Reviewer’s report

Title: Targeting Molecular Resistance in Castration-Resistant Prostate Cancer

Version: 1
Date: 13 May 2015
Reviewer: Bruce Montgomery

Reviewer’s report:

- Accept for publication in BMC Medicine with major revision.
- Not suitable for publication unless extensively edited

The review is written by a group with significant experience and reputation in prostate cancer research. However, the manuscript requires very significant editing before it will be appropriate for publication.

The primary issues in the MS are:

Language and phrasing throughout which appears unscientific and in many cases uninformative for the casual reader.

Specifics

• "leading" in the abstract does not apply
• The sentence commenting on the prognostic significant of PSA seems both out of place and awkward unless couched in other discussion of prognostic factors
• The last sentence in paragraph 4 is out of place as the next paragraph discusses intratumoral androgen synthesis as well as the AR and non-AR driven mechanisms of resistance. Consider deleting.
• Consider providing more background regarding AR ligand independent mechanisms of resistance
• Docetaxel is a standard of care but not "the" current standard of care for CRPC. Use of AR targeting agents as the first intervention is significantly more common. This phrasing, which is used in multiple parts of the MS needs to be edited.
• Change enza to enzalutamide at initial use in the manuscript
• Describe what COU 301 and AFFIRM are and the population treated for this general audience at the first use of the titles of these studies
• Define "non response"
• The approach of frontline docetaxel per
the CHAARTED study is indicated ONLY, not "primarily" in high risk de novo patients. The acronym for CHAARTED, the study design and the details of what constitutes high risk de novo disease should be delineated.

• Docetaxel binds the β tubulin subunit, stabilizing total microtubules, not through specific stabilization of β tubulin.
• The primary mechanism of resistance mediated by BIII tubulin is through reduced MT stabilization, not altered binding of taxane to this specific isotype
• It is not clear that CBZ has a novel mechanism of action but due to reduced PGP export may simply have higher tissue levels of taxane.
• Consider including a schematic of androgen conversion as the paragraph describing androgen metabolism will be very difficult for the average reader to understand.
• The paragraph describing reactivation of steroidogenesis in response to abiraterone needs extensive editing.
• The text does not describe mutation of enzymes of steroidogenesis
• Glucocorticoid receptor upregulation should be discussed as another mechanism of resistance to enzalutamide
• Most CAP cell lines do not express AR splice variants. This statement should be modified.
• The Hornberg study did not establish that ARsv led to CRPC. It defined the presence of ARsv in a subset of CRPC mets and a worse prognosis associated with presence of ARsv.
• In the schematic docetaxel is shown inhibiting nuclear transport of AR – I do not find the portion of the MS describing the work of Kyprianou or Giannakakou

Quality of written English: Not suitable for publication unless extensively edited

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

Declaration of competing interests:

- Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this paper, either now or in the future?
I receive research funding for clinical research from the companies, Janssen, Medivation, ESSA, all of whom have agents which are mentioned in this paper.

- Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper, either now or in the future? No
- Do you hold or are you currently applying for any patents relating to the content of the manuscript? Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript? No
- Do you have any other financial competing interests? No
- Do you have any non-financial competing interests in relation to this paper? No