**Reviewer’s report**

**Title:** A retrospective feasibility study of biweekly docetaxel in patients with high-risk metastatic castration-naïve prostate cancer

**Version:** 1  **Date:** 12 Feb 2019

**Reviewer:** Tanya Dorff

**Reviewer’s report:**

The authors describe a retrospective cohort of men with castration-naïve prostate cancer (i.e. mHSPC) treated with an alternate dosing schedule for docetaxel - q2 weeks instead of q3 weeks. Unfortunately, there is not a clear hypothesis. the reader believes the hypothesis was that q2 weekly dosing might be less toxic but similarly effective, but this is not clearly laid out. It is possible the hypothesis was that Korean men with mHSPC might have differential results with docetaxel in the HSPC setting based on a statement in the discussion. The authors conclude that the biweekly regimen is feasible (though this was already shown in the CRPC setting) but do not draw a conclusion as to what further study would need to be done, what endpoints would need to be achieved, in order for this to become an alternative option to standard docetaxel as per CHAARTED.

Strengths of this manuscript include prior publications on the biweekly regimen and uniform treatment and follow up of patients. weaknesses include a small sample size, lack of compelling rationale and clear explanation of impact of results.

**Minor**

In the background the authors fail to mention that TAX-327 contained a weekly docetaxel arms, which was found to be less effective than the 3 weekly dosing. is there any hypothesis why 2 - weekly dosing would be better than 3-weekly, while weekly was not better? is the hypothesis that Korean men may not benefit from Docetaxel (this is hinted at in a statement in the discussion) and so the study was undertaken to determine whether they do benefit?

the last paragraph in the results does not make sense. the last sentence of the preceeding paragraph should be connected to the last paragraph. why did only 7 patients receive treatment upon development of CRPC? were the others transitioned to hospice? if so it would seem the OS would be lower at 1 year. the others were progressing but not enough to warrant initiation of additional treatment perhaps?

**Major**

the discussion should be re-written to more clearly lay out the background and why this study was performed. Ex: docetaxel q3 weekly became a standard therapy based on survival benefit
over mitoxantrone in mCRPC. then it was shown to prolong survival in mHSPC (or CNPC, as the authors label it) in CHAARTED/STAMPEDE. however toxicity resulted in discontinuation of XX% of patients in CHAARTED/STAMPEDE. (do some patients opt out altogether due to toxicity?) docetaxel q2 weekly has been found to have better tolerability. etc etc

the discussion would also benefit from re-writing for clarification in the section that follows as well. it seems the authors aim to contextualize their OS results with those of CHAARTED/STAMPEDE but this section is lengthy and unclear. The authors then attempt to compare toxicity, and here again things could be stated more clearly. in CHAARTED there were XX% with grade 3 or 4 adverse event [name it] whereas in this small experience YY% had grade 3 or 4. The authors could comment on how many patients required GCSF support or other similar parameters.

in the discussion, as mentioned earlier, there seems to be some hint that docetaxel with ADT may not be beneficial in Korean men. what is the basis for this? if the authors feel that Asian prostate cancer patients were not well represented in the q3 weekly docetaxel trials, that would help support this line of reasoning. this could be added to the background. also, if there have been any data suggesting differential outcomes or toxicity, this should be added to background and discussion. otherwise, the sentence that "a prospective trial is needed to determine whether early docetaxel chemotherapy in combination with ADT is beneficial in Korean men with mCNPC" doesn't fit with all that comes before it. based on CHAARTED and STAMPEDE we can say that "men" with CNPC benefit, which should include Korean unless there is some reason to believe otherwise. perhaps the authors were trying to say prospective study is needed to determine whether biweekly docetaxel is more beneficial than q3 week docetaxel? the reader is left with many questions after the discussion.

the first sentence of the Conclusion section can be removed as it does not have a conclusion in it. to state that biweekly docetaxel should be an option based on 35 patients is an overstatement. the authors should justify why further study of this dosing regimen is the most important question to be answered after CHAARTED/STAMPEDE - are there compelling toxicity reasons why the biweekly regimen should be studied to see whether it could become an alternative to q3 weekly dosing? would the endpoint for such a trial be non-inferiority? and QOL?

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