Peer Review File

Article information: https://dx.doi.org/10.21037/tbcr-24-15

Reviewer Comments

Reviewer A

Comment 1: The Title is concise and clearly describes the subject of the manuscript, however, it mentions "2024 edition". I am not sure (and it is not clear in the text) if there was a previous edition or not. Please consider removing this reference form the title or just mention 2024 to state the year of the work.
Reply 1: There was not a previous edition, we delete the word "edition"

Comment 2: A very important and vital comment is that the reader misses an explanation on the processes related to the consensus. Adding a Methodology section (expanding what is mentioned about the Chinese Society of Clinical Oncology) would be informative and important for the readers. For example, what was the format of the consensus session (s), number of experts involved, criteria for selecting the literature included, and importantly criteria for reaching the consensus and the levels of evidence or grade of recommendation, if they were employed. If pertinent and relevant, conflicts related to funding should also be disclosed. All of this is very critical information that relates to the credibility the manuscript will eventually carry.
Reply 2: The methodology section has been added.

Comment 3: If possible, adding levels of evidence for all recommendation statements would add significant value to the manuscript.
Reply 3: The level of evidence and strength of recommendation have been stated, and we summarized them in Appendix table 3.

Comment 4: In section 1.1, I believe it would be important to mention the percentage of patients achieving a pCR and not only the difference.
Reply 4: The percentage of patients achieving a pCR has been added.

Comment 5: The sentence starting, "Guidelines or consensus from….", I believe refers to all patients as long as they do not show evidence of progression of their disease, so the reference to "pCR" should be removed, as it is an outcome known only after surgery.
Reply 5: We have removed the expression of pCR to enhance the precision of our statements.

Comment 6: The end of the following sentence is not clear and should be rephrased or removed (interim assessment to evaluate optimal surgical timing).
Reply 6: We have adjusted the phrasing for improved clarity of meaning.

Comment 7: In recommendation 1, it is unclear how to perform the efficacy evaluation. While patients should be followed with physical examination of the breast before each

cycle (general recommendation), the statement without clarification may be interpreted as requiring imaging exams, that I believe are not justified with that frequency (q2 cycles).
Reply 7: Based on the clinical practice in China, experts agree that imaging-based efficacy evaluations every 2 cycles during the course of treatment enables effective monitoring of disease progression, facilitating timely treatment plan adjustments and preventing potential delays in surgery timing.

Comment 8: The last sentence of this first recommendation classifies patients into those with "good response" and those with "no response". While it is clear that patients that have progression of their disease during therapy should be switched to alternative treatments (other chemotherapies or surgery…) patients that have stable disease (or less than a clinical partial response or arguably "no response") are generally kept on the initial regimen until surgery in the absence of progression. I would recommend to clarify this last sentence of this recommendation.
Reply 8: We have clarified the final sentence of recommendation 1.

Comment 9: FDA and NMPA acronyms should be spelled.
Reply 9: FDA and NMPA acronyms have been spelled out.

Comment 10: In paragraph 1.4, I would recommend to consider removing the word "usually" and substitute for "have", as the statement should address the fact that the group that achieves a pCR does have a good prognosis.
Reply 10: We have removed the word 'usually' to enhance precision in our statement.

Comment 11: In the discussion on early BC, it would be important to comment on the negative results of trials where immunotherapy was administered in the adjuvant setting and arguably justifying the neoadjuvant approach.
Reply 11: We complement this in paragraph 1.1, including a preclinical study and a clinical phase III study.

Comment 12: In line 120, the word "higher" should be changed to "larger".
Reply 12: We have changed the word "higher" to "larger".
Changes in the text: After long term follow-up, 5-year absolute benefit of EFS (92.2% vs 88.2%)

Comment 13: When referring to the OlympiA trial, it would be important to refer to the fact that there was an OS benefit as well.
Reply 13: Due to the unavailability of OS data specifically for the subgroup of TNBC patients who did not reach pCR after neoadjuvant therapy, we have added OS benefits for the total population and demonstrated consistent benefits across subgroups.

Comment 14: It is not clear if Toripalimab is an approved agent in China.
Reply 14: We have added information of the approval of the new marketing application

for toripalimab.

Comment 15: In the paragraph addressing toxicity, consider that the expression T lymphocyte “toxicity” may be better understood by “activity”. Please clarify if this is correct.
Reply 15: Based on your suggestion, we have revised the statement.

Comment 16: Considering lines 214-215, note that some of the irAEs are not reversible, may need to explain better.
Reply 16: Acknowledging your comment, we have refined the text for clarity regarding the reversibility of irAEs.

Comment 17: Recommendation 9, addresses the need for education (delivering information) of patients. It would be a good opportunity to mention the need for education of the medical team as well.
Reply 17: We have expanded Recommendation 9 to include education for both patients and the medical team on irAE management.

Comment 18: Recommendation 12 should use the more standard term “paraffin embedded tissue”. As well, there is a comma where it should be a dot.
Reply 18: We have revised the expression accordingly and appreciate your correction.

Comment 19: The section on “other biomarkers” seems too long and could be summarized. The recommendation may be rephrased in a single sentence stating that: “There is lack of evidence that these biomarkers are prognostic or predictive.
Reply 19: In response to your feedback, the section on "other biomarkers" has been streamlined.
Changes in the text: There is lack of evidence that these biomarkers such as TILs, TMB, and MSI are prognostic or predictive, large-sample studies are needed to validate their clinical utility. (see Page 19, line 426-428)

Comment 20: To complete the set of recommendations it would make sense to state more definitive recommendations for the use of IO in both HR-positive and for HER2-positive disease.
Reply 20: We have added specific recommendations regarding the application of immunotherapy (IO) in both HR-positive (HR+) and HER2-positive (HER2+) breast cancer contexts.

Comment 21: The two sections on combinations with targeted drugs and the use of IO in second and later lines may be summarized in a couple of paragraphs. As they do not end up in specific recommendations they are more informative and make more sense to be detailed or be part in a review manuscript.
Reply 21: We have integrated these two sections based on your suggestion. Thank you for your input.

Comment 22: The authors should be congratulated for this important effort in a very challenging and important subject with a significant impact in clinical practice. I will be happy to further review this manuscript after these suggestions are considered.
Reply 22: We are deeply honored to have received your review and have proactively taken your suggestions into account in amending the manuscript. We eagerly anticipate your re-evaluation of the paper in its subsequent stages, as your professional opinions are of paramount importance to us.

Reviewer B
Comment 1: Knowledge gap clarification
"Most guidelines from both domestic or international have recommended Immune therapy as the important approach in breast cancer, but there are many challenges or questions unsolved during clinical daily practice, such as proper patient selection, optimized chemotherapy partner, predictive biomarkers, the scientific management of side effect and etc."
The guidelines should be cited here. Also, the description of the knowledge gap is too vague, as the guidelines have extensive descriptions of patient selection, as well as descriptions of chemotherapy partner and management of side effect. The authors need to make it clear when the guidelines for patient selection do not make PROPER recommendations, when the guidelines for chemotherapy partner do not give OPTIMIZATION recommendations, and when there are still gaps in the guidelines for management of side effect. This is the premise on which consensus exists. Stating this clearly is critical to the future clinical value of this consensus in the community.
Reply 1: We have rephrased this statement to more effectively convey the identified "knowledge gap".

Comment 2: Methods
The text lacks a Methods Section that describes the methodology and process of consensus building in sufficient detail. Include:
-Selection of Consensus Topics: How were the consensus questions selected in the text (brainstorming? Literature search?), including consensus items 1~5.
-Literature search strategy: search terms, timeline, databases, ranking criteria, whether or not the search is systematic to ensure that all clinical trials that meet the ranking criteria are not missed, the literature ranking process, the level of evidence assigned to the literature (who is responsible for it, and according to what criteria rating).
-Consensus expert group formation: considerations for composition (how to ensure representativeness), how to recruit the expert group
-Consensus methodology: "This consensus has been deeply discussed and modified several times," is insufficient. How many times has this consensus been deeply discussed and modified, what are the criteria for the consensus, is a Likert Scale used, and if so, what is the Likert Scale? How are elements that cannot be agreed upon resolved, and how is the objectivity of the consensus process ensured (e.g., pressure on the identities of individual members that prevented the consensus experts from

objectively stating their dissenting views)?
Reply 2: According to your suggestions, we have augmented the Method section to address each of the four aspects in greater detail

Comment 3: Results/Recommendations
I suggest that the authors make a table that integrates the core 14 comments of the article and is equipped with citations of the core evidence behind these recommendations, so that the reader can quickly understand them.
Reply 3: We summarized them in Appendix table 3.

Comment 4: Results/Recommendations
For each of the 14 recommendations, what is the consensus rate among all experts? This needs to be made publicly available as an attached table.
Reply 4: In the stratification of CSCO evidence levels, the consensus rate is already incorporated, hence we did not separately list the consensus rates for each recommendation.

Comment 5: Results/Recommendations
In addition, for each recommendation, the level of evidence and strength of recommendation should be stated.
Reply 5: The level of evidence and strength of recommendation have been stated, and we summarized them in Appendix table 3.

Comment 6: Recommendation 1
The eligibility of "For early-stage TNBC patients eligible for neoadjuvant chemotherapy," is not clear, and it is necessary to specify which early-stage TNBC patients are eligible for neoadjuvant chemothrapy, either by citing existing guidelines or by stating it explicitly, so as to avoid ambiguity and loss of the essence of the recommendation.
Reply 6: We have provided a specific definition for early-stage TNBC and supported it with references to two guidelines mentioned in the previous text.

Comment 7: Recommendation 1
"It is recommended to do efficacy evaluation every 2 cycles during the course of treatment." is given in Recommendation 1. However, the authors in the previous paragraph relied on the results of the KEYNOTE-522 study, which showed that neoadjuvant immunotherapy in combination with chemotherapy for 8 cycles, with midterm evaluation at 4 cycles. In this way, the authors' recommendation (every 2 cycles) is inconsistent with the supporting literature (at 4-cycle). The authors need to clarify why this recommendation was made and whether it was from an expert consensus discussion
Reply 7: Based on the clinical practice in China, experts agree that imaging-based efficacy evaluations every 2 cycles during the course of treatment enables effective monitoring of disease progression, facilitating timely treatment plan adjustments and

preventing potential delays in surgery timing.

Comment 8: Recommendation 7
“For PD-L1 positive mTNBC patients, based on current evidence, combination of chemotherapy and immune checkpoint inhibitors can be recommended. Pembrolizumab + chemotherapy (nab-paclitaxel, paclitaxel, or gemcitabine + carboplatin) (CPS≥10) or Toripalimab +nab-paclitaxel (CPS≥1) can be considered as the first-line treatment.”

In recommendation 7, “or Toripalimab +nab-paclitaxel (CPS≥1) can be considered as the first-line treatment”, the recommendation comes from the evidence: “The phase III TORCHLIGHT study (22) from China showed Toripalimab+nab-paclitaxel treatment group significantly prolonged PFS benefit of mTNBC patients in PD-L1-positive (CPS≥1) and ITT populations, and there was also a significant trend of OS benefit. It may provide a new treatment option for mTNBC patients in China”.

Therefore, I suggest that Recommendation 7 should clearly state that mTNBC patients IN CHINA can be considered as mTNBC patients.
Reply 8: We have revised our expression based on your suggestions.

Comment 9: Recommendations 9 and 10
I don't think these two consensus opinions are as clear as the previous 8 recommendations. These two are honestly hard to apply, and while they say all the right things, they feel like they don't say anything at all. Routine monitoring and knowledge education are well known. For example, in recommendation 9, what I would like to see is for the recommendation to be specific: how to monitor and how to prevent? Recommendation 10, because there is already a corresponding document published "The management principles can refer to the "management of immune checkpoint inhibitor-related toxicity" published by the Chinese Society of Clinical Oncology. by the Chinese Society of Clinical Oncology (CSCO)." This is not recommended to be a separate recommendation, but rather to be integrated with recommendation 9 as a single recommendation.
Reply 9: Based on your feedback, we have decided to integrate Recommendations 9 and 10 into a single, more comprehensive recommendation.

Comment 10: Recommendation 11
The comment in Recommendation 11, "It is recommended to select corresponding PD-L1 antibody clone, testing platforms, and scoring methods based on different anti-PD-1/PD-L1 agents. It is recommended to select corresponding PD-L1 antibody clone, testing platforms, and scoring methods based on different anti-PD-1/PD-L1 agents" is not very instructive. The root cause is that there is not enough detail in the evidence trail: "In clinical practice, the approved indications and testing standards for PD-L1 testing vary by different ICIs Therefore, it is recommended to choose the corresponding PD-L1 antibody clone, testing platforms, and scoring methods based on different anti

PD-1/PD-L1 agents. -1/PD-L1 agents." Here, it should be further broken down as to what exactly is the appropriate PD-L1 assay, what are the matching platforms, and what are the scoring methods for receiving treatment with different anti-PD-1/PD-L1 drugs. It needs to be expanded upon! I think this is important because the authors also point out that the positive overlap between the different assays is not really high enough, no more than 70%. This directly determines the subsequent choice of treatment regimen.
Reply 10: We've added Appendix Table 4 to specify the suitable PD-L1 testing methods for different anti-PD-1/PD-L1 agents.

Comment 11: Conflict of Interest Statement
This article states that Zefei Jiang is the Editor-in-Chief of TBCR, which is fine. However, as part of the consensus, each expert participating in the consensus needs to declare any potential conflict of interest they have with the drug vendor mentioned in the consensus. These need to be formulated to ensure that the consensus recommendation is conflict-free to boot.
Reply 11: These disclosures have been included in footnotes to guarantee that the consensus recommendations are free from bias.

Comment 12: Clarify in the abstract what exactly the challenges and questions unsolved are "but there are many challenges or questions unsolved during clinical daily practice"
Reply 12: In the abstract, we have concisely expounded upon the particular challenges and unresolved inquiries pertinent to daily clinical practice.

Comment 13: "The Chinese Diagnosis and Treatment Expert Group of Breast Cancer gathered to reach this consensus according to most update of clinical trials and real-world data on immunotherapy."
This is ambiguous. The authors need to have a methodology section, in which the abstract details how many people were selected, what criteria were used to select them, what clinical trials were searched (databases searched, criteria for inclusion in clinical trials, date of completion), how consensus was reached, and what criteria were used to reach consensus.
Reply 13: We have added a brief methodology overview in the abstract, detailing the expert selection, trial sourcing, and consensus approach.

Comment 14: "This paper will help to enhance the standardization and qualification of proper management of immunotherapy in clinical daily practice in the therapeutic area of breast cancer."
This needs to be preceded by a unique core of recommendations that are not found in the most central previous guidelines and consensus of this consensus.
Reply 14: We have augmented the abstract with a recommendations central to this consensus.

Comment 15: "Guidelines or consensus from both domestic and globally usually

recommend patients with pCR to complete the standard duration of 6-8 cycles therapy before surgery. (7,8,9)."
What does domestic refer to here? I think the article is facing a worldwide audience after it is published in TBCR. The authors should avoid writing in such a localized way. According to literature 7,8,9, the authors could directly write: Guidelines or consensus from China and Canada recommend patients with pCR to complete the standard duration of 6-8 cycles therapy before surgery. before surgery.
Reply 15: Based on your advice, we have revised the statement.

Comment 16:
"Cytological specimens, handled with differently, usually choose methods such as ethanol fixation, direct smear, or liquid based sectioning, so it is not recommended to test them in cytological specimens now."
I fail to see the causal logic of using SO in this sentence.
Reply 16: We have adjusted the wording to improve clarity.

Comment 17: References
The following mentioned places all need references to back up the claims.
Reply 17: References have been added to support the respective statements.

Comment 18: The full names of all abbreviations should be given when they first appear. The article needs to be checked in its entirety, and there are some errors, such as the full name of TIL being given but the abbreviation appearing before the full name is given, as well as other similar issues (full name not given, errors in order of precedence) please check them as well.
Reply 18: We have conducted a full review and standardized the usage of abbreviations throughout the article, ensuring that each abbreviation's full name is introduced before its first use and correcting any order precedence errors. Thank you for pointing this out.