Peer Review File

Article information: https://dx.doi.org/10.21037/pcm-23-19

Review Comments

General comments:
This is a generally well-written paper discussing both biological and clinical aspects of TRK inhibitors. However, there are a few aspects that need to be improved before the manuscript is ready for publication:
• TRK inhibitors are classified as tissue agnostic drugs, which must be mentioned and discussed in the introduction of your paper: Please see FDA, Tissue Agnostic Drug Development, October 2022 (https://www.fda.gov/media/162346/download), N Engl J Med. 2017; 377: 1409-1412, and Expert Rev Mol Diagn. 2020; 20: 583-592.
• In the introduction and the running title, you mention NSCLC. However, reading your manuscript it is not very clear that NSCLC is the focus. Please consider making a table on the outcome for the lung cancer patients treated in the different studies.

Dear Reviewers,

Thank you very much for carefully reading our work and giving us ideas for improving it. As suggested in the general comments, we have expanded the introduction section by explaining the definition of agnostic drugs, citing the FDA's approval of pembrolizumab as the first tissue-agnostic therapy, and using the suggested bibliography. We have also created a paragraph dedicated to the efficacy of TRK inhibitors in NSCLC patients (6.1.2) and included a specific table (Table 3).
Below are responses to specific comments.

Specific comments:

Comment 1: Line 24: Trka in the abstract must be changed to TrkA
Reply 1: Thanks for reporting the oversight, we have changed the text.

Comment 2: Line 43- 51: The introduction is very short. Please expand the introduction with a general discussion of tissue agnostic drugs. For your information, the first cancer drug to achieve this status was pembrolizumab, when it was approved for the treatment of adult and pediatric patients with unresectable or metastatic, MSI-H or dMMR solid tumors in 2017 (N Engl J Med. 2017; 377: 1409-1412).
Reply 2: Thank you for this important elucidation. We edited the introduction and cited the approval of pembrolizumab as the first tissue-agnostic drug (lines 44-59).

Comment 3: Line 217-276: Molecular assays that are used to select patients for a specific medical therapy, are in both US and Europe classified as companion diagnostics and regulated by the FDA and EMA. In the US, this requires an FDA approved assay, and in Europe it will soon be required that a CE-marked assays must be used. Please briefly mention this issue and briefly discuss the concept of companion diagnostics.
Reply 3: Thanks for highlighting this issue. We introduced the definition of companion diagnostics and briefly discussed the issue of FDA and EMA regulations (lines 285-302).

Comment 4: Line 289-319: In order to put NSCLC in focus, please describe the outcome for the lung cancer patients in the Drilon et al. paper (N Engl J Med. 2018; 378: 731-739).
Reply 4: Thank you for your specific request, we have added a dedicated paragraph in which we reported in more detail the outcome for lung cancer patients in the Drilon et al. paper (lines 392-417).

Comment 5: Line 313-315: You mention that larotrectinib was the first histology-independent agnostic cancer drug to be approved in Europe in 2019. For your information the first approved tissue agnostic drug pembrolizumab. In May 2017, the FDA approved this drug for MSI-H or dMMR solid tumors in the USA, which should be mentioned.
Reply 5: Thanks for the correction, we have reworded the text (lines 338-340).

Comment 6:
Line 320-342: Please describe the outcome for the NSCLC patients in the Doebele et al. paper (Lancet Oncol. 2020; 21(2): 271-282).
Reply 6: Thank you for your specific request, we have added a dedicated paragraph in which we reported in more detail the outcome for lung cancer patients in the Doebele et al paper (lines 424-443).

Comment 7:
Line 343-367: Please describe the outcome for the lung cancer patients in the Iannantuono et al. paper (J Pers Med. 2022; 12(11): 1819).
Reply 7: Thank you for your specific request, we have added a dedicated paragraph in which we reported in more detail the outcome for lung cancer patients in the Iannantuono et al. paper (lines 418-423).

We hope that we have fully responded to all Reviewer comments.

Sincerely,
Maristella Bungaro
Edoardo Garbo