Peer Review File

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Reviewer #1

Using established and cheap routine blood-based markers like ALP and LDH to predict early response to therapy with Enzalutamid is clinically important. The authors could show the first time that early ALP bouncing is a phenomenon which occurs during therapy with enzalutamid in ~20% of the patients. Nevertheless, it is rarer than reported than under therapy with AA (~40%). Despite the fact that both marker are not independent predictive and prognostic markers, the analysis is of interest.

Title

Comment 1: As bouncing of ALP and LDH normalization are both not independent preditive and prognostic markers in multivariable analysis the title is misleading. I would rather call it:
ALP bouncing and LDH normalization in bone-metastasic castration-resistant prostate cancer under therapy with Enzalutamide: an exploratory analysis
Response: We agree that the title is misleading and changed it according to your suggestion.

Abstract

Comment 2: The argument ALP-bouncing and LDH normalization may add identification during early therapy is misleading. The definition "LDH normalization" is not restricted to week 8 and can not add identification during early therapy. This needs correction.
Response: We agree and corrected it.

Introduction: Appropriate

Methods/Results:

Comment 3: Please add a CONSORT diagramm.
Response: Thank you very much for your helpful advice. We agree and added a consort diagram.

Comment 4: The definition of PFS should be stated.
Response: We added the definition of PFS.

Comment 5: Please report number of patients alive at last follow up and the median time to first imaging after initiation of therapy as no regular imaging was performed. In how many patients enzalutamid was discontinued due to progressive disease on imaging and in how many patients enzalutamid was discontinued due to worse ECOG, pain or PSA-rise?
Response: Thank you very much for your comment. That's a good point. We added the number of patients alive at last follow-up and the median time to first imaging. All of our patients discontinued due to progression as defined according to comment 4 or death. No patient discontinued due to toxicity.

Comment 6: Three important variables which are known to influence outcome in mCRPC were not included into both models (PFS and OS): age, ECOG >1 and visceral metastasis. They should be included. Instead PSA flare, ALP rising after week 12 and Enzalutamide before chemotherapy could be discarded.
Response: Thank you very much for your comment. We totally agree, the variables you mentioned are important. We focused on ECOG and visceral metastases. In our experience age is not commonly used to drive treatment decisions with the exception of extreme outliers, e.g. very old patients. Therefore we did not include it. ALP rising after week 12 and Enzalutamide before chemotherapy showed relevance in UV, we have retained it. But we discarded PSA-flare.

Comment 7: It is not clear if it is ALP bouncing at week 12 or if it could also be the pure decline of ALP at week 12 which has an effect on the outcome. Please add ALP decline at week 12 to the model.
Response: We agree that an ALP decline after 12 weeks could also have had an effect on the outcome. Although it has not been significant in UV. Nevertheless, we performed MV with ALP decline at week 12 instead of rising ALP after 12 weeks and it did not change the results. Enzalutamide before chemotherapy remained the only significant parameter. Therefore, we kept the original version.

Comment 8: The group of all 18 patients with ALP bouncing could be presented in a waterfall plot including information of PSA-decline and LDH normalization.
Response: This is a very valuable advice. However, LDH normalization cannot easily be displayed in a waterfall plot since it is no relative change but just a yes vs. no change. But we liked the idea and added a waterfall plot with the information of PSA decline for patients with and without ALP bouncing.

Discussion:
Comment 9: A recently published paper should be discussed too: Rescigno et al., Eur Urol Oncol 2020 (doi: 10.1016/j.euo.2019.06.008)
Response: Thank you very much for your comment. We discussed the from line numer 334 of the manuscript.

Comment 10: Reference 17 (Mikah et al.) should be discussed in more detail and compared to the actual findings.
Response: Thank you very much for your comment. We discussed the reference in more detail from the line number 373.

Comment 11: The irregular imaging intervalls should be mentioned as potential bias in the recording of PFS in the limitation section.
Response: We added the potential bias.

Reviewer #2
In this retrospective paper, the authors examined the parameters ALP, LDH and PSA in bmCRPC under therapy with enzalutamide to evaluate the prognostic ability of these markers. The authors could show that ALP-bouncing and LDH-normalization may improve the identification of bmCRPC-patients with favorable prognosis during early therapy with Enzalutamide.

In the manuscript presented here, the authors were able to show connections between the named markers and enzalutamide in metastatic PC. The results are clinical relevant and can contribute to an improvement in the assessment of the treatment response of enzalutamide. The paper is well structured and shows an adequate statistical analysis of the data. I therefore recommend the presented manuscript for publication in TAU with **minor revisions**.

Before publication the following revisions should be made.

Background:
Comment 1: The introduction is very detailed but seems too long and should be shortened.
Response: We changed the detailed information and shorted the introduction.

Methods:
Comment 2: ALP-bouncing: definitions of the increase and decrease of ALP should be explained and defined in more detail. How were possible physiological fluctuations dealt with and defined?
Response: Thank you very much for your comment. Probably there are fluctuations due to biological reasons or measurement. We think these fluctuations exist, but we expect the changes to be far lower than those we have observed in the patients with ALP-bouncing. We added more detailed information.

Results:
Comment 3: Some patients had already received osteoprotective therapy at the time of blood examination. Is this to be expected to affect the results, especially ALP? If so, this should be taken into account in the discussion.
Response: Thank you very much for your comment. We did not expect the osteoprotective therapy to affect the results since all patients were on a stable dose that was not changed during the treatment period.