Reviewer’s report

Title: Plasma HER2ECD a promising test for patient prognosis and prediction of response in HER2 positive breast cancer: Results of a randomized study - SAKK 22/99

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Reviewer: Elda Tagliabue

Reviewer's report:

Although the American Society of Clinical Oncology advised clinicians not to use soluble HER2 levels to guide their therapeutic approach for patients with HER2-positive breast cancer, different clinical studies are still investigating this biomarker as an indicator of progression and response to therapy especially in metastatic setting.

In this study, Eppenberger-Castori and co-authors investigated HER2ECD in plasma rather than serum samples obtained from HER2-positive advanced breast carcinoma patients randomly assigned to trastuzumab alone followed at progression by combination with chemotherapy or the upfront trastuzumab+chemotherapy. These patients were enrolled in the SAKK22/99 clinical study. Considering the usual threshold of 15ng/ml, HER2ECD did not impact on disease progression. Nevertheless multivariate and univariate analyses considering HER2ECD as continuous variable, showed a significant association of this biomarker with OS. Redefining a more appropriate threshold, patients with HER2ECD baseline ≥35ng/ml showed a worse prognosis compared to those with levels <35ng/ml. Interestingly, a higher benefit from trastuzumab alone than trastuzumab plus chemotherapy was observed in pts with low levels of baseline HER2ECD. On the contrary, pts with high levels of baseline HER2ECD benefited more from trastuzumab plus chemotherapy.

Overall, this paper is well written and the idea to monitoring HER2ECD levels for defining the optimal time point for the introduction of chemotherapy in patients under trastuzumab monotherapy is attractive in principle. Therefore it deserves publication after minor changes.

Minor remarks:

Although SAKK22/99 clinical study has been already published, it would be better to detail in M&M the treatment of patients enrolled in Arm A and B.

The number of cases in which correlation between HER2ECD values before and after first Trastuzumab treatment was carried out should be indicated.

Since levels of HER2ECD only depend on tumor mass, did the authors investigate plasma values according to the number of metastatic sites?
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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I am able to assess the statistics

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