evaluate which treatment is more effective and in which men. Without direct comparisons available, network meta-analysis may provide the only reliable opportunity to compare their relative effectiveness. Our prior network meta-analysis using aggregate data to compare the relative effectiveness of treatments for mHSPC (7) suggested that abiraterone in combination with ADT was the optimal treatment, however some uncertainties remained that may be better addressed using IPD.

Specific Aims of the Project:

The primary aims are, in men with mHSPC, to:
1. Estimate the effect of androgen deprivation therapy (ADT) plus docetaxel (DOC) relative to ADT alone, updating and calibrating the results of our prior review of aggregate data.
a. In particular, we will use the individual patient data (IPD) to assess whether the effect of DOC varies across different types of men.
2. Estimate the effect of ADT plus abiraterone acetate plus prednisolone/prednisone (AAP) relative to ADT alone, updating and calibrating the results of our prior review of aggregate data using the IPD to assess whether the effect of AAP varies across different types of men.
3. Estimate the effect of ADT plus zoledronic acid (ZA) to ADT alone, updating and calibrating the results of our prior review of aggregate data.
4. To perform an IPD network meta-analysis, to assess the relative effectiveness of treatments used in combination with ADT (and ADT alone), notably:
• Celecoxib
• ZA
• Celecoxib and ZA
• DOC
• ZA + DOC
• AAP

We will also update and calibrate the results obtained in the prior aggregate data network meta-analysis (7) and identify whether any treatment benefits observed are robust in pre-specified subgroups (see PROSPERO CRD42019140591).

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
Confirm or validate previously conducted research on treatment effectiveness
Participant-level data meta-analysis
Participant-level data meta-analysis pooling data from YODA Project with other additional data sources
Develop or refine statistical methods

Research Methods

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

Trials have been systematically identified through routine searches conducted during the course of the STOPCAP project (5-7) including electronic databases of medical literature (MEDLINE, EMBASE), trial registers (Cochrane Central Register of Controlled Trials, ClinicalTrials.gov), and conference proceedings. Additionally, we hand-search the bibliographies of trial reports and review articles.

Eligible trials are appropriately randomised, compare ADT alone with ADT in combination with any of the additional agents listed above and randomise men with mHSPC, starting or responding to first-line hormone therapy were co-administered on the experimental arm only, or additional agent(s), e.g. docetaxel, were co-administered in both

arms. The data to be pooled with LATITUDE will come from the following trials: STAMPEDE (arms A, B, C, D, E, F & G)(NCT00268476), CHAARTED (NCT00309985), CALGB 90202 (NCT00079001), GETUG15 (NCT00104715), ZAPCA (NCT00685646), and ZABATON-PC (UMIN000001137) (see Table 1 of the attached protocol).

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

Our primary outcomes are as follows:
• Overall survival – defined as the time from randomisation until death by any cause. Patients remaining alive and those lost to follow-up will be censored on the date of the last follow-up.
• Prostate cancer-specific survival – defined as the time from randomisation until death from prostate cancer. Deaths from unknown causes or from any cause after progression will also be included, because it is assumed that prostate cancer is the most likely cause of death in these cases. Patients remaining alive, as well as those who die of non-prostate cancer causes (including treatment-related deaths, second primary cancers etc) and those lost to follow-up, will be censored on the date of the last follow-up.

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

For analyses by patient-level characteristics, we will aim to categorise below variables as follows:
• Age [years] (continuous)
• Performance Status (0 / 1 / 2+)
• Clinical T stage (<3 / 3 / 4)
• Nodal involvement (N0 / N1 / Nx)
• Gleason Score (<8 / >=8, and as a continuous)
• Type of biopsy (No biopsy/ TURP or TRUS / transperineal / template)
• Baseline Alkaline phosphatase (continuous)
• Timing of entry into trials (De novo M1 disease/ progressed to M1 disease after prior diagnosis with localised disease)
• Lymph node disease only (Yes / No)
• Location of metastases (bone only, visceral only, bone and visceral)
• Number of bone metastases (continuous) - for patients with bone mets only
• Volume (CHAARTED definition*) (High / Low)
• Risk (LATITUDE definition**) (High / Low)
• Pain-related to prostate cancer (Yes / No)
• BMI [kg/m2] (continuous)
*High volume defined as any visceral metastasis and / or at least 4 bone metastases (8)
**High risk defined as any 2 of Gleason score >=8; at least 3 bone lesions; measurable visceral metastasis (9)

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

• Whether excluded from the original trial analysis
• Reason for the exclusion (ineligibility, other)

Statistical Analysis Plan:

Updated individual participant data from all relevant, randomised trials will be included. Analyses will be performed on an intention-to-treat basis. For the primary analyses for each of the three pairwise treatment comparisons, i.e.
1. ADT + docetaxel vs ADT
2. ADT + abiraterone acetate vs ADT
3. ADT + zoledronic acid vs ADT

Cox regression models on censored time-to-event data will be used to produce hazard ratio estimates of the effect of treatment. A hazard ratio will be calculated for each trial individually, and will then be combined across all trials using the fixed-effect inverse-variance meta-analysis model (10). Chi-squared tests for heterogeneity and the I2 statistic (11) will be performed to assess statistical heterogeneity between the trials being combined. Appropriate random-effects models (12-15) will be performed as sensitivity analyses. Results will also be presented as absolute differences at relevant time points calculated from the hazard ratio and baseline event rate for patients randomised to control. Confidence intervals for the absolute differences will be similarly calculated from the baseline event rate and the hazard ratio at the 95% CI boundary values.

For dichotomous outcomes such as toxicity, the number of events and numbers of patients will be used to calculate Peto odds ratio estimates of treatment effect (10). These odds ratios will be generated for individual trials and pooled across trials, using the fixed-effect model (10) and represent the odds of an event on treatment versus that on control.

Providing there are sufficient data available, we will investigate whether any observed treatment effect is consistent across well-defined patient subgroups (see section Main Predictors) based on the primary outcome of survival. Again, Cox regressions will be fitted within each trial individually, with the models including the treatment, subgroup, and a treatment-by-subgroup interaction term. Where there are more than two subgroups (e.g. performance status and nodal involvement), the linearity of effect across the subgroups is assumed to estimate a single coefficient each for the subgroup and for the interaction. Where any subgroups have insufficient numbers of participants, they will be combined. The interaction coefficients (i.e. the log of the ratio of HRs in the two subgroups, or the log of the change in HR per subgroup if more than two subgroups) will be pooled across trials using the fixed-effect model, with random-effects analyses performed for sensitivity. All p-values will be two-sided.
Network meta-analysis (16, 17), taking advantage of direct and indirect comparisons, is necessary to determine reliably which is the optimal treatment(s) for men with mHSPC. To date, the only direct comparison of individual systemic treatments, in combination with ADT, is from the STAMPEDE trial (18). Therefore, we aim to incorporate IPD collected for the pairwise comparisons described above into a full network meta-analysis, to assess the optimal systemic treatments for men with mHSPC. The design of this analysis model will ensure that the limitations and complexities identified in our prior network meta-analysis are appropriately addressed.
Software Used:
STATA
Project Timeline:

Proposed Timelines
1. Pairwise IPD meta-analyses
Collate, check and verify incoming data (Winter 2019 - Spring 2020)
Finalise the statistical analysis plan (Spring 2020)
Analyse individual trials & complete the IPD meta-analysis (Spring / Summer 2020)
Report preliminary results to Collaborative Group (Autumn 2020)
Publish and present final results (Autumn 2020)

2. Network IPD meta-analysis
Collate, check and verify incoming data (for trials outside the scope of the pairwise IPD meta-analyses) (Spring 2020)
Analyse individual trials (Summer 2020)
Complete the network meta-analysis (Autumn 2020)
Report preliminary results to Collaborative Group (Winter 2020)
Publish and present final results (Spring 2021)

The timelines have been amended in coparison to those in the attached protocol.

Dissemination Plan:

The authorship of the systematic review manuscript will comprise the Project Management Group, International Advisory Group, representatives from the included trials and Patient Research Partners. Author names will be listed “for the STOPCAP Collaborative Group”. We aim to present the findings at an appropriate international meeting (ESMO, ASCO or ASCO GU) and publish the reviews, irrespective of the findings, in a peer-reviewed journal - the aimed journals are The Lancet / The Lancet Oncology. Manuscripts will be drafted, circulated to the Collaborative Group for comment prior to being submitted for publication.

Initial results of the IPD review will be presented to a closed meeting of the Collaborative Group.

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Supplementary Material:

https://yoda.yale.edu/sites/default/files/stopcap_m1_ipdnma_protocol_v1.0_16may2019_final.docx