Peer Review File

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Reviewer A

Comment 1

- *"This Editorial Commentary manuscript is average, including about 4 studies that adversely reflect the knowledge significance of the paper and references 2, 3, and 4 must be updated they are too old and there are updated statistics about small-cell lung cancer."*

Response 1

- We have updated the refences and instead reference the latest statistics from the American Cancer Society in their published *2023 Cancer Facts and Figures*. We have deleted previous references 2-4 but added a new reference 2 which is from the American Cancer Society

Changes in the text

"*The histological subtype small-cell lung cancer (SCLC), which represents about 13% of lung cancer cases (2, 3), has a very poor prognosis with a 1-year survival rate of only 36% (4).* "

Has been changed to:

"*The histological subtype small-cell lung cancer (SCLC), which represents about 13% of lung cancer cases (2), has a very poor prognosis with a 2-year survival rate of only 16% and 19% in men and women, respectively (2).*" (p. 2 l. 25-27)

Comment 2

- ***"****The presented studies in this manuscript have to be more deeply discussed. However, the manuscript pools information together concerning ctDNA in a rare form of lung cancer (small-cell lung cancer) but the presentation of these informations can be improved****"***

Response 2

- This is an editorial comment focusing on the study by Sivapalan et al. published in Clinical Cancer Research. We have therefore focused our interest on the details of this particular study. We have compared the results of this study to other similar studies in SCLC where these studies are discussed in smaller detail. However, we have added a more information about the similar studies in the revised version.

Changes in the text

Added to the section about the Iams et al. study "*The ctDNA is detected using a targeted NGS panel designed by the authors to specifically identify mutations frequently observed in SCLC (13).*" (p. 3 l. 68-69) and

"*As an example, in the study by Iams et al. from 2020 which uses targeted NGS panel specifically designed for SCLC RB1 mutations is detected in 11/23 (48%) patients (11).*" (p. 5 l. 128-129)

Added to the section about the Feng et al. study "*They also demonstrated that ctDNA responses correlated with radiographic responses and in some cases could detect disease progression earlier than CT scans*." (p. 3 l. 81-83)

Comment 3

- "*Like what do authors expect to tell readers from this manuscript what is the authors' opinion about ctDNA in clinical use …?"*

Response 3

- We have added a section which describes how we recommend that standardization of ctDNA dynamics is necessary to implement ctDNA in clinical practice (see response to reviewer C). In addition, we have refenced an ongoing prospective randomized clinical trial in NSCLC and we highlight that similar studies performed in SCLC will be needed to implement ctDNA for SCLC patients as well (see response to reviewer B).

Changes in text

See response to reviewer B and C

Reviewer B

Comment 1

- **"***The authors rightfully note that "The method would be highly relevant if it was possible to detect disease progression earlier with ctDNA, given that molecular progression could be used as a predictive marker for change in treatment strategy". Possibly the authors of this commentary could support some of their statements in the final paragraphs on the above matter with some references, such as: https://www.sciencedirect.com/science/article/pii/S2468294221001088. We are indeed all looking forward to studies that compare ctDNA-guided treatment to care guided via the more invasive (and possibly more slowly responding) imaging-based standard-of-care. (Not only for treatment, but also for diagnosis by the way, see: https://www.sciencedirect.com/science/article/pii/S0169500223000442)"*

Response 1

- We have added two refences (where one of them was suggested by reviewer B) to the paragraph about early progression. In addition, we have added a paragraph about an ongoing clinical trial in NSCLC using ctDNA guided treatment decisions in a randomized controlled setting. We suggest that this should also be made for SCLC

Changes in text

Added two references to the sentence "*The method would be highly relevant if it was possible to detect disease progression earlier with ctDNA, given that molecular progression could be used as a predictive marker for change in treatment strategy (9,19)*" (p. 5 l. 136-138)

Added the following section "*One very interesting prospective randomized clinical trial for NSCLC (PRELUCA, NCT05889247) is currently ongoing. The study will assess how tumor-informed liquid biopsies can be used to make treatment decisions for NSCLC patients receiving immunotherapy. In the future, similar studies will hopefully also be conducted for SCLC as the field of ctDNA in SCLC is expanding.* " (p. 5-6 l. 143-149)

Reviewer C

Comment 1

- *"Whilst the conclusion is not unsurprisingly that more clinical studies are needed, I think it would have been useful to also comment or even 'recommend' that attempts at some sort of methodology standardisation would also be useful. Especially as the authors do explain very nicely how many of the existing studies are not easily comparable due to the different methodologies utilised."*

Response 1

- We have now added a section where we suggest how ctDNA dynamics could be standardized where we include a reference to a recent paper which suggests the use of ctDNA-RECIST.

Changes in the text

Added the following section "*In order for ctDNA to be used in clinical practice to guide treatment strategies we regard standardization of ctDNA dynamics as essential. One approach could be to implement ctDNA-Response Evaluation Criteria in Solid Tumors (ctDNA-RECIST) (14). Using ctDNA-RECIST it would be possible to compare different studies using ctDNA for monitoring patients and thereby enabling wider implementation of liquid biopsies in clinical practice*." (p. 4 l. 91-96)