Peer Review File

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Reviewer Comments

Reviewer A

Comment 1: Line 60: Would remove the word "Unfortunately".
Reply 1: Thanks. I have changed "Unfortunately" by "Notably". (Line 105)

Comment 2: Line 63: In line 63, would add that this refers to neoadjuvant therapy. An added important concept is that even though there is a significant recurrence and mortality rate in this group of patients, it should be noted that if the patients achieve a pCR they have around a 90% cure rate, and even if not achieve a pCR about 50-60% of these patients may achieve cure or long-term survival. I would recommend that rather than saying "high" recurrence and mortality authors may just state the numbers. This is an important message for the overall community of physicians and patients.

Reply 2: Thanks for your constructive comments. I have added the specific recurrence rate and mortality rate of TNBC compared to other subtypes of breast cancer. (Line 108-114)

Comment 3: Lines 66-67: I would add the concept: of resistance of "some of the TNBC patients" to our current treatment options… in line with my previous recommendation.

Reply 3: Thanks. This is indeed a precise statement and I have revised it as suggested. (Line 115)

Comment 4: Line 75: I would add PD-L1 expression on immune cells as well.
Reply 4: Thanks for the addition, I have added it in the sentence. (Line 124)

Comment 5: Line 84: remove "their".
Reply 5: Thanks. I have modified it. (Line 133)

Comment 6: Line 118: Note that Atezolizumab has also been approved in many countries around the world for metastatic TNBC.
Reply 6: Yes. Atezolizumab was once the first approval ICI inhibitor till April 2021, based on earlier data from the phase 3 IMpassion130 trial. However, the phase 3 IMpassion131 trial (NCT3125902) missed the study's primary end point. Given the two discordant clinical results, the FDA withdrew the indication for atezolizumab. To date, Pembrolizumab is currently the only ICI approved for metastatic TNBC.

Comment 7: Line 127: Would remove the first sentence as it is a repeated concept.

Reply 7: Thank you. I have changed. (Line 203)

Comment 8: Line 133: Would reference these numbers.
Reply 8: Thank you. I have changed the number more accurately. (Line 208-209)

Comment 9: I would recommend adding a short discussion on the author's opinion on whether it is better to use neoadjuvant vs adjuvant immunotherapy (or both). This discussion should be included in a section addressing challenges, controversies or unresolved issues (see my final comment).
Reply 9: Thanks. We have added it. Please take a look at the section 'Unleashing the Power of Early Intervention: Neoadjuvant Immunotherapy as a Transformative Approach

Comment 10: Lines 180-184: Is the CPS score different in the approval for NMPA from what it is in other countries? If that is the case, it should be clearly stated and explained for the non-Chinese reader to understand.
Reply 10: Yes. They are the same. At present, the CPS is scored according to the formula provided in Keynote 181 and Keynote 590. (Line 258)

Comment 11: Line 189: Would remove "clinically relevant", the concept is debatable and not uniformly accepted.
Reply 11: Thanks. I have rewritten the sentence and I hope you would accept this version. (Line 265-267)

Comment 12: Line 194: Would consider changing "INDEX" for Endpoint as it a more accepted wording.
Reply 12: Thanks. And I have changed it. (Line 274)

Comment 13: Line 224-226: Would suggest adding this discussion as part of another subtitle addressing challenges or controversies as mentioned before (see final comment).

Reply 13: Thanks, I have revised it according to the final comment（Line 303）

Comment 14: Line 227: would remove the sentence, it is a repeated concept.
Reply 14: Thank you and I have removed it. (Line 462)

Comment 15: Line 233: the concept is not clear and should refer to the size of the tumor (arbitrary) when you recommend neoadjuvant vs, adjuvant therapy.
Reply 15: I have removed this ambiguous concept. (Line 471-472)

Comment 16: Line 235-237: The available evidence consistently suggests that the addition of platins increases the pCR rates. If the authors disagree with this concept they should clarify and justify why this remains unclear (their position would be

important).

The issue of the best chemotherapy backbone is another controversial issue. Anthracycline or not, platin salts or not, dose-dense or not, etc. Another controversy is to be included.

Reply 16: I apologize for confusing you with my statement. I have rewrite the sentence and I hope can understand what I mean. As for the next question, it is indeed a matter of debate. (Line 474-477)

Comment 17: Line 238: would change "often" to "can be".

Reply 17: Thanks for your comment. However, around 60 to 80% patients carrying a BRCA1 germline mutation are characterized by TNBC phenotype(PMID: 18779615) . Moreover, ESMO claim to genetic testing due to the 47% prevalence of deleterious BRCA1 mutations in TNBC(https://www.annalsofoncology.org/article/S0923-7534(19)43799-X/fulltext). So, consideration is that 'often' is the more appropriate word. (Line 477~478)

Comment 18: Line 242: Note that here, authors refer to platin salts as "recommended" (see previous comment lines 235-237).

Reply 18: Thanks. I have restricted this statement to the neoadjuvant phase and include the specific clinical studies below, for the reasons described above. (Line 486~491)

Comment 19: Lines 253-256: Impassion 031 trial is not mentioned.
Reply 19: Thanks for your reminder. And I have added it to the sentence. (Line 501)

Comment 20: Lines 275-277: Impassion 031 showed a pCR benefit with no Carboplatin.
Reply 20: Thanks. And I have corrected my statement. (Line 523-529)

Comment 21: Lines 286-289: These concepts were already discussed. Consider removing.
Reply 21: Thanks. I have removed it. (Line 539-540)

Comment 22: Line 291-292: Would add this subtitle to a section addressing controversies/challenges as mentioned before.

Reply 22: Thanks. I have added it (Line 544)

Comment 23: Line 293: Would ask the authors to clarify this sentence. There is evidence for PARP inhibitors in the adjuvant setting (for TNBC) and the KN522 regimen has been approved with the adjuvant portion of the treatment included.
Reply 23: Thanks. I have rewritten the sentence to clarify my opinion. (Line 546-55)

Comment 24: Line 328: TCs refers to Tumor cells, correct? If that is the case, the sentence should be corrected.
Reply 24: Thanks. I have unified TCs into TC. (Line320)

Comment 25: Line 346: Would remove "given to this" and say "The potential…"
Reply 25: Thanks. And I have modified it (Line 663)

Comment 26: Line 351: The KN522 was already presented, so I would not give the details here, just mention the name of the trial. (would remove: "randomized stage II or III TNBC patients to receive neoadjuvant treatment with paclitaxel and carboplatin plus pembrolizumab or placebo".
Reply 26: Thank you and I have removed them mentioned above. (Line 666)

Comment 27: Line 355: Remove the pCR results they have been presented already.
Reply 27: Thanks. And I have removed it. (Line 670)

Comment 28: Lines 367-368: Would rephrase: "patients receiving PD-L1 enrichment". Probably "having PD-L1 expression" would be better.
Reply 28: Thanks. I have rewritten it. (Line353)

Comment 29: Line 386: would remove "scores".
Reply 29: Thanks. I have removed it. (Line 702)

Comment 30: Line 387: would use HER instead of Her.
Reply 30: Thanks. And I have changed it to'HER'. (Line 703)

Comment 31: Lines 389-392: Note that here authors are discussing TILs and not PD-L1 (previously discussed). Would remove.
Reply 31: Thanks. And I have removed it. (Line 704-708)

Comment 32: Line 425: Would remove the word "However"
Reply 32: Thanks. And I have removed it

Comment 33: Line 429-431: Would not give the details and just refer to the trial. At the end of the sentence in line 431 there is a comma instead of a dot.
Reply 33: Thanks. I have fixed it. (Line 744-747)

Comment 34: Line 433: There is a “The” with capital letters to be corrected.
Reply 34: There is a “The” with capital letters to be corrected. (Line 410)

Comment 35: Line 440: would remove the word “more”.
Reply 35: Thanks. I have removed it. (Line 417)

Comment 36: Lines 441 and 443: “TNBCS” needs correction.
Reply 36: Thanks. I have made a correction. (Line 420)

Comment 37: Lines 457-461: I would consider re-writing these two sentences as the concept the authors want to convey is not clear.
Reply 37: Thanks. I have rewritten it.

Comment 38: Line 467: Again, here the concept is not clear.

As a general comment, I would consider addressing the section of ctDNA again (re-writing) to make the message the authors want to convey better understood to the interested reader.

Line 477: What is a “strong” combination?
Reply 38: Thanks. And I have made a supplementary explanation in the text. (Line 853)

Comment 39: Lines 484-486: The message is not clear I would rewrite it.
Reply 39: Thanks. And I have rewritten it. (Line 450)

Comment 40: I would add a section on important ongoing trials that the reader should be aware of. Here I would mention the two trials the authors are conducting (and remove them from the Conclusion section) and refer to other questions being addressed.
Reply 40: Thanks. I have added. Please take a look at the section titled ONGOING TRIALS AND FUTURE PERSPECTIVES

Comment 41: I would consider organizing the manuscript and give it a more didactic flow. Consider the following just as an example that may not include all possible subjects:

• Current landscape
o Monotherapy
o Combinations
o Best Endpoints
• Controversies – Challenges
o Chemo Backbone
o Adjuvant vs neoadjuvant vs both
o Adjuvant for pCR patients?
o Adjuvant for Residual disease patients?

o BRCA positive patients?
• Biomarkers
• Ongoing Trials and Future Perspectives
• Conclusions
Reply 41: Thanks. We have reorganized the manuscript. (see the section modified)

Reviewer B
Comment 1: There are sentences with inadequate expressions. Did authors apply the manuscript for professional English editing?
Reply 1: Thanks. We have polished it.

Comment 2: The authors described that "anthracyclines has improved the pCR rate from approximately 35% to over 50% in TNBC" (Line 231-232). It had discordance to describing at starting of the introduction (Line 63).
Reply 2: Thanks. The improved results of adding platinum into classic chemotherapy regimens are in the neoadjuvant phase mentioned here, different from the description mentioned above in the introduction. However, it reminds me of changing 'less than ' to "about only", in order to make it more rigorous.(Line 469-470)

Comment 3: Pembrolizumab is the second immune checkpoint inhibitor accepted as a therapy for metastatic TNBC. The first ICI for mTNBC is Atezolizumab. This sentence is incorrect (Line 118-120)
Reply 3: Yes. Atezolizumab was once the first approval ICI inhibitor till April 2021, based on earlier data from the phase 3 IMpassion130 trial. However, the phase 3 IMpassion131 trial (NCT3125902) missed the study's primary end point. Given the two discordant clinical results, the FDA withdrew the indication for atezolizumab. To date, Pembrolizumab is currently the only ICI approved for metastatic TNBC. (Line 188)

Comment 4: Is the title "ADJUVANT TREATMENT STAGE" correct (Line 226)? The authors described in this chapter primarily preoperative chemotherapy.
Reply 4: Thanks. And I have changed it to 'NEOADJUVANT'(Line 458-461)

Comment 5: The authors should also discuss BRCAness if they cite 44(Line 238-241).
Reply 5: Thanks. And I have made a supplementary statement. (Line 483-485)

Comment 6: I have difficulty understanding the argument being made in this sentence (Line 287-288). The endpoint of a clinical trial should essentially be OS, and whether others can be substituted.
Reply 6: Clinical studies often have more than one endpoint. A single endpoint may not capture the important effects of an intervention to the satisfaction of all end-user groups, so multiple endpoints are usually selected, which are categorized as primary, secondary, or tertiary. The primary endpoint(s) are typically efficacy measures that address the main research question. Secondary endpoints are generally not sufficient to influence decision-making alone but may support the claim of efficacy by

demonstrating additional effects or by supporting a causal mechanism (PMID: 31799474). Thus, ORR, PFS, and OS can all be designed as endpoints. (Line 538-539)

Comment 7: Please provide a more detailed description of ctDNA and treatment effects.
Reply 7: Thanks. And I have rewritten it. (Line 427)

Comment 8: the technical terms are different in each section.
Early TNBC, early stage TNBC
Reply 8: Thanks. I have unified them as eTNBC.(Line 82)

Comment 9: Are PD-1 and PD-L1 antibodies different drugs as a classification? (Line 79-80)?
Reply 9: Though PD-1 is predominantly expressed on the surface of T cells while PD-L1 is primarily expressed on the surface of tumor cells, I still believe that they can be classified into one category. The reason is that PD-1/PD-L1 therapy targets the same pathway, other than CTLA-4. Moreover, the combination of ipilimumab and nivolumab has shown efficacy in melanoma, kidney cancer, and rectal cancer (PMID: 31196207). But there is no successful example of PD-1 combined with PD-L1 inhibition therapy in solid tumors. This may reflect the fact that PD-1/PD-L1 monoclonal antibodies can be classified into one group at present. (Line 130)

Comment 10: I'm not at all familiar with the term "late TNBC"(Line 392). Please explain and cite or remove.
Reply 10: My apology, for confusing you with my presentation. I've changed my sentence and hope you can get my point. (Line 708)