Reviewer's report

Title: Evaluation of protein biomarkers of prostate cancer aggressiveness

Version: 1 Date: 22 January 2014

Reviewer: Charis Kalogirou

Reviewer's report:

In their article “Evaluation of protein biomarkers of prostate cancer aggressiveness”, Rizzardi et al evaluate a multi-biomarker signature in a n = 153 prostate cancer (PCa) cohort, identifying HMMR, IGF1, SIAH2, SMAD4, HOXC6 and MAP4K4 among 33 tested candidate genes as relevant for predicting biochemical failure in PCa.

Identifying new Biomarkers for prostate cancer is, as the authors rightly stated, most relevant for therapy and diagnosis of this heterogenous malignant entity regarding disease progression and ultimatively, death. Regarding this issue, multibiomarker concepts are urgently needed. The data is collected and analyzed carefully. Methodology and statistical analysis is without obvious flaws. All mentioned genes/proteins included in the multibiomarker concept are discussed compellingly and placed well in the scientific context (especially the SMAD4 part). There is no reason for an objection concerning the scientific style of writing and written English.

Major compulsory revisions:

1) I disagree that high Gleason score PCa samples (Gleason 9+10) should be excluded due to the fact that they have “poor prognosis” and that “discrimination between moderate grade tumors is most relevant”.

If aggressiveness is to be studied, aggressive tumors with a higher chance of undergoing BF, clinical failure and cancer specific mortality should be included. If moderate tumors are to be studied, only moderate tumors should be included. As high-risk specimen with Gleason score 8 (according to PCa risk-stratification of Grimm et al, BJU Int. 109 suppl. 2012, 22-29) have been included in the study, I disagree to the point that only “moderate tumors” have been analyzed.

Please, either include the Gleason 9+10 specimen or exclude high-risk specimen. In the view of the fact that ~14% of the patients in the collective suffered BF, the inclusion of these high-risk tumors would be most desirable.

2) I also disagree that BF poses as a “gold standard” for progression of PCa. As clinical progression (as rightly mentioned) averagely takes place 8 years after BF and cancer specific death averagely 5 years after that, BF – in my point of view – remains a soft endpoint regarding progression of PCa.

There is no information if clinical failure, cancer specific mortality or death of other causes occurred in a significant number in the collective. If so, please provide statistical analyses regarding these endpoints. Also, please provide a
separate table which precisely describes the clinical demographics and relapse events of the cohort (e.g. page 11: if range is displayed, please also provide median time to BF in the running text or a table, etc.). Table 2, in this case, is not sufficient.

Minor essential revisions:

1) It is not clear to me, whether the patients in the collective underwent (neo)adjuvant therapy (e.g. hormone deprivation therapy or radiation therapy) before/after prostatectomy. This fact is very important, as these therapies may have impacted outcome of the patients included in this study significantly. Please provide these important informations and – if there was any additional therapy – discuss them and point out limitations of the study.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

I declare that I have no competing interests