Reviewer's report

Title: HER2 overexpression and amplification is present in a subset of ovarian mucinous carcinomas and can be targeted with trastuzumab therapy

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Reviewer: Karina Dahl Steffensen

Reviewer's report:

Major Compulsory Revisions: Comments number: 2,4,9
Minor Essential Revisions: Comments number:3,5,6
Discretionary Revisions: Comments number:1,7,8

The HER2 overexpression and amplification is present in a subset of ovarian mucinous carcinomas and can be targeted with trastuzumab therapy

The paper by McAlpine et al investigates the HER2 expression and amplification in mucinous ovarian carcinomas and in mucinous borderline ovarian tumor. Furthermore, they aim at evaluating the potential for trastuzumab therapy for this histological subtype of ovarian cancer.

Development of targeted treatment represents a new option with the hope of improving the outcome for patients with epithelial ovarian cancer. Promising results have been observed in VEGF directed therapy, where rather high response rates have been reported, even in heavily pretreated patients.

Nevertheless, results from HER2 directed therapy has been less promising and far from the results in breast cancer. The growing literature on HER2 expression in ovarian cancer also indicates that only a minority (< 10 %) of ovarian tumors are strongly positive for the HER2 receptor compared to breast cancer where 20-30 % of breast tumors show HER2 overexpression.

Epithelial ovarian cancer consists of many subtypes of ovarian cancer and recent data has shown that some subtypes of ovarian cancer show different types of mutations compared to the more common serous type (ref: Kurman RJ and Shih IeM, J Int J Gynecol Pathol. 2008 Apr;27(2):151-60). Therefore, it may be of relevant interest whether some subtypes of ovarian cancer show HER2 overexpression rendering this receptor of potential interest for HER2 targeted therapy for some subtypes of ovarian cancer where current available treatment is rather limited.

Overall, this manuscript is interesting and well written. The study design and methods used are appropriate. Although, it would benefit for some improvements and alterations, especially concerning the conclusion that HER2 amplification is not of prognostic significance. Please see the comments below.

I have the following comments and suggestions for the authors:
1. Page 3:

2. Page 5:
   I strongly believe that the methods section would benefit from a flow chart or a more detailed explanation on how 34+3+3 ovarian carcinomas and 15+7 borderline tumors add up to the 33 ovarian cancers and 16 borderline tumors as described in the results section. What is the reason for the missing samples? The selected cases consist of cases from different sources. Have all the paraffin embedded tumors from the different sources been uniformly treated and preserved under the same circumstances? (same formalin treatment, preservation time, etc.?) Were all the tumors from the primary debulking surgery prior to any chemotherapy treatment?

   The authors should address in more detail the characteristics of the included patients, e.g. age, grade, stage, and also parameters like carcinosis and residual tumor after primary debulking surgery since these are classic parameters with influence on prognosis beside the potential influence of HER2 expression.

3. Page 7:
   Line 4 from bottom: “were had”? (just a minor detail)

4. Page 8:
   Line 5: I might be mistaken, but I am not sure for what reason the statistics described on page 7 were chosen and used for describing the lack of association between HER2 status and recurrence.

   A much simpler association could be provided by showing the data in a 2 x 2 cross tabulation when reporting a significantly or non-significantly association between variables and to show these data as cross tabulations with p-valuables (using #²statistics or Fisher Exact test) in the tables. In that way the data compared are presented more clearly to the reader.

   Ovarian Cancer HER2 normal HER2 amplified Total
   No recurrence 17 6 23
   Recurrence 10 0 10
   Total 27 6 33
   #² = 3.19, P = 0.07 Fishers Exact test: P = 0.09 (one-tailed), 0.14 (two-tailed)
5. Page 7:
Line 19: Trastuzamab. Please correct to Trastuzumab.

6. Page 10:
Case 2: This is an unusual clinical presentation (brain metastasis) for a patient with ovarian cancer. We used to think that mucinous ovarian tumors were very common, but newer data seems to agree that most mucinous tumors apparently growing in the ovaries are metastatic disease from other primary tumors such as colorectal tumors or cervical tumors. Clinicians should be aware when an answer comes back from a frozen section that says mucinous tumor – they should comprehensively look for a primary occult cancer. Were any pathology revision performed on this patients’ tumor to re-evaluate the diagnosis?

7. Page 11:
Line 7-10: Regarding correlation between IHC and FISH. Other Authors have also reported on correlation between HER2 IHC and HER2 FISH in ovarian cancer. (E.g.: Steffensen KD et al: “The prognostic importance of COX2 and HER2 expression in epithelial ovarian cancer.” Int J Gynecol Cancer 2007, 17, 798-807). I think it would be relevant to add this reference to the discussion since it is in line with and supports the data discussed in this section.

8. Page 11:
Line 11: Have the authors considered that the mismatched results may be due to intratumoral heterogeneity of HER2 status, especially in TMA where only a smaller fraction of the tumor is evaluated for HER2 expression and therefore the evaluated spot may not always be representative for the tumor?

9. Page 8:
The major caveat in the presented paper is the missing data on patient characteristics, survival data and time to recurrence – especially concerning that the authors are making a conclusion of the prognostic impact of HER2 status. (This was also not a part of the presented aims of the study). The authors describes that 10 out of the 33 ovarian cancer cases recurred. I guess none of the borderline tumors recurred due to their usually very good prognosis? How long was the follow up time for recurrence? If the majority of the ovarian cancer cases were FIGO stage I and II then a much larger material is required to make any firm conclusions on the prognostic impact of HER2 expression in mucinous tumors. Since the number of events (recurrence and deaths) in stage I and II tumors are rather low then usually a very large number of included patients are necessary to achieve sufficient statistical power to estimate the prognostic value of a potential marker.

In this case no survival data are reported and I think that the authors should modify (or better leave out) their conclusion that HER2 is not of prognostic significance since I am not convinced that this statement if adequately supported by their data in this small patient material.
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests