Peer Review File

Article information: http://dx.doi.org/10.21037/tlcr-20-772

Reviewer A: Major Revision

Comments:

This review covers an interesting topic, discussing the use of immunotherapy in NSCLC harbouring oncogene alterations.

Review Comment 1: the review is well written but too long and sometimes out of focus. Please focus only on activity data and report data of safety, exclusively in a table.

Reply 1: Thank you for this feedback – we have consolidated our paper further. Discussion around safety data has been removed from each section and summarised in the attached tables with a focus on safety data and efficacy. In particular we have consolidated the "BRAF" and "KRAS" sections significantly to ensure they are in line with our key message around immunotherapy in oncogene addicted tumours. We have utilized specific subheadings such as "TKI + immunotherapy" or "Immunotherapy combinations" to help simplify our discussion for each oncogene group.

Review Comment 2: line 29: consider to modify application with some synonymous more appropriate for the clinical setting

Reply 2: We have now removed the term "application" and replaced it with "use." Please see line 29.

Review Comment 3: reduce length of paragraphs discussing immuno-combo in trials that did not include patients with EGFR mutations

Reply 3: We have consolidated these sections further to limit discussion on the immunotherapy combination studies not including EGFR patients. Please see lines 165-180 for changes to the EGFR combination immunotherapy discussion. We have now focused on the upcoming studies that will look at this approach in EGFR mutant patients i.e. the Illuminate and Checkmate-772 studies.

Review Comment 4: to date, no target therapies are available for the treatment of KRAS positive NSCLC, on the contrary we have different agents (tepotinib and capmatinib) approved for the treatment of MET skip15 lung tumors. Please, consider to develop a specific paragraph for the MET mutations, moving data of KRAS in the last combined paragraph with ROS, RET and HER2.

Reply 4: Thank you for this feedback. We have expanded our discussion on MET mutant lung cancer and mentioned the efficacy of TKIs particularly that of capmatinib, tepotinib and savolitinib. Our paragraph on lines 408-415 highlights the role of TKIs in MET altered lung cancers. An in depth discussion of TKI therapy in MET mutant lung cancer is beyond the scope of this paper where the focus is on immunotherapy. We feel KRAS mutations remain an important subgroup of lung cancers to review when discussing immunotherapy and thus have kept this subgroup in its own section. Immunotherapy has shown much promise in KRAS-mutant NSCLC and a particular focus here has been on the various co-mutations that occur. We have, however, consolidated this discussion significantly so it is more in focus with our discussions around immunotherapy. Please see 255-338 for the changes to this section.

Review Comment 5: 6) for this kind of review, a couple of figures are required to improve the scientific impact of the manuscript
Reply 5: Thank you for this suggestion – we have added an additional figure describing the frequency of oncogenic mutations in NSCLC.

Reviewer B: Minor Revision

Comments:
The authors summarize the value of immunotherapy in oncogene addicted NSCLC and review the current literature on this important topic. The manuscript is well written, straight forward and informative. Never the less there are some minor points to reconsider:

Review Comment 6: - Most patients with driver mutations will receive chemotherapy and/or IO in later lines due to the good efficacy of TKIs. However, in most cases response to chemotherapy is quite good. Please discuss your approach to a sequential Treatment. When should checkpoint inhibitors be given? With our without chemo? At last attempt or earlier? When do you suggest rebiopsies?
Reply 6: We have added discussions about our therapeutics approaches to the paper and summarized current approaches at the end of each section under the heading "Summary." (i.e lines 182-186 for EGFR NSCLC, 240-242 ALK NSCLC, 333-337 KRAS NSCLC, 388-393 BRAF NSCLC).
We have summarized our current approach including the practice of re-biopsy in current clinical practice on lines 435-442.

Review Comment 7: Please give your view on patients with more than on oncogenic driver mutation. There is a current publication, that collected a cohort of 23 patients with multiple mutations and their response to immune checkpoint Inhibitors (Oncol Res Treat. 2020;43(6):289-298)

Reply 7: Thank you for this suggestion. We have included discussion around co-mutations in regards to KRAS mutant tumours – please see lines 266-278. Other co-mutations (i.e TP53) have less clinical applicability currently and require further prospective research. We have reviewed the suggested paper and included it in our discussion. Please see lines 417-418.