Reviewer's report

Title: Targeting Molecular Resistance in Castration-Resistant Prostate Cancer

Version: 1  Date: 1 June 2015

Reviewer: Martin E Gleave

Reviewer's report:

This review paper entitled TARGETING MOLECULAR RESISTANCE IN CASTRATION-RESISTANT PROSTATE CANCER provides a succinct and well written review of the current understanding of mechanisms of resistance in castration-resistant prostate cancer (CRPC) and overview of currently approved therapies for CRPC including chemotherapy (docetaxel and cabazitaxel) and AR pathway inhibitors enzalutamide and abiraterone. In general it is accurate and provides some original synthesis and insights from the authors own primary research, but would be improved by adding discussion on additional AR targeting agents in clinical development like Bayer ODM201, ARN509, the ISIS/AZ AR antisense drug (Yamamoto et al CCR 2015), galaterone, VT-486, and the OGX427 (targeting the AT co-chaperone hsp27), all in Phase II or III development.

While they do mention the recent work on AR-V7 in CTC being prognostic for poor outcome, a more recent study used combination of copy number profiling and AR sequencing to identify AR amplifications and mutations in the cfDNA of mCRPC patients progressing on novel systemic agents (Azad et al CCR 2015), reporting how AR amplifications or mutations accompanied enzalutamide resistance, and were were predictive for adverse outcomes on enzalutamide. This worth mentioning alongside of the AR-V7 work as liquid biopsies that may prove useful as predictive or prognostic markers.

Minor comments:

They mention AR and CRPC as abbreviations and define them in parenthesis several times on the first page and throughout the paper – should only be defined once then use the abbreviation thereafter.

3rd paragraph first page - Maha Hussain should be Hussain et al

Several references are either incorrect or suboptimal

For example –
Ref 3, 10
Ref 15,16 should be either or both
Mostaghal Cancer Research 2007 67(10): 5033-41
or Locke et al Cancer Research 2008 Aug 1;68(15):6407-15
55-57 should be


They may want to update to include STAMPEDE presentation and press release for ASCO 2015 in support of CHAARTED data

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

No conflicts