

## Peer Review File

Article information: <https://dx.doi.org/10.21037/atm-23-1465>

### Reviewer A

In my opinion, this topic analyzed is interesting enough to attract readers' attention. The goal of this study is to review the evidence regarding testing and reporting of HER2 mutations in uterine serous cancers and define the role of HER2 targeting agents in these cases.

Methodology is accurate and conclusions are supported by the data analysis. Nevertheless, authors should clarify some points and improve the quality of manuscript:  
- I suggest a round of language revision, in order to correct few typos and improve readability.

Reply: We have corrected minor grammatical mistakes and improved flow of language within the manuscript.

- It would be interesting to discuss results of this study in scenario of the current molecular classification and recent evidence in the literature of endometrial cancer. (In particular, I suggest these articles: PMID: 36833105 and 36983243)

Reply: Added

Changes in the text: (Page 6-7; Lines: 186-231) and (Page 27 Lines 1040-1042)

Tables are clear and detailed. Because of these reasons, the article should be revised and completed. Considering all these points, I think it could be of interest for the readers and, in my opinion, it deserves the priority to be published after minor revisions.

Reply: We thank the reviewer for their comment.

### Reviewer B

Please spell tumor instead of tumour

Reply: Corrected (all through the document)

Lines 62-63: Please add references

Reply: Added

Changes in the text: (Page 4, Lines: 93-95)

Line 84: Please spell correct T-DM1

Reply: Corrected

Changes in the text: (Page 5, line 153)

Line 92-93: These needs rewording. Slit like space- is this correct?

Reply: Sentence re-worded. Slit like spaces is factually correct (Ref: doi: 10.1016/j.ygyno.2021.04.029)

Changes in the text: (Page 6, line 180)

Line 93: TCGA is now the standard classification, not only an advancement. Consider to emphasize this more clearly in text.

Reply: Corrected

Changes in the text: (Page 6-7; Lines: 186-231)

Line 98: The last sentence from this paragraph needs an extra short introduction. The authors jump from TCGA classification to UPSC gene mutations.

Reply: Corrected in a way that the flow of language is seamless

Changes in the text: (Page 6-7; Lines: 186-231)

Line 132: Heavy ICH staining should be revised since heavy is no scientific wording. Consider maybe- Staining with an intensity score of 3 or something like this.

Reply: 'Heavy expression' was the phrase used in the original article referenced and in the ASCO guideline. But we appreciate that this might be confusing for the reader and hence, we have introduced 3+ in brackets after 'heavy'

Changes in the text: (Page 8, lines 272-273)

Line 143-144: Please add references

Reply: Added

Changes in the text: (Page 12, Line 331)

Lines 146-148: I would add more information regarding HER2neu testing differences between breast and endometrial. I think it would be interesting for the reader to go more deep into these differences.

Reply: Differences in morphological IHC expression between breast and endometrial cancers have been emphasized in more detail. Since there are no differences in percentage expression for designating a tumour as 3+ IHC (> 30% cells in both breast and serous endometrial cancers), this has been left as such.

Changes in the text: (Page 12, lines 332-337)

Line 204: Consider to keep only the name of ADCs. Although the ADCs are targeting trastuzumab, adding this can cause confusion for the reader.

Reply: Corrected

Changes in the text: (Page 14, Line 541)

Line 199: Targeting Her2/neu in Uterine Serous Papillary Cancers

Since trastuzumab is the only drug investigated in clinical trials in patients with UPSC, I would recommend to organize this paragraph into two sections: drugs with demonstrated clinical activity (here also discussion on enrolling criteria and testing, small number of available patients to be enrolled in such trials) and drugs with data limited to in vitro work. It is of course promising to have so many in vitro data on drug activity in different cell lines but usually there is a big jump from bench to bedside. Since none of the mentioned preclinical data was further investigated in clinical trials there is some concern.

Reply: Corrected

Changes in the text: (Page 14, Lines 536-549)

Line 360: Since this paragraph is very briefly, consider to address it as a last paragraph from Mechanisms of resistance for Her2neu targeted therapy in UPSC.

Reply: Corrected

Changes in the text: (Page 25, Line 843)

Line 374: Consider to expand more this paragraph on the design of DESTINY-PanTumour02.

Reply: Corrected

Changes in the text: (Page 26, Lines 966-972)

Line 377-378: Same observation as above. These trials are important for the reader.

Reply: Corrected

Changes in the text: (Page 26, Lines 963-965)

Line 391: I would make an open discussion also on testing and feasibility to perform it in the daily clinic.

Reply: Added

Changes in the text: (Page 28, Lines 1076-1077)

## **Reviewer C**

This manuscript reviews HER2 testing and HER2-targeted therapy for endometrial serous carcinoma. The authors successfully integrated the relevant literature and the writing is well-organized. This reviewer felt that the authors might be slightly overemphasizing the lack of standard diagnostic criteria; as the authors imply in lines 156-60 and 396-7, many recent studies are reporting their results using the criteria used in the 2018 JCO article. But it is true that an authoritative guideline is yet to be established (This statement is not a recommendation to revise the manuscript).

Minor comments:

1: Strictly speaking, this might be outside the scope of this review manuscript as indicated by its title, but the manuscript could mention recent studies (see below) indicating high-grade / p53-aberrant endometrial carcinomas (not limited to those with histological diagnosis of serous carcinoma) are often HER2-amplified. The current NCCN guideline also recommends: Consider HER2 IHC testing in TP53-aberrant endometrial carcinoma regardless of histotyping.

Reply: We thank the reviewers for bringing out this valuable point. We have included the NCCN recommendations and the implications of her2/neu testing in TP53 mutated tumours.

Changes in the text: (Page 6-7, Lines 181-231) and (Page 27, Lines 1038-1047)

Vermij L et al. HER2 Status in High-Risk Endometrial Cancers (PORTEC-3): Relationship with Histotype, Molecular Classification, and Clinical Outcomes. *Cancers*. 2020 Dec 25;13(1). Available from: <http://dx.doi.org/10.3390/cancers13010044>

Ross DS et al. Histopathologic features and molecular genetic landscape of HER2-amplified endometrial carcinomas. *Mod Pathol*. 2022 Jul;35(7):962–71.

Joehlin-Price AS et al. HER2 IHC Expression and Gene Amplification in p53-aberrant High-grade Endometrial Endometrioid Carcinoma Suggests That This Population May Benefit From HER2 Testing and Targeted Therapy. *Am J Surg Pathol*. 2023 May 1;47(5):580–8.

\*Consider this comment as an optional suggestion.

Reply: We thank the reviewer for pointing out these articles for us. We have taken their suggestion and have added this article.

2: line 73 "mutations" Maybe the authors meant "overexpression/amplification", as two lines below?

Reply: Corrected

Changes in the text: (Page 5, line 142)

3: Some sections seem to be misnumbered (eg line 89).

Reply: Corrected

Changes in the text: (Page 6, Line 177)

4: lines 150-4. These sentences seem to confuse individual cells and the entire tumor.

Reply: Corrected

Changes in the text: (Page 12, Lines 340-343)

5: line 163 "modification" Modification to what? The foregoing sentence does not contain criteria to be modified.

Reply: The sentence has been changed

Changes in the text: (Page 12, Lines 353-356)

6: line 174-5 "FDA criteria ... ASCO/CAP scoring system" This reviewer finds this somewhat confusing and recommends that the authors specify for what disease these criteria are originally for.

Reply: This has been clarified

Changes in the text: (Page 13, Lines 472-473)

7: line 230 "from 2000 to November 2022" This sentence describing a study reported in 2010 seems to contain some errors.

Reply: Corrected

Changes in the text: (Page 15, Line 675)

8: line 422 "mutation" Here again, this reviewer does not believe the authors really meant "mutation".

Reply: Corrected

Changes in the text: (Page 28, Line 1099)

9: Table 1. This is an interesting table and one would think is a highlight of the article. But, unfortunately, this table is somewhat disorganized. For one thing, the description of criteria is not standardized from row to row and it is difficult (or cumbersome) to compare one against another. Also, it might be better if the authors created another column to describe the criteria (algorithm) to arrive at positive/negative status using the results of IHC/FISH (instead of cramming this information into the cells for IHC scoring criteria).

Reply: We agree with the reviewer. Since the aim of the table is to bring out the lack of standardization among various studies, the table looked very crowded and cumbersome to read. To make it easier for the readers to understand, we have re-organized the table, outlined the scoring criteria in the table and have described it in the footnote.

Changes in the text: (Table 1)

10: The authors use two abbreviations, UPSC and USC, apparently referring to the same disease (correct me if wrong). This makes the manuscript unnecessarily confusing and

should be avoided. If the authors have a good reason to use two different terms, explain it in the manuscript.

Reply: USC used as a singular abbreviation. (Throughout the document)

## **Reviewer D**

The authors provide a timely and comprehensive review of HER2-targeted therapy for uterine serous carcinoma. The manuscript is well-written, and this reviewer believes it will be useful to the majority of readers. Only minor points should be brought up.

#1. The terminology for serous carcinoma must be standardized throughout the entire manuscript.

Reply: Corrected (Throughout the document)

#2. The symbol for the gene should be written in italics.

Reply: Corrected (Throughout the document)

#3. Several typos should be fixed. e.g., T1-DM in line 84.

Reply: Corrected

Changes in the text: (Page 5, line 153)

#4. A reader-friendly flowchart illustrating how to select the literatures would be useful. Could you provide this figure as a supplement?

Reply: Added

Changes in the text: (Figure added)

#5. Tables must be self-explanatory. Could you provide appropriate abbreviations/foot note in all the tables?

Reply: Provided

Changes in the text: (for all tables)

#6. The STATICE clinical trial has been published in the Journal of Clinical Oncology. The reference (#82) needs to be revised.

Reply: Revised

Changes in the text: (reference 82)