Peer Review File

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Review Comments

Reviewer A

Thank you for submitting good paper.
Based on your review paper, I think ICIs might be another option in uncommon emerging driver mutations after progression on targeted therapy instead of chemotherapy. No comments for further revision.
Reply 1: Thank you very much for your review.

Reviewer B

This is a review on immunotherapy use in NSCLC patients with uncommon/emerging driver mutations. Overall, the essential information is included in the manuscript.

Comments as follows
1) The authors may consider to cover ROS1 and NRG1 as these are generally considered "uncommon mutations"; they are not exclusionary criteria from IO studies.
Reply 1: Although not specified, we excluded ROS-1 due to the already consolidated role of target therapies such Crizotinib and Entrectinib in this molecular subgroup, as per EGFR and ALK. Regarding NRG-1, we excluded this molecular target because we considered the data gathered in clinical trials too premature to express an opinion.

Changes in the text: We modified the main text (lines 81-82 and 105-109) in order to better specify why we excluded ROS-1 and NRG-1 mutations.

2) I do not agree with the comment "the vast heterogeneity found in KRAS population is the main reason for the several failures in developing a targeted therapy".
We modified the sentence (line 119) underlining the reference to the mutational and

co-mutational variety.

3) It may be worthwhile to mention the WCLC 2022 data on liver toxicity secondary to KRAS G12C inhibitor / IO combination

Reply 3: Thank you for the suggestion, we added the data in the corresponding paragraph.

Changes in the text: Lines 151-161.

4) It is worthwhile to mention that METex14 tumors harbor higher PD-L1 (Sabari et al. Ann Oncol 2018; Xu et al. Onco Targest Ther 2020). Recently, a report on Clin Lung Cancer actually reported fair clinical outcome (ORR 43%) for patients with PD-L1 high MET ex 14 NSCLC treated with pembrolizumab (Guisier et al. Clin Lung Cancer 2022)

Reply 4: We added the suggested data in order to give more details about the interaction between MET alterations and ICIs.

Changes in the text: Lines 259-261 and 269-275.

Minor edits:

1) Line 131. should be KP sub-type rather than KC sub-type

Reply: Thank you, we modified the text as advised.

Reviewer C

GENERAL COMMENTS:

This is a very valid and interesting theme to review. The analysis of the data can inform of new treatment regimens for patients with specific mutations in NSCLC for which treatment options are limited. I appreciate the effort of the authors in this review.

In general, I find that the information can be better organized, it is hard to follow sometimes. Also, I would appreciate more consistent details regarding the different trials mentioned in the manuscript. For some trials there are numbers regarding

progression free survival (PFS) or overall response rate (ORR) (i.e. lanes 111-115), while for others it just states a benefit on the outcome (i.e. lanes 176-177).

The title emphasizing "immunotherapy" and "uncommon emerging" driver mutations is not very accurate with the content of the review. For most of the genes included here the low incidence makes the immunotherapy information available very limited. For this reason, I feel that some of the statements and conclusions in the manuscript are too strong. In fact, the review presents more information regarding gene-targeted therapy, such as TKIs, than for immunotherapy.
Reply: we modified the text trying not to be too strong with che conclusions. We're also willing to change the title of the review: Emerging Drivers in NSCLC: is there a role for immunotherapy?

It is not clear how the list of genes was selected for the research. NSCLC have hundreds of mutations, most of them not shared between patients and therefore most of them are "uncommon". A rationale describing why those genes were selected or prioritized based on incidence, activating vs. loss of function mutations, mutations with known targeted therapies, etc. would be helpful.
Reply: We excluded genes with already approved and experienced first line options (ALK, EGFR, ROS-1). We considered as emerging all those targets with active TKIs but no phase III data of efficacy.

In addition, the manuscript would benefit from more specific language regarding which NSCLC sub-type are they talking about. In particular, I think the review should differentiate between the main 2 sub-types of NSCLC, lung squamous cell carcinoma (LUSC) and lung adenocarcinoma (LUAC). These two sub-types are very different regarding mutations and also response to immune checkpoint inhibitors (ICI). LUSC is highly smoking related, present one of the highest rates of mutations of all cancer together with melanoma, we don't know the driver mutations for LUSC, and these patients respond better to ICI treatment. On the other hand, LUAC is highly heterogenic, the range of mutations in these patients varies enormously, and those with a few mutations in driver oncogenes (such as EGFR, KRAS), frequently non-smokers, are the ones that do not respond to ICI. I understand that the division of

NSCLC in sub-types would make even harder to analyze the data for those mutations with low frequency in the patients. However, I would recommend to make the distinction at least for KRAS (see comments below for details). Also, in line with this, I would probably not consider KRAS as an "uncommon" or "emerging" mutation in NSCLC.

Reply: thank you we modified the text as advised. Almost all drivers are mainly expressed in adenocarcinomas, except for KRAS.

Changes in the text: We modified the text as advised (lines 71-74 and 130-135).

SPECIFIC COMMENTS:

1. Abbreviations that should be spell out: CPis, PFS, HR, ORR, OS, MSI-H.

Reply 1: We added an abbreviations index.

2. Figure does not add information to the manuscript, I recommend to remove it.

Reply 2: Figure has been removed.

3. Term "oncogene-addicted tumors" is confusing for me, I think the authors mean "tumors with oncogenic driver mutations" but I am not sure.

Reply 3: We modified the text.

4. The reference to or definition of "common" oncogenic drivers seems a bit arbitrary. For instance, EGFR and KRAS are among the most commonly mutated genes in NSCLC, but the authors include KRAS in the "uncommon emerging molecular targets" group (Abstract, lines 33-34; Introduction, lines 76-78). In fact, in the section of KRAS mutations, they agreed that "KRAS mutations are the most frequent proto-oncogene mutations in NSCLC, with a prevalence of 20 to 30%".

I think language should be reviewed through the manuscript to re-evaluate the use of the terms "common", "uncommon" or "emerging".

Reply 4: We modified the title and the text to be more accurate.

5. Discussion, lane 118-120: "Differently from the classic non-smoker pattern in the oncogene-addicted family, KRAS G12C mutations mostly happen in smoker or former-smoker patients, as also confirmed by their strict association with tobacco-induced mutations"-

They way this written it seems that for all NSCLC, those with smoking history have more mutations in KRAS, which is not true. NSCLC is subdivided in 3 subtypes:

squamous cell carcinoma (LUSC), adenocarcinoma (LUAD) and large cell carcinoma, the most common being LUSC and LUAD. The statement might be true for LUAD but definitively not for all NSCLC cases. For instance, LUSC is highly smoking related and still the prevalence of KRAS mutations in LUSC is about <2% according with the TCGA data. Also, TCGA data shows about 11% KRAS mutations in never-smokers LUAC patients, so I recommend to modify the sentence: "strict association with tobacco-induced mutations" (Lane 120).

Reply 5: We modified the text in order to better specify the correlation between KRAS and smoking status (lines 130-132).