Reviewer’s report

Title: Gene aberrations of RRM1 and RRM2B and outcome from gemcitabine plus docetaxel versus docetaxel alone in advanced breast cancer

Version: 1 Date: 2 October 2013

Reviewer: Marjanka Schmidt

Reviewer’s report:

This manuscript concerning the association of gene aberrations of RRM1 and RRM2B with advanced breast cancer outcome is clearly and well written, including a discussion well balanced for strengths and weaknesses of the study. The authors conclude righteously that there is no evidence of an association. There is some challenge to the interpretation of the data, as there is not much published earlier in breast cancer patients. On the other hand, that makes the paper also more newsworthy.

I have a few comments:

Compulsory Revisions

1. Please provide a definition of time to progression..
2. The cut-off for amplification seems a bit arbitrary, the cut-off for amplification, i.e. a 2:1 ratio makes sense, but the cut-off ratio for deletion of 0.8:1 seems less straight-forward. The range of ratio’s for normal tissue are much smaller 0.92-1.20 so in the sensitivity (explorative) analyses, might it make sense to use a 1.3 ratio instead of 1.5?
3. I wonder whether it is most correct to censor for any death for the TTP definition? If death was due to disease progression, even though not measured as such, it would make sense to include this as an event.
4. There are only 22 patients with locally advanced disease and 229 patients with metastatic disease; in those groups both TTP and OS maybe different; it would make sense to mention whether the results changed if the 22 locally advanced patients were excluded.
5. The curves for RRM2B also do not seem to fulfill the proportional hazard assumption. Can you please clarify?

Minor Essential Revisions

6. In general in the tables it is difficult to see if a variable has many subcategories to which comparisons the p-values refer; e.g. Table S1, type of metastatic site, prior chemotherapy; similarly for S2. Please clarify in tables by different format or footnotes.
7. Table 2: please provide definitions for PAM50 and a reference other than the unpublished paper. le 3 it is unclear what is meant by measurable disease.
8. Legends for Figure 2 and 3 are switched; and there is a typo: ‘Figure Legneds’ should be Legends.

Discretionary Revisions

9. The title is slightly misleading because it suggests a comparison between two regimens while this comparison is only shortly mentioned in the results with no evidence for interaction. Even though I appreciate that this was the actual research question, the data are not really strong enough to answer the question. Hence it may be better to leave the treatment indications out of the title or change the title to e.g. ‘Gene aberrations of RRM1 and RRM2B and outcome of advanced breast cancer after treatment with docetaxel with or without gemcitabine’.

10. It might be clearer to mention in the abstract that ‘there was a time-dependent association between RRM1 aberrations and OS, with a decreased OS in the time interval 1.5-7.4 years (hazard…)’.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests