Peer Review File

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Reviewer A

The commentary by Thu and Yoon is a well written manuscript that summarizes the current knowledge on the potential role of ATM genetic alterations in lung cancer.
I have only few suggestions that the authors may want to take into consideration to further improve their manuscript:

Comment 1: The authors may want to add a table summarizing the main findings of the two commented manuscripts on the molecular and clinical characteristics of ATM mutant lung cancer

Reply 1: We agree that a table to summarize the key characteristics and findings of the Ricciuti and Vokes studies would improve our manuscript. This was also suggested by Reviewer B. We have added Table 1 to the manuscript.

Changes in the text: Please see the revised manuscript for Table 1 (pages 8-9).

Comment 2: The data related to ATM mutations might be discussed in a more general context on the role of potential germline pathogenic variants in lung cancer (PMID: 37992258) and more generally in cancer (PMID: 37568048; PMID: 37167765) in the context of tumor-only sequencing.

Reply 2: We thank the reviewer for pointing out these highly relevant recent publications. We agree that they should be referenced in our commentary. Our revised manuscript cites these papers to describe the frequency of germline pathogenic variants in lung cancer in order to highlight their clinical significance, and to further indicate that tumor only sequencing can be used as a tool to identify them.

Changes in the text: We have added the following text to highlight the recent and relevant papers noted by Reviewer A [Ref 5 = Sorscher et al, 2023; Ref 21 = Tung et al, 2023; Ref 22 = Normanno et al 2023],

(Page 5, Paragraph 2) “Recent reports that 4-15% of lung cancers harbor PVs not only in *ATM* but also in *BRCA1*, *BRCA2*, and *CHEK2* (5,19,20) emphasize that studies to understand the clinical significance of these variants are also warranted since they could inform the clinical management of patients.”

(Page 5, Paragraph 3) “However, in recognition of their clinical implications, analytical methods to confidently identify germline PVs from tumor only sequencing data are emerging (19,21,22).”

Reviewer B

The commentary by Drs. Thu and Yoon provides sufficient background information to contextualize the recently published report to understand the role of ATM in Non-Small Cell Lung Cancer. The questions are clearly stated and justified based on the existing literature, objectives of the study, highlighting the implications of the findings of ATM in NSCLC, co-mutational landscape of ATM mutant NCSCL for advancing our understanding of lung cancer tumor biology and limitations.

Comment 1: Although authors mentioned that "the correlations reported between ATM status and patient outcomes were not consistent between the studies" (Vokes et. al and Ricciuti et.al – it would be helpful for the readers if authors provide detailed description and differences in the patient characteristics and samples size that resulted in the inconsistency in the two studies. Including the comparison of the outcome data in the two studies would further strengthen the article.

Reply 1: We agree that these details with respect to the studies described and their findings regarding outcomes can be more clearly articulated. As such, we have now included Table 1 (as suggested by Reviewer A) to provide a clear and simple head to head comparison of the study cohorts and the findings, including those pertaining to outcome.

Changes in the text: Incorporation of Table 1 as shown above in response to Reviewer A, Comment 1 (pages 8-9).

Comment 2: It would be important to also note that Vokes et.al. data might overlap with Ricciuti et.al study cohort - it is not clear the extent of the overlap.

Reply 2: We thank the reviewer for raising this point. The newly added Table 1 aims to provide some context regarding potential overlap in the cohorts examined. However, we found that the extent of the overlap cannot be determined based on the information provided. It should be noted, however, that the survival analyses from the Vokes study were limited to the Immunostain shows intact expression of fumarate hydratase (FH, fumarase).-FMI CGDB cohort.

Changes in the text: Please see the revised manuscript for Table 1. We have also added the following text to acknowledge the potential overlap in data between the studies,

(Page 3, Paragraph 1) "It is worth noting that since both studies included NSCLC samples from the Memorial Sloan Kettering (MSK) Cancer Center and the Dana Farber Cancer Institute (DFCI), overlap between the patient cohorts analyzed is probable. Thus, although the extent of overlap is unclear from the sample information provided, this could contribute to similarities in the study findings. It should be noted, however, that the survival analyses in the Vokes et al.'s study was limited to the FH-FMI CGDB cohort."

Overall, it is well-written and logically organized, with clear language and provide a valuable contribution to the field of cancer research by elucidating the role of ATM in NSCLC.

Reply: Thank you.

Reviewer C

Comment 1: Yes, I concur with the author's commentary on the article titled 'Clinicopathologic, Genomic, and Immunophenotypic Landscape of ATM Mutations in Non-Small Cell Lung Cancer' by Ricciuti et al., published in Clinical Cancer Research 2023. The thorough review of recent studies and existing literature lends an asset to the idea that ATM mutations bear potential clinical significance regarding overall survival and therapeutic response in non-small cell lung cancer (NSCLC) patients. However, the inconsistent clinical associations documented in the literature warrant additional studies to firmly establish the clinical significance of ATM mutations in NSCLC. The suggestion of coordinated genetic testing led by oncologists, especially in regions with limited access to genetic counseling, is a valuable proposal for refining clinical management. Hence, I recommend accepting this commentary article by L et al.

Reply 1: We thank the reviewer for their enthusiasm and praise for our commentary.