Peer Review File

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Reviewer A

I read with great interest the Manuscript titled " Is “Immune checkpoint inhibitors: Here to Stay" which falls within the aim of the Journal.

Although the manuscript can be considered already of good quality, I would suggest following recommendations:

- I suggest round of language revision, in order to correct few typos and improve readability;

Reply: Thank you for calling our attention to these errors. We reviewed the text and indeed identified some of them. We hope we didn't miss any.

- The authors could extend and improve the discussion by evaluating and citing current evidence about the use of various and possible therapeutic strategies analyzed in recent years. I suggest authors to read and insert in references the following articles PMID: 37314974 and 29958629

Reply: These two articles are really very interesting and well done. However, the first (PMID 37314974) doesn’t mention endometrial cancer, only ovarian. Although the article brings important insights that can be extrapolated to other tumors, including endometrial carcinoma, we can get lost in the discussion, mainly because our article is an Editorial commentary about ICIs.

The other is very updated, even though it is from 2018. As the editor prefers related literature published within a year, we included in the last paragraph a comment about biomarkers from another review article:

“Other biomarkers studied, such as intratumoral PD-L1 and tumor mutational burden, and others under investigation, such as tumor-infiltrating lymphocytes and ARID1A alterations, have not proven useful (20).”

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

Reviewer B

summarized well. One

- Line 64-65: pembrolizumab and dostarlimab are "PD-1" inhibitors, NOT PD-L1 inhibitors; please change

Reply: Sorry! This was a mistake. Thanks so much for identifying it. The correction was done in line 65: ...the FDA approved the two PD-1 inhibitors,….

- It is very important that the differentiation between eligibility for dostarlimab and pembrolizumab is included here. GOG 018 did not include carcinosarcoma subtypes but RUBY included carcinosarcoma - this allowed the FDA to approve dostarlimab for carcinosarcoma types, this is important to include in a summative editorial.

Reply: You are reason. We added a paragraph after line 97: “It is important to mention the different eligibility criteria for dostarlimab and pembrolizumab. The carcinosarcoma (CS) was not included in NRG-GY018, but it was in RUBY, which allowed the FDA to approve dostarlimab including for CS (16).”

- paragraph on lines 81-90 could probably be condensed (one line on grade 5 would be more succinct); would recommend adding what the "common" grade 3 and higher complications were in the first line. I am note sure if dividing the AE into dMMR and pMMR provides any value - a better report would be C/T vs C/T/Pembro group. it would also be helpful to list the percentage of immunotherapy AE (and what the most common were)

Reply: We agree with you about the description of the AE according to MMR status. The reason we made in this way was because the authors did. However, we calculated the frequencies with the Tables data and reported as you suggested.

Changes in the text:

We added in the first line “Adverse events were seen in at least 15% of all patients. Fatigue, peripheral sensory neuropathy, anemia, and nausea were the most common.”

We recalculated the frequencies of AE grade 3 or more according to pembro vs. placebo.

We added the immune-related AE: In descending order, these events were infusion reaction, hypothyroidism, hyperthyroidism, colitis, pneumonitis, glucose intolerance, acute kidney injury, hepatic failure, myositis, hypophysitis, pancreatitis, and adrenal insufficiency (18).

a few minor suggestions:

- line 25-26: the probability is misleading as it is such a small number. I think a more representative statistic would be 66,200 new cases each year or about - 27 in every 100,000 women are diagnosed with endometrial cancer each year (same reference)

Reply: We accepted the suggestion.

Changes in the text: We added the information as suggested in line 25-26: In the United States, uterine corpus cancer is women's fourth most diagnosed cancer, with an incidence of 27 per 100,000 women each year (2).

- Line 41-42: add that p53 is determined from IHC

Reply: We added the suggested information about IHC in line 41-42: "The remaining tumors are classified according to p53 protein expression determined from immunohistochemistry as aberrant or normal (6)."

- Line 73 - please add how long patients were kept on chemo (ie. for 6 cycles followed by pembro maintenance for X cycles).

Replay: As suggested, we included in line 73: "…..for 6 cycles followed by pembrolizumab or placebo maintenance every 6 weeks for up to 14 cycles."

- A similar line describing RUBY should be provided that is the same as Lines 70-73

Reply: As suggested we added in line 91: "The study with dostarlimab, the RUBY trial (NCT03981796), randomized in a 1:1 ratio 494 patients to receive dostarlimab or placebo in combination with carboplatin for 6 cycles, followed by dostarlimab or placebo every 6 weeks up three years or until disease progression."

Line 112 - would recommend you provide an example of other "biomarkers" you have referred to

This discussion would benefit from considering how to deal with universal pembrolizumab to the entire population. there should be a discussion about the judicious use of pembrolizumab in the pMMR population (is this benefit worth the risk of complications?)

Reply: We modified the last paragraph to provide the suggested information. In line 114 we added:

" The studies have proven that the benefit of ICI extends to patients who do not have dMMR, and we need to know who these patients are. Other biomarkers studied, such as intratumoral PD-L1 and tumor mutational burden, and others under investigation, such as tumor-infiltrating lymphocytes and ARID1A alterations, have not proven useful (20). However, we must insist on the search for robust predictive biomarkers because it is the best way to guarantee safe and effective indications for any drug."