Peer Review File

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Reviewer A:

Comments:

1. As a (very) minor comment, as Authors mention neo-adjuvant trials with ICIs in NSCLC, they are invited to mention adjuvant ongoing trials as well (e.g. PEARLS study). In addition, Authors should mention (here or in later in the manuscript) that the large majority of evidence on ICI-related pneumonitis in NSCLC has been obtained in pretreated populations, while now ICIs have moved to the first-line setting, either as mono-therapy or in combination with chemotherapy. Chemo-ICI combinations could make the differential diagnosis even more challenging (paclitaxel/pemetrexed-related pneumonitis).
   Response: We thank the reviewer for this comment and have added reference to the PEARL study and first-line therapy and the implications of this (line 23)

Epi

2. "Wang et al. interrogated the WHO pharmacovigilance database of irAEs, describing the nature and range of immune related fatal events…" after reporting the data by Wang et al., Authors are invited to discuss the recent study by Moey et al on Eur Resp Journal 2020 "Increased reporting of fatal pneumonitis associated with immune checkpoint inhibitors: a WHO pharmacovigilance database analysis".
   Response: We have added reference to the letter by Moey et al.(line 124)

3. The paper by Suzuki et al "Assessment of Immune-Related Interstitial Lung Disease in Patients With NSCLC Treated with Immune Checkpoint Inhibitors: A Multicenter Prospective Study" JTO 2020 should be mentioned as well.
   Response: Added (line 128)

4. In order to provide the most complete view on this topic, I suggest Authors to perform a systematic search in order to gather all the published evidence (including the retrospective ones) on ICI-related pneumonitis in NSCLC (only published papers, no conference proceedings). Such studies report potential risk factors (pre-existing ILD, radiotherapy) and other the differential outcomes (in terms of survival) following the development of pneumonitis. Still with the limitation of retrospective studies, often not "rigorous" in precisely assessing lung toxicities, these real-life data could be nevertheless of interest.
   Response:We thank the reviewer for this comment. However we believe an extensive literature search it is outside the scope of this narrative review.

Risk factors

5. I agree that pre-existing idiopathic interstitial pneumonia is a relevant risk factor. Authors are nevertheless invited to report phase II prospective trials evaluating ICIs in pre-existing (mild) idiopathic interstitial pneumonia -patients, that globally proved safe (e.g. Fujimoto Lung Cancer 2017; Fujimoto Lung Cancer 2019).
   Response: We agree that discussion of the work by Fujimoto et al does add balance to the coversation about risk and have added reference accordingly (line 141)

Reviewer B:

Comments:

Scientific value: High. Pneumonitis is definitely a more common toxicity experienced in patients treated with PD(L)1 +/- CTLA4. At least from clinical experience, the incidence is likely higher than reported in the randomized phase 3 studies.

Quality of writing: Very good.

Literature search: Very comprehensive. But some additional information may be needed:

1. For CT related features related to pneumonitis, the authors have provided a very comprehensive review of the literature on the radiological features and biopsy finding. A couple of papers have been published which provided some additional information:
- Rashidan et al. Lancet Respir. Med 2018;6:472, which described lymph node enlargement, reverse halo sign denoting alveolar damage.
- Colen et al in IND 2018;36:601-17 described radiomics features of skewness and angular variance that measures dispersion at baseline predicted development of pneumonitis. Inclusion of papers that evaluated baseline radiological features that predict pneumonitis is very important for any practicing oncologists.
Response: Thank you for alerting us to these papers which do provide additional information. We have included a discussion of the paper by Rashdan et al. in the 'Clinical Features' section (line 215), and that by Colen et al. in the 'Early detection and prevention section' (line 278).

2. Treatment and Unknowns and Research Priorities Sections: Although there are recommendations of the use of steroids is recommended starting grade 2 pneumonitis, there are still many questions unanswered:
- in clinical trials, grade of pneumonitis and other immune related toxicity are universally reported, but the incidence and duration of steroid and other immunosuppression medications are not reported. So I think we should make reporting the use of these medications mandatory in the manuscript especially these information are collected in the case report forms. This will provide the practicing oncologists how clinically significant is the immune related toxicity.
Response: We thank the reviewer for this comment and agree that standardized reporting of pneumonitis treatment would add greatly to our knowledge (line 340)

3. Throughout the manuscript, the authors have provided the risk factors, diagnostic features and therapy for pneumonitis, but there has been no discussion on the predictors for those patients who will require IV steroids and other immunosuppressants and those who die from toxicity. I think these are very important future direction.
Response: We agree this remains a critical unknown and have added a sentence to make this explicit. (line 328)