Peer Review File

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Reviewer Comments

Reviewer A

Comment 1: Line 66: the last sentence of the abstract reads awkwardly, particularly in regards to 'sequencing' of currently approved treatments. Did the authors mean "sequence" of therapies or "sequencing" of the tumor itself?

Reply 1: The intended meaning was sequencing of therapies, but the abstract has been rewritten to reflect this better.

Comment 2: Line 99: missing grammar (period).

Reply 2: Period added.

Comment 3: Line 101: aetiology is old English. "etiology" is the preferred word.

Reply 3: Spelling has been adjusted to preferred spelling.

Comment 4: Line 119: brief descriptions of the role of BRAF and NRAS will be helpful here, instead of being mentioned deep in the manuscript

Reply 4: Mechanism of BRAF and NRAS and their role has been moved to the introduction of the manuscript.

Comment 5: Line 120: 'targeted' therapy

Reply 5: Error has been corrected from target therapy to targeted therapy.

Comment 6: Line 134: it may be helpful for the general audience to briefly define 'immuno' vs 'targeted' therapies in this context prior to the subsequent description(s).

Reply 6: Definitions and examples of both terms added in context of the manuscript.

Comment 7: Lines 141-143 require a citation, as the text appears to be copied directly from Wikipedia.

Reply 7: Pub med citation inserted for the mechanism of CTLA-4.

Comment 8: Figure 4 and Table 1 should be better labeled. Are these guidelines based on current NCCN guidelines? If so, this should be mentioned. Furthermore, subtypes of various stages should be further delineated.

Reply 8: Table 1 and figure 4 have been labelled in response to this comment with ESMO, NCCN and NICE guidelines cited where relevant. The various cancer stages have been further delineated to include more detail on the management at each stage.

Comment 9: Lines 176-178: weren't these abbreviations already defined previously?

Reply 9: The repetition of this definition has been removed.

Comment 10: Line 209: regimen?

Reply 10: Spelling error replaced with regime.

Comment 11: Line 218: please describe the most common adverse events.

Reply 11: The most common adverse events have been added and cited in the manuscript.

Comment 12: Line 238: a paragraph that describes the weaknesses of these studies would be appreciated as well, with particular focus on the patient/sample population and the subtypes of advanced melanoma.

Reply 12: A paragraph reflecting this has been added to the end of this section.

Comment 13: Line 247: what is the frequency of these two mutations?

Reply 13: Frequencies of these mutations have been included and moved to the introduction of the manuscript.

Comment 14: Line 264: what are these instances?

Reply 14: Examples of these instances have been reflected in the document.

Comment 15: Line 269: would consider word change "positive" to "encouraging in reducing disease relapse". Delaying suggests that patients will inevitably have recurrence of disease.

Reply 15: Wording has been changed to convey a more appropriate meaning.

Comment 16: Line 318: again, please detail the incidence of NRAS mutant. Codons 12/13/61 is not helpful without being provided appropriate context (ie: what is the length of this protein?)

Reply 16: This has been rectified with additional context added and moved to an

earlier section.

Comment 17: Line 323: what are these rates? are they significantly different?

Reply 17: Study data has been added to reflect these differences in the rates shown.

Comment 18: Line 351: why is its clinical use limited?

Reply 18: Possible explanations on its limited use in clinical practice has been discussed in the manuscript.

Comment 19: Line 356: please refer to my previous comment revolving around the use of 'sequencing'

Reply 19: Change has been applied.

Comment 20: Line 382: what is the most common neoadjuvant regimen employed in the literature to date?

Reply 20: Examples of the most common neoadjuvant regimens have been added to address this comment.

Comment 21: Line 430-435: either in this section or subsequently, the mechanism of the function of oncolytic therapies is critical to define in such a review.

Reply 21: A paragraph on the mechanism of oncolytic therapies has now been included.

Comment 22: Line 473: what is ITL-168? this has not been defined before.

Reply 22: This is the name of the drug; I have added some more clarity on this.

Comment 23: Line 512/516: these statements appear contradictory. most of the guidelines were focused on current US FDA approvals. there was not much mention towards the European/British rulings. furthermore, did the authors not review preliminary clinical trials (ie: NCT03618641)?? these have not yet been published, to my knowledge.

Reply 23: Author reflection has been rewritten to reflect this.

Comment 24: Line 517: it is highly suggested to detail how these articles included in the review were obtained. Such as, did the authors search pubmed? using what terms and definitions?

Reply 24: Greater clarity on the authors' search protocol has been included.

Reviewer B

This review article describes the standard of care in melanoma and enlightens future perspectives. Overall, the text is interesting and useful for clinicians. well written and presented in a logical and structured way. However, I have some remarks that will hopefully improve the manuscript.

1. Language: In general, English is understandable and correct. I have no major comments on that field.

2. Major comments:

Comment 1: As the texts describes not only issues related to metastatic melanoma but also those in localized disease, I suggest to change the title to be more manuscript-oriented

Reply 1: The title has been changed to a more appropriate title that fits the manuscript's subject matter.

Comment 2: The abstract is too vague, it should contain more details about the content of the manuscript

Reply 2: More detail on the review has been added to reflect its content.

Comment 3: The table in the subsection 'current standard of care' is not very clear. I suggest adding more details in the first column with 'stage', as not everybody knows TNM classification by heart. Additionally, management of stage III is described 'in general' in the line with stage IIIa- it should be separated: general issues and then treatment in particular stages. Furthermore, data on adjuvant treatment, resected stage IV disease is missing. Maybe providing information in sub-points would be more transparent?

Reply 3: The table has been changed extensively to include further details on the management at different stages of disease and clarification on the TNM classification.

Comment 4: There is an update of the Checkmate-067 trial from the ASCO 2022 annual meeting after 7.5 years of observation.

Reply 4: The manuscript has been updated to include the most recent data from the Checkmate-067 trial.

Comment 5: I suggest adding information about the results of the Checkmate 511 trial

with different doses of ipilimumab in metastatic melanoma in terms of the frequency of adverse events (lines 203- 218)

Reply 5: Information on this has now been added in reference to the frequency of adverse events.

Comment 6: there should be a separate chapter dedicated to radical treatment as suddenly in section ‘Targeted therapy’ there is a section on stage III disease and adjuvant immunotherapy. Moreover, there is a lack of data on omitting lymphadenectomy (MSCT trial and DeCOG-SLT trial).

Reply 6: A chapter dedicated to radical treatment has now been added following the current standard of care.

Comment 7: Please add the chapter about the current approach of ‘triple negative melanoma’.

Reply 7: A chapter on this has been included in the manuscript.

Comment 8: Adding information about colon cancer in lines 396-398 is redundant.

Reply 8: This information has now been removed from the manuscript.

Comment 9: In my opinion there are too many figures. I suggest to merge figures 1-3 together. Figures 4a and 4b are the same. Figure 5 is redundant and presented data can be added to merged figs. 1-3. In Figures 6-7 I suggest adding compounds which bind to molecular targets.

Reply 9: Figures 1-3 has been merged, an additional figure on the sentinel node algorithm has been added as figure 2, figure 4a and 4b has been merged and figure 5 has been removed. Molecular targets have been added to figures 6-7.

3. Minor comments:

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Comment 1: There are many misspellings (eg. check point in line 152, IVM1a in 431 line etc.)

Reply 1: Spelling errors have been corrected.

Comment 2: Abbreviations are first explained, then used again as abbreviations, then again explained. Additionally, once there is ICI, then ICIs, similarly to LAG-3/LAG3, PD-1/PD1 etc. The text should be homogenous in terms of abbreviations.

Reply 2: Abbreviations have been changed so that they are all homogenous.

Comment 3: The immunological background is explained in the introduction and repeated in the first paragraph of ‘immune checkpoint inhibitors”. Repetition of information should be avoided.

Reply 3: The repetition of in the “immune checkpoint inhibitors” section has been removed.