

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Fatigue, quality of life and metabolic changes in men treated with first-line enzalutamide versus abiraterone plus prednisolone for metastatic castration-resistant prostate cancer (HEAT): a randomised trial protocol
AUTHORS	Kvorning Ternov, Klara; Sønksen, Jens; Fode, Mikkel; Lindberg, Henriette; Kistorp, Caroline; Bisbjerg, Rasmus; Palapattu, Ganesh; Østergren, Peter

VERSION 1 – REVIEW

REVIEWER	Prof Sanjeev Madaan Department of Urology & Nephrology Darent Valley Hospital Dartford UK
REVIEW RETURNED	21-Apr-2019

GENERAL COMMENTS	In this ongoing open-label randomised (1:1) clinical trial, enzalutamide is compared with AAP as first-line treatment for men with mCRPC. The protocol is well written. Main limitation is short follow up of only 12 weeks. Thus, the trial lacks assessment of intermediate and long-term side effects. This has already been acknowledged by the authors.
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REVIEWER	Susan Slovin Memorial Sloan Kettering Cancer Center, USA
REVIEW RETURNED	28-Jun-2019

GENERAL COMMENTS	<p>The authors provide results of an ongoing randomized open label trial assessing side effects associated with the use of first line enzalutamide versus abiraterone for men with metastatic castration sensitive prostate cancer. The primary endpoint was fatigue as assessed using the FACIT-F questionnaire with secondary endpoints to evaluate changes in body composition, glucose metabolism, serum lipids and quality of life. A planned sample is 170 participants with the focus on patients from Denmark.</p> <p>The investigators are endeavoring to provide a “real world” experience regarding how enzalutamide affects the day-to-day functionality of patients compared with abiraterone. However, there is a considerable body of literature that already had looked into this question and therefore, while this trial is ongoing, it is unlikely that it will result in a different toxicity profile than that already published. What have not been previously evaluated</p>
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	<p>though are the concerns about metabolic issues including glucose metabolism and lipid changes.</p> <p>1) Introduction needs to be updated given recent clinical trial results using enzalutamide earlier.</p> <p>2) Response criteria radiologically was defined by PCWG2 not 3. Of note, NaF PET scans have not been a validated modality in PCWG2; these scans have high false positives.</p> <p>3) Given that patients will start ADT, will either enzalutamide or abiraterone be given simultaneously? ADT will definitely change lipid profile, glucose metabolism, and fat distribution but how will the impact of addition of enzalutamide or abiraterone on these markers be assessed if these are all given together. How will timepoints for assessments of these parameters be determined.</p> <p>4) Given that fatigue is the primary endpoint, what will determine whether or not treatment should be stopped and how will it be determined whether it is due to the androgen signaling inhibitor versus the effects of ADT? How reliable will it be to use the FACT analysis to take a patient off the trial and how will these patients be subsequently treated?</p> <p>5) Reference #12 regarding the authors of the Prostate Cancer working group is abbreviated and should be working group 2 not 3. No role for reference #13. A number of relevant references are omitted including that for a "real world" paper on enzalutamide and seizure published in JAMA Oncology. Citations regarding other papers about fatigue and enzalutamide are not included.</p> <p>6) standard measures of glucose metabolism are being used but it would be better served to look at inflammatory cytokines, C reactive protein or aP2.</p>
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VERSION 1 – AUTHOR RESPONSE

Authors' answer to reviewers' comments.

Reviewer: 1

Please leave your comments for the authors below

In this ongoing open-label randomised (1:1) clinical trial, enzalutamide is compared with AAP as first-line treatment for men with mCRPC. The protocol is well written. Main limitation is short follow up of only 12 weeks. Thus, the trial lacks assessment of intermediate and long-term side effects. This has already been acknowledged by the authors.

Authors' answer: Thank you, for reviewing our manuscript and for your summary of our ongoing trial. We agree that this trial is not designed to assess intermediate and long-term side effects. The focus is treatment induced side effects, why we chose a short follow-up to avoid assessing symptoms of progressive disease.

Reviewer: 2

Please leave your comments for the authors below

The authors provide results of an ongoing randomized open label trial assessing side effects associated with the use of first line enzalutamide versus abiraterone for men with metastatic castration sensitive prostate cancer. The primary endpoint was fatigue as assessed using the FACIT-F questionnaire with secondary endpoints to evaluate changes in body composition, glucose metabolism, serum lipids and quality of life. A planned sample is 170 participants with the focus on patients from Denmark.

The investigators are endeavoring to provide a “real world” experience regarding how enzalutamide affects the day-to-day functionality of patients compared with abiraterone. However, there is a considerable body of literature that already had looked into this question and therefore, while this trial is ongoing, it is unlikely that it will result in a different toxicity profile than that already published. What have not been previously evaluated though are the concerns about metabolic issues including glucose metabolism and lipid changes.

Authors' answer: Thank you, for reviewing our protocol manuscript and for your summary of this ongoing randomized clinical trial. We would like to point out that the included patient population are men with metastatic castration-resistant prostate cancer (mCRPC), receiving first-line enzalutamide or abiraterone for castration-resistant prostate cancer. We have clarified the patient cohort in aim of the abstract (line 35 page 1) and the definition of mCRPC (line 120-121, page 3).

While previous real-world and randomized placebo-controlled trials have reported adverse events associated with enzalutamide or abiraterone, there is a lack of published head-to-head comparisons primarily exploring patient-reported outcomes and metabolic changes. We are glad that the reviewer finds evaluation of glucose metabolism and lipid changes novel.

1) Introduction needs to be updated given recent clinical trial results using enzalutamide earlier.

Authors' answer: Thank you, for your comment. The focus in the introduction is previous literature on enzalutamide and abiraterone administered as first-line mCRPC treatment, since this is the included patient cohort of this ongoing trial. In line 101-104, page 3, we refer to trials on enzalutamide and AAP for hormone-naïve prostate cancer. The trials investigating enzalutamide versus placebo for men with hormone-naïve prostate cancer (ARCHES and EMBARK) are still active and have only been published as abstracts. The paper from the ENZAMET trial has been added to the references (reference 10, page 10).

2) Response criteria radiologically was defined by PCWG2 not 3. Of note, NaF PET scans have not been a validated modality in PCWG2; these scans have high false positives.

Authors' answer: Thank you, for sharing your insights in PCWG criteria. As per protocol, biochemical and radiographic progression (in bone and lymph nodes) are based on the PCWG 3 criteria in this trial. The criteria are described in Table 1, page 14. Reference 13, referring to the modified Response Evaluation Criteria in Solid Tumors 1.1., is removed. Thank you, for your comment on NaF PET

scans, this will be an important point to discuss in the later coming paper with the results from this trial.

3) Given that patients will start ADT, will either enzalutamide or abiraterone be given simultaneously? ADT will definitely change lipid profile, glucose metabolism, and fat distribution but how will the impact of addition of enzalutamide or abiraterone on these markers be assessed if these are all given together. How will timepoints for assessments of these parameters be determined.

Authors' answer: Thank you for the comments. The patients do not initiate ADT simultaneously with the allocated treatment. The included patients have metastatic castration-resistant prostate cancer (mCRPC). Thus, patients are included when they have progressive disease on continuous ADT and have serum testosterone levels < 1.7 nmol/L (described in table 1, page 14 and specified in line 120-121, page 3). The time from initiation of ADT until progressive disease varies in our patient cohort and is an important baseline characteristic that could be included in the statistical analysis if necessary. However, the duration of ADT prior to inclusion in the trial should be equal in both treatment arms, due to the randomised design of the trial. Timepoints for assessing metabolic changes are at baseline and after 12 weeks on allocated treatment (line 180-181, page 5 and Table 2, page 15).

4) Given that fatigue is the primary endpoint, what will determine whether or not treatment should be stopped and how will it be determined whether it is due to the androgen signaling inhibitor versus the effects of ADT? How reliable will it be to use the FACT analysis to take a patient off the trial and how will these patients be subsequently treated?

Authors' answer: Thank you for the comments. As described under authors' answer to comment no. 3, participants do not initiate ADT and androgen signalling inhibitors simultaneously. Regarding cessation of allocated treatment, this is either at time of progression or at the discretion of the treating physician, e.g. unacceptable treatment related side effects (line 166-173 page 4-5). All adverse events will be registered using the common terminology criteria for adverse events version 4 (line 250-251, page 6). The choice of subsequent treatment will be decided at multidisciplinary team conferences as per standard of care (added in line 170-173 page 5).

5) Reference #12 regarding the authors of the Prostate Cancer working group is abbreviated and should be working group 2 not 3

No role for reference #13.

A number of relevant references are omitted including that for as "real world" paper on enzalutamide and seizure published in JAMA Oncology.

Citations regarding other papers about fatigue and enzalutamide are not included.

Authors' answer: Thank you, for directing our attention to this interesting paper on enzalutamide, seizures and adverse events including fatigue. References from real world studies about fatigue during enzalutamide treatment are now included (reference no. 25-26, page 11). The first three authors of the references (including reference no. 12) are now manually edited in accordance with BMJ criteria for references (page 10-11). In this trial, biochemical and radiographic progression (in

bone and lymph nodes) are based on the PCWG 3 criteria as described under authors' answer to comment no. 2. Reference 13 has been removed.

6) standard measures of glucose metabolism are being used but it would be better served to look at inflammatory cytokines, C reactive protein or aP2.

Authors' answer: Thank you for this comment. We agree that analysis of other metabolic and inflammatory biomarkers may also be interesting in this setting. Samples of full blood and serum are prospectively collected at baseline and 12-week post-intervention for future assessment of cardiac, adipose and inflammatory biomarkers (line 254-255, page 6). We thank the reviewer for pointing out C reactive protein. C reactive protein is already being measured as part of the protocol (added in line 235-236, page 6). By mistake it was not included in the submitted manuscript but was registered as an endpoint prior the trial on EudraCT (European online trial registration, EudraCT no. 2017-000099-27).