Peer Review File

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Reviewer A:

Comments:

The authors are presenting a systematic review and meta-analysis evaluating ICI outcomes in oncogene addicted NSCLC. The topic is of high interest, and the work is well conducted.

Minor comments are following:

- in order to better address the relevance of the findings, the authors should comment on the heterogeneity test performed (only available in the tables)

We thank the Reviewer for the comment. We have added a paragraph in the Methods, with the aim of better describing the measures of heterogeneity. In addition, we added details of heterogeneity (that as correctly noted by the Reviewer were reported only in the Tables) also in the main text.

- in the section "EGFR-driven NSCLC and ICIs", the authors should include also data on PD-L1 upregulation in EGFR mutant NSCLC

We agree with Reviewer's comment. We have provided a sentence in this regard in line 169, adding to references (Chen et al. JTO 2015; Zhang et al. Int J Oncol 2016).

Reviewer B:

Comments:

The authors presented an extensive review on the role of immunotherapy in oncogene-addicted non-small cell lung cancer. I honestly congratulate the authors for the great work they did. They managed to gather a large amount of data on this interesting and still debated topic. There are just a few points that need to be addressed:

1. Title: "Immune checkpoint inhibitors in oncogene-addicted non-small cell lung cancer: A Systematic review and meta-analysis" I think just speaking about "PD(L)-1 inhibitors" would be better since it sounds to me more adherent to the actual content of the review.

We globally agree with this point, but actually tables contain data regarding ipilimumab trials. Albeit the contribution on these trials to the review (and to the current standard of care in oncogene-driven diseases) is limited, we would prefer to maintain the current title.

2. Abstract: Since a quantitative synthesis has been performed, I would expect some numbers to be reported in the "results" section of the abstract. Please add at the least the percentages of objective response rates.
We agree with Reviewer's suggestions and we provided response rates for EGFR-, KRAS-, ALK- and BRAF-driven diseases

3. English language: Overall, both the grammar and the syntax are very good. There are only a few mistakes somewhere. Please take care. Just a few examples below:
Line 59 "Differently from the others targetable alterations" other
Line 68 "resistance to targeted agents invariably occurs, and this open many questions" opens
And again.. Line 153, line 174, line 403..

We thank the Reviewer's for the careful reading of the manuscript and for signaling us these elements, that will contribute to its improvement. A grammar check has now been provided.

4. Novelty: please better highlight both in the introduction and in the discussion what this paper is adding to the field, since there are similar papers in the available literature. Just a few examples:
• Lee CK, Man J, Lord S, et al. Checkpoint Inhibitors in Metastatic EGFR-Mutated Non-Small Cell Lung Cancer-A Meta-Analysis. J Thorac Oncol. 2017 Feb;12(2):403-407. doi: 10.1016/j.jtho.2016.10.007. Epub 2016 Oct 17. PMID: 27765535.
• Jeanson A, Tomasini P, Souquet-Bressand M, et al. Efficacy of Immune Checkpoint Inhibitors in KRAS-Mutant Non-Small Cell Lung Cancer (NSCLC). J Thorac Oncol. 2019 Jun;14(6):1095-1101. doi: 10.1016/j.jtho.2019.01.011. Epub 2019 Feb 6. PMID: 30738221.

We agree with the Reviewer's that a large amount of literature is already available on this topic. Nevertheless, this is the first systematic review and meta-analysis to approach all the molecular entities defining oncogene-addicted lung malignancies. Gathering this evidence separately for individual gene aberrations is the first step to comprehend the real role of immunotherapy in different "molecular populations" of lung cancer patients. We decided to include both prospective and retrospective studies as both provided relevant data, still separating prospective and retrospective data as they are characterized by a global differential "quality".
We added a sentence in the introduction pointing out the main characteristics of

originality of our systematic review.

5. Methods: Please better define inclusion criteria for the trials/studies included in the quali-quantitative synthesis. You only properly stated the exclusion ones.
In addition, some methodology is missing in the meta-analysis. I recognize that the effort to collect all these data has been probably huge. However, some comments on heterogeneity and the chosen method should be add.

We thank the Reviewer for the request of a better definition of inclusion criteria of the studies in the synthesis. We have approached this relevant element in the Methods.
t about methodology to test heterogeneity (see also response to Reviewer A). We have added a paragraph in the Methods, with the aim of better describing the measures of heterogeneity. In addition, we added details of heterogeneity also in the main text.

6. Results: Authors performed a meta-analysis of the ORR. However, they did not show any comparison between mutated and wt patients, namely they did not report any odds ratio or p value. I think that could definitely add value to the paper.

We thank the Reviewer for this suggestion. We have added Odds Ratio between mutated and wild type patients, for EGFR and KRAS. However, in order to respect a study-level information allowing the exploration of heterogeneity among studies, we performed the calculation of Odds Ratio only for prospective studies, because in all prospective studies information was available for paired groups of mutated and wild type patients. On the contrary, not all retrospective studies included the information for both mutated and wild type patients, so retrospective studies were not included in the calculation of Odds Ratio.

7. Other scatter remarks throughout the text: KRAS/STK11/TP53 are STK11 and TP53 mutually exclusive? Please add some comments on that.

We found this comment very interesting. Indeed, Skoulidis et al (Cancer Discovery 2015) queried TCGA database and reported that only 4% of KRAS-mutated lung cancers harbored both STK11 and TP53 mutations. Albeit this cannot be strictly considered as a mutual-exclusive pattern, they reported that the occurrence of triple mutation is less frequent then expected by chance. Similar rates of co-occurring triple mutations have been reported by Schabath et al (Oncogene 2016).
We have detailed this information in the text.

And what about different codon mutations?

We agree on the fact that different codon mutations have been reported to potentially condition PD-L1 expression and ICI activity (see Jeanson et al JTO 2018). Nevertheless, authors deal only with four mutations occurring on the same codon G12 and on the G13C mutations. Globally, we do not estimate necessary to report the data on different KRAS codon mutants, also trying to limit the burden of information already present in the Review.

Line 338 "Although the results have not been published yet.."what are the authors referring to here?

We thank the Reviewer for having pointed out this expression was not clear. In this systematic review, we avoided to include data from congresses, in order to limit the evidence only to peer-reviewed studies. Nevertheless, we mentioned that KRAS status does not influence pembro + chemo activity and efficacy, but this have only been presented in congresses. We prefer to maintain the information, but we then remove the introduction sentence reported by the Reviewer, that can only be misleading.

8. Table 2: "Data about EGFR-positive patients in phase 1 or 2 clinical trials" you should probably add "one-arm trials" here.

We agree with Reviewer's comment and we added "single-arm trials".

9. References: Overall, I think the review is really comprehensive. Also the concluding remarks are really well-written and helpful for the reader. I only suggest to add some recent evidences from real-life studies.

• Line 494.. "additional pathological or molecular characteristics, that may help to select patients more likely to respond to ICIs, have been suggested" consider Cortellini A, Friedlaender A, Banna GL, et al. Immune-related Adverse Events of Pembrolizumab in a Large Real-world Cohort of Patients With NSCLC With a PD-L1 Expression ≥ 50% and Their Relationship With Clinical Outcomes. Clin Lung Cancer. 2020 Jun 21:S1525-7304(20)30204-7.10.1016/j.cllc.2020.06.010. Epub ahead of print. PMID: 32680806. Also consider Cortellini A, Tiseo M, Banna GL, et al. Clinicopathologic correlates of first-line pembrolizumab effectiveness in patients with advanced NSCLC and a PD-L1 expression of ≥ 50%. Cancer Immunol Immunother. 2020 May 30. doi: 10.1007/s00262-020-02613-9. Epub ahead of print. PMID: 32474768.

• Line 508.. “but a careful selection of patients is necessary, considering increased treatment toxicities” see Cantini L, Merloni F, Rinaldi S, et al. Electrolyte disorders in advanced non-small cell lung cancer patients treated with immune check-point inhibitors: A systematic review and meta-analysis. Crit Rev Oncol Hematol. 2020 Jul;151:102974. doi:10.1016/j.critrevonc.2020.102974. Epub 2020 May 4. PMID: 32416348;

• Line 510.. “when patients’ performance status has already worsened, and this may limit its efficacy” see also Facchinetti F, Mazzaschi G, Barbieri F, et al. First-line pembrolizumab in advanced non-small cell lung cancer patients with poor performance status. Eur J Cancer. 2020 May;130:155-167. doi: 10.1016/j.ejca.2020.02.023. Epub 2020 Mar 25. PMID: 32220780.

• Other are missing along the main text (e.g. line 440.. “While dabrafenib-trametinib combination is the novel standard of care for BRAFV600E mutant NSCLC” ref?)

We agree with the suggestions of the Reviewer, that we have incorporated in the references. Indeed, reference on dabrafenib/trametinib treatment for BRAFV600E NSCLC is already present (Planchard Lancet Oncol 2017).