Reviewer's report

**Title:** The mitochondrial transporter SLC25A43 is frequently deleted and influences cell proliferation in HER2-positive tumours

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**Reviewer:** Marcella Mottolese

**Reviewer's report:**

The manuscript entitled “The mitochondrial transporter SLC25A43 is frequently deleted and influences cell proliferation in HER2-positive tumours” by E Tina et al. analyzed copy number variations in a series of HER2 positive breast carcinomas using whole-genome single nucleotide polymorphism arrays. The authors aimed to identify unexplored proteins directly or indirectly involved in HER2 signaling, potentially affecting tumor progression and treatment response. This issue may be of particular clinical interest mainly in breast cancer patients. In fact, despite the benefits shown by trastuzumab both in the metastatic and (neo)adjuvant setting, a percentage of these patients frequently demonstrate unexpected clinical resistance and to date, there are no clinically validated markers of resistance to HER2-targeted therapies, although several mechanisms have been proposed. In this context, the investigation of copy number variations (CNV) might play a critical and important role in understanding whether human genomic instability may influence targeted therapy response in HER2 positive breast cancer.

In view of the importance of this issue, in my opinion, the study should focus only on breast carcinomas, since no data are so far available on cervical and lung cancer treatment with trastuzumab. In addition, HER2 expression has not been determined nor in cervical or in lung cancer series included in this study. The lack of this data is in contradiction with the title of the article.

Concerning breast carcinomas, results described throughout the paper are interesting and exhaustive, but not always convincing and sometimes appear unclear.

A number of major questions and comments are in order:

1. **Background:**

   Page 3, line 9: The sentence “the initial response rate to trastuzumab is relatively low...” is unclear. Do the authors refer to therapy in the metastatic or the adjuvant setting? Authors should change the sentence.

2. **Materials and Methods**

   a) Page 5, “Patient material” paragraph:

   the description of the patients included in the study is confused, often unclear and should be better organized. Are the HER2 positive breast cancer patients
treated with trastuzumab? This is a key point since authors could correlate SLC25A43 gene alterations with the response to therapy.

b) In particular, I do not understand why HER2 negative breast cancers are included with cervical and lung carcinomas as “other malignancies”. It would be better to consider HER2 negative breast cancer patients as a control group.

c) Page 9, “Immunohistochemistry”: Authors should add a brief description of immunohistochemical staining of HER2 as well as of the other conventional breast cancer biomarkers described in table 1 (ER, PgR). Moreover, completely lacks the description of the method used for the evaluation of HER2 gene amplification and S-phase.

3. Results

a) Generally, the description of the results obtained are not clear and should be clarified and, in some parts, better detailed.

b) Page 11, line 8: Has the Xq24 deletion been observed only in breast cancer or also in cervical and lung cancer? In the latter case, I can suppose that the deletion is present also in 80% of cervical and lung cancer independent of HER2 expression.

c) Page 11, lines 15-22: this part of results should be included in the discussion section.

d) Page 13, lines 3-5: The sentence “There was no association between SLC25A43 expression and LOH, which could in part be explained by the few number of cases with LOH in the SLC25A43 gene (n=16)” appears in contradiction with the sentence written on page 12, line 13 “The high frequency of LOH found in SLC25A43…”. Please, explain this discrepancy.

e) Page 13, lines 5-7: Authors analyzed S-phase fraction to evaluate the proliferation index of breast cancer (I suppose only in the group of HER2 positive patients). Why did they not use an anti Ki-67 antibody by immunohistochemistry? Proliferation index evaluated by the means of Ki-67 is a method now entered into clinical practice as highlighted in the last St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer (A. Goldhirsch Annals of Oncology 22: 1736–1747, 2011)

4. Discussion

The discussion is confused and addresses general topics without discussing the results in the context of the proposed aims (i.e. unexplored proteins potentially associated to trastuzumab resistance in breast cancer patients.) Moreover, it should be important to discuss the meaning and the biological link occurring among the chromosomal deletion, LOH, protein expression detected using different techniques.

**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