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Reviewer A

In this indirect comparison metanalysis, Passiglia et al have conducted a systematic review of eleven randomized clinical trials comparing efficacy and safety outcomes among first-line IO treatment strategies versus conventional chemotherapy according to PD-L1 expression level. The study showed that anti-PD1 & anti-CTLA-4 combination had limited role in the treatment of patients with PD-L1 high (≥50%) and/or low (1-49%) metastatic NSCL, while it might be an option patients with PD-L1 negative disease. The manuscript provides relevant data as direct comparisons among distinct strategies are limited in this clinical setting.
I have some concerns regarding this manuscript:
-When the authors compared the rate of adverse events (especially G3-G4) between distinct studies, did they take into account that some trials provide treatment-related adverses events while other studies report global adverse events (treatment-related or not)?

R: Thank you for the clarification. We have effectively reported and focused on treatment-related adverse events (as named TRAEs in the included studies).

-The authors did not incorporate the Keynote-598 to this metanalysis (https://ascopubs.org/doi/10.1200/JCO.20.03579). This study is consistent with the results of this metanalysis for patients with high PD-L1 expression.
-It would be of great interest to incorporate the CheckMate-9LA study and compare it with other ICI strategies according to PD-L1 expression.

R: Thank you for your valuable comment and suggestion. We updated the systematic review of the literature and we performed new analyses incorporating the available outcomes within the CheckMate-9LA and EMPOWER-Lung 1 trials. However, the KEYNOTE-598 trial did not present the standard platinum-based chemotherapy as common control arm, and did not meet the inclusion criteria of the current meta-analysis. The update analyses did confirm that patients with high PD-L1 expression seem to benefit the most from a single-agent IO treatment, as recently proved by the KEYNOTE-598 and EMPOWER-Lung 1 studies. Of note, the contribution of the limited CT course in the CheckMate-9LA trial (two cycles) must be considered when compared to other CT backbones (at least 4 cycles) of the other trials included in this meta-analysis. Accordingly, we modified all the figures and the results while implementing the discussion section with these most recent trials.

-Could the authors take into consideration the histological subtype in their analysis (squamous versus nonsquamous) as they with PD-L1 expression.

R: Thank you for your interesting suggestion. However, we could not perform any analyses in consideration of the missing hazard ratios according to both the histological subtype and PD-

L1 expression. Therefore, we additionally implemented the discussion and limitations section.

-The authors did not mention that one of the advantages of combining chemo plus ICI is to prevent hyperprogression which it may happen when patients receive ICI alone or dual ICI blockade.

R: Thank you for your clarification. We have implemented the text as suggested (lines 566-577).

Reviewer B

In this review paper, Passiglia and colleagues compared the efficacy and safety of three IO-based treatments as first-line therapy for metastatic NSCLC patients. I read the review paper with interest. This review was well written; however, I have some comments to improve it.

Comments;

1. The title says "is there any place for PD-1/CTLA-4 inhibitors combination …"; however, the authors did not include CheckMate 9LA which had investigated the combination of nivolumab, ipilimumab and platinum doublet chemotherapy.

2. Recently, the results of KN598 which had evaluated the combination of pembrolizumab and ipilimumab for NSCLC patients with PD-L1>50%. The addition of ipilimumab to pembrolizumab did not improve survival of these patients. The authors should cite the KN589 study and discuss the findings.

R: Thank you for your valuable comment and suggestion. We updated the systematic review of the literature and we performed new analyses incorporating the available outcomes within the CheckMate-9LA and EMPOWER-Lung 1 trials. However, the KEYNOTE-598 trial did not present the standard platinum-based chemotherapy as common control arm, and did not meet the inclusion criteria of the current meta-analysis. The update analyses did confirm that patients with high PD-L1 expression seem to benefit the most from a single-agent IO treatment, as recently proved by the KEYNOTE-598 and EMPOWER-Lung 1 studies. Of note, the contribution of the limited CT course in the CheckMate-9LA trial (two cycles) must be considered when compared to other CT backbones (at least 4 cycles) of the other trials included in this meta-analysis. Accordingly, we modified all the figures and the results while implementing the discussion section with these most recent trials.

3. On page 4, the authors mentioned IO-CT and PD-1-CTLA-4 combo have been approved for NSCLC patients with low and negative PD-L1 expression; however, pembrolizumab monotherapy is also approved to use for this population in some countries.

R: Thank you for your clarification. We have implemented the text as suggested.

4. On page 13, line 311-312, same sentence is repeated twice.

R: Thank you and sorry for the misprint. We have deleted the repetitive sentence.

5. Supplementary Figure 14a is wrong.

R: Thank you again. We have modified the figure according to the reported safety outcome results.

6. Although the authors concluded that IO+chemo is the most effective strategy for PD-L1 low subgroup, there is very little survival data of these population who had been treated with IO or combo IO.

R: Thank you for your clarification. We have tempered the text accordingly.