Reviewer’s report

Title: Temporal and geographic variation in the systemic treatment of advanced prostate cancer

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Reviewer: Chang-Hsien Lu

Reviewer's report:

This is an interesting paper about temporal and geographic variation in the systemic treatment of CRPC in US. The method and writing are appropriate. However, I still have some questions:

1) This study only describe the difference of frequency distribution, timely prescription change of 6 focus agents.

There is no wonder for "prescription evolution" after a positive Ph3 trial of new agents showing superior effects than old standard and being approved by FDA. What's the explanation of these prescription difference in difference area? The authors might list some points and show evidences of association with these differences in these areas. Related to urban area? available/affordable agents? treatment by oncologist/urologist?

In Fig 3. The authors demonstrate the difference of observed and expected focus drug use. For example, the use of Docetaxel and abiraterone showed huge difference between WNC and PAC. What's the reason?

2) This agents have different indication for CPRC treatment: symptomatic or minimal/asymptomatic, visceral metastasis or only bone metastasis.

It would be interesting to dissect these patient population. This indication limitation could explain the steady low use of Rd -223 or Sipuleucel-T.

3) Abiraterone and enzalutamide are now both approved for CPRC in 1st line setting. How to choose which agent to be used first remain challenge for their effects and toxicities.
In this study, the use of both agents seems the same in year 2015. What's the reason of decreased use of abiraterone and increased prescription of enzalutamide? any geographic reason/difference?

4) In the selected patients (n=4275), ~20% are M0CPRC. There is no standard care of these patient population yet. To further analyse their treatment pattern and outcome would be interesting.

5) The sequence of these focus agents use would affect the outcome of CRPC patients. I would suggest to link this analysis and drug sequence with survival data for further study.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.
Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.
Unable to assess

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