TLCR TRANSLATIONAL LUNG CANCER RESEARCH
AN OPEN ACCESS JOURNAL FOCUSING ON CLOSING THE GAP BETWEEN "BENCH AND BEDSIDE"
IMPACT FACTOR 5.132

Peer Review File

Article information: http://dx.doi.org/10.21037/tlcr-21-15

Reviewer Comments:

The purpose of your meta-analysis was to provide more clarity on the use of first line immunotherapy in NSCLC patients with poor PS (PS≥2). This goal has only partially been achieved mainly due to limited access to this type of data as well as data quality in general. The manuscript needs to be improved/corrected before it is ready for publication. I have the following more specific comments to your manuscript:

Page 3:
1. You write: 'Atezolizumab (anti-PDL1) combined with carboplatin, paclitaxel, bevacizumab is approved for the treatment of EGFR mutated NSCLC patients after progression to targeted inhibitors (4)'.
This does not seem to be in consistency with the EU EPAR for atezolizumab (Tecentriq): https://www.ema.europa.eu/en/documents/product-information/tecentriq-epar-product-information_en.pdf). Please explain.

Reply: We thank the Reviewer for the request of explanation. In the document https://www.ema.europa.eu/en/documents/product-information/tecentriq-epar-product-information_en.pdf, it is written that "Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC). In patients with EGFR mutant or ALK-positive NSCLC, Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies (see section 5.1)."

Page 6:
1. You write: 'Exclusion criteria were: articles not written in English, reviews, commentaries, opinions, case reports, not relevant articles. Case reports tend to describe the positive outcomes of patients? in specific situations of interest, suggesting an intrinsic publication bias (i.e. the histories of poor PS NSCLC receiving ICIs are normally published only if successful).'
According to Thoracic Cancer your Ref. 31 (https://onlinelibrary.wiley.com/doi/10.1111/1759-7714.13713) is a Case Report. This is a violation of your exclusion criteria? Furthermore, the data from this Case Report seems not to be report correct. The patient with a TPS PD-L1 of 100% who responded to pembrolizumab had a PS score of 4.

Reply: We agree with Reviewer's comment, as ref 31 could be misleading. We were indeed going to not include it, but reading carefully it is stated in the paper introduction

that "…we retrospectively reviewed a total of 250 cases of advanced NSCLC treated with pembrolizumab as first-line treatment at our hospital between May 2017 and December 2019 and identified a total of four patients with high PD-L1 expression (TPS ≥50%) who had poor PS (≥3) and were driver-mutation negative…", meaning that these four patients represent a consecutive, unselected population.
With regard to the performance status of the patient who responded to pembrolizumab, it is written that "Her PS was 4. After undergoing palliative radiation therapy for the bone metastases and surgery followed by whole-brain radiation therapy for the massive brain metas- tasis, her left upper and lower limb paralysis improved slightly, but her PS was still 3. Pembrolizumab (200 mg/ bodyweight) was started as first-line treatment..". So, at pembrolizumab start (the moment of interest in our analysis), ECOG PS was 3.

Page 11:
1. Table 3. You use both ORR and RR in this table. You need to be consistent with regards to the use of abbreviations. Please also check for a consistent use of mPFS/PFS and mOS/OS.

Reply: We thank the Reviewer for the careful reading.

Changes in the text: We have changed every referral to response into "ORR", and we have provided additional stylistic corrections.

2. Several of the studies listed in Table 3 and 4 includes patients with a TPS PD-L1 < 50%. Have you looked into the level of PD-L1 expression and patient outcome following ICI treatment?

Reply: We strongly agree with Reviewer, as every additional data addressing the outcomes of poor PS patients receiving immunotherapy is precious in sustaining future treatment algorithms. Nevertheless, no information regarding PD-L1 expression levels is available and no further clinical insight can be driven.

Page 12:
1. You write: 'Pooling the data, 489 and 205 PS ≥ 2 patients were evaluated for ORR [seven studies (28,29,40,41,45,46,51)] and DCR [four studies (29,37,40,70)]'.
It is difficult to control your data, but to me it seems that it should be 491 instead of 489. With respect to DCR, you mention Ref. 70 but it is not included in Table 5? Please explain.

Reply 1: We thank the Reviewer for the accurate control of patient number. Indeed, the correct number of patients evaluated for ORR is 491 (there was a mistake of 2 units when dealing with ref 51).

Changes in the text: As a consequence, both the text and the meta-analytic data have been reviewed and corrected.

Reply 2: Concerning reference 70, this is a mistake of bibliography reporting, as indeed we intended to refer to ref 36, that is already included in the Table.

Changes in the text 2: We have corrected the reference number.

Page 14:
1. See my comments above with respect to the Case Report by Inaba-Higashiyama R et al. (Ref. 31), which is included in Table 5. According to your exclusion criteria this should be removed from the table.

Reply: Please refer to the response we provided above.

2. If it should be possible to control your data, you will need to include the number of none evaluated patients in Table 5.

Reply: We agree with the Reviewer, as this is a noteworthy information to report. We have included it in Table 5.

Page 15:
1. In Figure 2 you report Total HR for both fixed and random effect. Please explain the difference.

Reply: Please note that the measure reported in the Figure is not a relative measure of efficacy like HR, but the absolute proportion of ORR and DCR. However, as explained in the Cochrane handbook, in the presence of heterogeneity, a random-effects meta-analysis weights the studies relatively more equally than a fixed-effect analysis. The fixed-effect model starts with the assumption that the true effect size is the same in all studies. When studies are gathered from the published literature, the random-effects model is generally a more plausible match [Kuan Y, Tam K. The selection of fixed- or random-effect models in recent published meta-analyses. In: Filtering the information overload for better decisions. Abstracts of the 23rd Cochrane Colloquium; 2015 3-7 Oct; Vienna, Austria. John Wiley & Sons; 2015]. Some authors choose random-effects model (that is associated with larger confidence intervals) in the presence of a significant heterogeneity that, in our analysis, was present both for ORR and DCR. In the text, we report results of the random-effects model.

Page 16:
1. You write: '18 studies provided studies on PFS of poor PS patients, some of them only reporting their numbers and the comparison with PS 0-1 cases (Table 6)'. According to Table 6 there is only data on mPFS on poor PS patients from 15 studies. Please explain.

Reply: We thank the Reviewer for the adequate comment. Indeed, out of the 21 studies included in Table 6, 18 reported statistical comparison for PFS between poor and good PS patients, while 15 reported the median values of PFS in poor PS patients.

Changes in the text: We have modified the text accordingly, clarifying numbers of studies and respective information.

Page 19:
1. You write: 'Almost invariably, OS was statistically worse in poor PS patients compared to good PS ones, in the 17 studies reporting any survival information, with not significant trends only in report with a relative low number of PS ≥ 2 cases (Table 8)'.
According to Table 8 there are only information on mOS from 14 of the 19 studies listed in the table. Please explain.

Reply: We thank the Reviewer for the comment, that allowed us to check our numbers. Similarly as above, out of the 20 studies reported in Table 8, 14 reported the mOS of poor PS patients. Nevertheless, the statistical difference between poor and good PS patients (to which we referred) was reported in 16 studies.

Changes in the text: We have modified the text accordingly, clarifying numbers of studies and respective information.

2. I looked at a few of the listed publication in Table 8;
a. M Mouritzen et al. study (Ref. 60) is an abstract from last years ESMO Meeting (https://www.annalsofoncology.org/article/S0923-7534(20)41644-8/fulltext). According to the abstract only 578 patients were included in the 'study'. Furthermore, in the abstract it is stated that 15% of the patients had a PS ≥ 2. From where do you have the 90 patients? Please explain.

Reply: We agree with Reviewer comment. The information we included in our analysis was obtained from the corresponding poster available on-line.

b. H Kano et al. is another 'study' included in Table 8 with 527 patients and 79 patients with a PS ≥ 2 (https://onlinelibrary.wiley.com/doi/epdf/10.1111/cas.14590). In Table 8 you state that the number of patients was 85 including 16 with a PS ≥ 2. How do you end up with these numbers? Have you corrected for the missing data on PD-L1 expression? Please explain.

Reply: We thank the Reviewer for the request of clarification. Indeed, in the study by Kano et al, NSCLC patients treated with immunotherapy regardless of treatment line were included. On the other hand, our analysis focuses exclusively on first-line

immunotherapy. We obtained the corresponding information ("cohort 1") from the section 3.3 of the paper and the corresponding figures and supplementary materials.

Page 21-23:
1. Section 3.3 and 3.4 seems more as a discussion rather than listing of results and belongs to the Discussion paragraph.

Reply: We agree with Reviewer's comment. Nevertheless, both sections 3.3 and 3.4 contain precise data on the study included in the analysis. It is true that, especially for 3.3 section, the way of report data is in line with discussion, but we would like to keep the two sections here, in order to "discuss" in detail studies issues here, mentioning them again in a more general way in the "real" discussion.

Page 23:
1. Please include a discussion of possible differences in the level of PD-L1 expression among studies included in your meta-analysis and if this could have influence on patient outcome following treatment with ICI.
2. Please, include a critical evaluation of the data quality available for the meta-analysis.

Reply 1: We agree with Reviewer's suggestions, as PD-L1 levels have been shown to condition immunotherapy efficacy either as monotherapy or in combination with chemotherapy.

Changes in the text 1: We have included a paragraph, with the relative references, in the discussion.

Reply 2: We thank the Reviewer for this suggestion, as indeed almost all the studies included in our analysis are retrospective ones.

Changes in the text 2: We have included a paragraph in the discussion dealing with the quality of data included in our meta-analysis.

Page 25-32:
1. Please correct the reference list, it is not prepared with sufficient care and must be updated in accordance with the TLCR Guidelines for Authors. Below please find a few examples from your refence list that must be changed/corrected.
a. For Ref. 3. You state: 'Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüş M, Mazières J, Hermes B, Çay Şenler F, Csőszi T, Fülöp A, Rodríguez-Cid J, Wilson J, Sugawara S, Kato T, Lee KH, Cheng Y, Novello S, Halmos B, Li X, Lubiniecki GM, Piperdi B KD. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. N Engl J Med. 2018; September 25 [epub ahead of print].'

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This article was published in November 2018 and the correct reference for this publication is N Engl J Med. 2018; 379 :2040-2051.

b. For many of the references listed volume and page number is missing. It is not sufficient to write Thorax 1990, Clin Lung Cancer 2020, Oncologist 2020 etc.

Reply: We acknowledge that reference style is not adequate. Nevertheless, we had used a reference software to organize the bibliography, envisaging that, at the moment of potential publication, reference would have been modified and optimized by the editorial team with a more performant software. In the opposite case, we will eagerly provide the references manually.

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