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SCOPUS ID:
Requires Data Access? No

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/wp-content/uploads/2024/04/SV_57KskaKADT3U9Aq-R_2QKzMrMc6zRs3p5.pdf
https://yoda.yale.edu/wp-content/uploads/2024/04/SV_57KskaKADT3U9Aq-R_2Vjg8hEnN3c3JYZ.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. 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
2. NCT01695135 - ABI-PRO-3001 - A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate (JNJ-212082) Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy
3. NCT02257736 - 56021927PCR3001 - A Phase 3 Randomized, Placebo-controlled Double-blind Study of JNJ-56021927 in Combination With Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone in Subjects With Chemotherapy-naive Metastatic Castration-resistant Prostate Cancer (mCRPC)

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

Research Proposal

Project Title

Evaluation of Bellmunt Risk Score as a prognostic score in metastatic castration-resistant prostate cance

Narrative Summary:

Metastatic castration-resistant prostate cancer (mCRPC) is an aggressive, incurable and often lethal condition. It is characterized by two factors: A prostate cancer which has spread beyond the prostate, forming so-called metastases. Moreover, the cancer no longer responds to anti-hormonal treatment, requiring further therapy. In a western population, about 6 in 1000 men suffer from mCRPC and approximately 2 in 1000 men are newly diagnosed per year.

Patients often want information about how long they will survive with this disease given their individual life plans or family and relationship bounds. Therefore, we aim to provide patients and their doctors an easy tool to predict the survival times.

The so-called Bellmunt Risk Score looks at the three factors: overall health status, blood count (hemoglobin) levels, and whether the cancer has spread to the liver. A score of 0 - 3 can quickly be built only from these factors.

In a small study involving 125 men with mCRPC, we already found that the Bellmunt Risk Score could be useful in predicting survival. While men with a score of 0 lived for approximately 4 years, men with scores larger than 2 only lived for about one year. With overall health status collected more accurate, a modified Bellmunt Risk score even improved these predictions. However, we need proof for these findings in studies with larger groups of patients.

We aim at extracting Bellmunt Risk Score and survival times from the data of large controlled studies. We want to discover, if we can confirm our previous findings. This is possible by comparing the survival times of men with each score of 0, 1, 2 and 3 using the established statistical tools "Cox regression analysis" and "Log-Rank analysis". If we find significant differences between these groups, this score could become a valuable tool for doctors and patients, helping them to be informed and make better decisions about treatment.

Scientific Abstract:

In our previous retrospective pilot analysis, the Bellmunt Risk Score as well as a slightly modified Bellmunt Risk Score (described below) provided easy and significant prognostic information in patients with metastatic castration-resistant prostate cancer (mCRPC). Attached Figures 1+2 show the corresponding plots.
Objective: To validate these findings in a large dataset
Study design: Pooled analysis of 4 trials, with each trial also analyzed seperately
Participants: Men with mCRPC
Main Outcome Measure(s): Overall survival (OS)
Statistical Analysis: Kaplan-Meier-method, uni- and multivariate Cox regression analysis, time-dependent Area under the Curve, Concordance indices

Brief Project Background and Statement of Project Significance:

Metastatic castration-resistant prostate cancer (mCRPC) remains a disease of limited prognosis, however, overall survival is subject to individual factors (1). Several prognostic models have been proposed to refine the outcome prediction of men with mCRPC. Risk factors or models previously described include alkaline phosphatase (AP), lactate-dehydrogenase (LDH), Eastern Cooperative

Oncology Group performance status (ECOG PS), Hemoglobin (Hb), Prostate-Specific Antigen (PSA) at mCRPC diagnosis, PSA response to therapy, duration until mCRPC development, and genomic landscape (1-12). However, to date, these models remain marginally used in clinical practice (13). The underlying causes for this are not well understood. However, conducting individual prognostic assessments for each patient could enhance decision-making, especially when considering treatment plans with significant side effects, such as those encountered in the mCRPC context.
The drawbacks of the models published so far may involve their validation in trial cohorts, potentially limiting their applicability in real-world settings. (1,3,8,11,14). Some models include genomic markers or liquid biopsy that are not collected as part of routine diagnostics and may not be included in the standard range of a budgeted physician (2,6,7). If an evaluation of PSA dynamics is necessary, the risk cannot be appraised before the commencement of treatment (4). Additional questionnaires, requirement of counting metastases and ultimately complex calculation formulas from the collected data may prevent utilization of existing risk models (3,13).
Therefore, a risk model, in addition to its prognostic importance, should enable straightforward application and incorporate only routinely assessed values. Several analyses have demonstrated a predictive value of the following factors in mCRPC: ECOG PS, Hb and the presence of liver metastases (3,8,9,15). Furthermore, these can be considered pan-cancer predictive markers 16-18. All three are summarized in the well-known Bellmunt Risk Score, which was initially developed for a different genitourinary cancer entity – urothelial carcinoma (19). Here, the Bellmunt Risk Score is routinely employed including major phase III trials (20,21). Its components (metastatic sites, Hb and ECOG PS) are routinely evaluated in nearly every cancer patient before initiating therapy.

Specific Aims of the Project:

We aim to validate our pilot study findings in the high-quality data of phase III clinical trials. The overall goal is to provide patients and physicians an easy-to-access score allowing for quick survival prediction.

Study Design:

Other

Study Design Explanation:

We plan on both meta-analysis and individual trial analysis, given they cover different treatment lines in mCRPC

What is the purpose of the analysis being proposed? Please select all that apply.

Participant-level data meta-analysis

Meta-analysis using data from the YODA Project and other data sources

Research on clinical prediction or risk prediction

Research Methods

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

Given the trial protocols, all participants should meet the inclusion criteria:

1. ECOG PS at Baseline documented
2. Hemoglobin levels at baseline documented
3. Presence of liver metastasis documented
4. Data on overall survival

There are no exclusion criteria defined.

Additionally to this request, we currently request data of NCT01193257 and NCT01308567 at Vivli (https://vivli.org/). All trial data will be analyzed in the R environment of Vivli.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

The primary endpoint is overall survival (OS) and will be defined as the time from date of random assignment to date of death of any cause or last follow-up.

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

Bellmunt Risk Score: Determined by assigning one point each for

1. ECOG PS ≥1
2. Decreased serum hemoglobin (< 10 g/dL)
3. Presence of liver metastasis.

Patients are then stratified into the respective group of 0 – 3 score points.

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

Modified Bellmunt Risk Score: Determined by the semiquantitative ECOG PS (0 - 5), with one point each added for decreased serum hemoglobin (< 10 g/dL) and the presence of liver metastasis. This results in a score 0 – 7 stratifying the patient cohort.

Further Variables for multivariate risk adjustment:
1. Further sites of metastases
2. Opioid analgesic use (y/n)
3. Measurable disease (y/n)
4. Age
5. LDH (and ULN for LDH)
6. Hemoglobin
7. PSA
8. Alkaline phosphatase
9. Albumin
10. C-reactive protein
11. Race/ethnicity

Statistical Analysis Plan:

The data of the 3 trials will be analyzed alongside NCT01193257 and NCT01308567 in the R environment provided by Vivli.

Fisher’s exact, Mann–Whitney U, and Kruskal–Wallis tests will be applied to perform intergroup comparisons. The overall survival (OS), including 95% confidence intervals will be estimated with the Kaplan–Meier method and compared with log-rank tests. To compare Bellmunt Risk Score groups, baseline patient (age, Body-Mass-Index) and tumor-related parameters (e.g, serum prostate-specific antigen levels, previous primary therapy) on OS, univariate and multiple Cox regressions will be conducted. Independent variables will only be included in the multiple regression if the respective effect is significant in the univariate analysis. Concordance indices and time-dependent Receiver Operating Characteristics will be conducted to test for predictive potential. Statistical analyses will be performed R-Studio via the vivli research environment. All statistical tests will be two-sided, and p-values < 0.05 will be considered significant.

Software Used:

RStudio

Project Timeline:

Expected start of project: 01-SEP-2024
Expected end of Data analysis: 01-DEC-2024
Expected date of manuscript drafted: 01-MAR-2025
Expected date of submission for publication and data results reported bach to the YODA Project: 01-MAY-2025

Dissemination Plan:

The results will be presented at International meetings such as EAU and ESMO congress. The first abstract is planned for EAU in April 2025. Manuscripts will be published open-access aiming at journals like European Urology Oncology

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Supplementary Material:

https://yoda.yale.edu/wp-content/uploads/2024/04/Figure-1.pdf
https://yoda.yale.edu/wp-content/uploads/2024/04/Figure-2.pdf