Peer Review File

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Review Comments

Reviewer A

In this commentary article, Corbett et al. nicely described recent advances in SCLC particularly focusing on RB. I have some minor comments as below:

1. Line 51: The study by Fabres-Aldana et al. is not cited.

Reply 1: We appreciate your feedback and close attention to this text. Thanks for catching this oversight!

Changes in text: We have added the citation for Fabres-Aldana et al.

2. Line 67: “inhibiters” should be “inhibitors.”

Reply 2: We appreciate your feedback and close attention to this text.

Changes in text: We have corrected this error.

3. Line 122: “serious” should be “series.”

Reply 3: We appreciate your feedback and close attention to this text.

Changes in text: We have corrected this error.

4. Line 148: There are no references provided to support the claim that “tumor microenvironment plays a crucial role in regulating plasticity even without therapeutic pressure.” Furthermore, I recommend to refer to the important involvement of epigenetic mechanisms driving SCLC heterogeneity supported by several studies (e.g., Science.2018;362:91-95; eLife.2021;10:e66524; Nat Cell Biol.2023;25:1346-1358).

Reply 4: Thanks very much for this feedback and for the interesting resources. This is a very important point and emphasizing this will improve the paper significantly.

Changes in text: Further details have been added about the role of epigenetic remodeling driving SCLC.

Reviewer B

There is no reference to the paper by Febres-Aldana.

Reply 1: We appreciate your feedback and close attention to this text. Thanks for catching this oversight!

Changes in text: We have added the citation for Fabres-Aldana et al.

The main take home lesson for me is that NGS does not give information on whether genes are expressed or not. IHC does. This point could be stressed more, also in the light of the information that epigenetic regulation plays a role in the differentiation into subtypes od SCLC.

Reply 2: We appreciate your feedback, this is an important point highlighted this paper.

Changes in text: We have added additional details emphasizing the importance of epigenetic regulation in determine subtypes of SCLC with potential therapeutic implications.

Reviewer C

The Editorial Commentary is well-written, and aside from minor revisions, it appears to be no problem.

#1 Line42

The reviewer thinks that the readers would find it easier to understand if this part is explained as chemotherapy combined with PD-L1 blockade instead of 'PD-L1 blockade'

Reply 1: We appreciate your feedback and close attention to this text. Thanks for catching this oversight!

Changes in text: We have changed the text to say "chemotherapy combined with PD-L1 blockade"

#2 Line 61

Please standardize the capitalization throughout the entire document, as in this section, 'Tp53' and 'Rb1' are written in lowercase. Please ensure consistent uppercase formatting for these gene names.

Reply 2: We appreciate your feedback and close attention to this text. Thanks for catching this grammatical oversight!

Changes in text: We have changed the text so that all gene names use consistent uppercase formatting.

Reviewer D

The topic of this commentary is very interesting. To date, the most appropriate therapeutic choice

for SCLC remains a topic of debate. Identifying biomarkers and prognostic/predictive factors therefore represents an urgent unmet need as at present SCLC, unlike diseases such as NSCLC, remains orphaned of targeted therapies.

The subdivision of SCLC into transcriptomic subgroups aims to identify prognosis and, if possible, increasingly specific therapeutic choices. To date, however, it remains difficult to apply this classification in a real-life context.

I believe that the title of the work is consistent with what is written within it; reading it allows a complete overview of the subject matter.

IHC, correlated with the analysis of p16 and CyclinD1, compared with NGS is in this context the most correct investigation for detecting Rb procient tumour. This allows us never to underestimate even earlier investigation techniques.

In this regard, it is worth mentioning here the paper by Wildey et al. The topic addressed and the possible new therapeutic scenarios could also be of interest to other diseases with neuroendocrine differentiation, such as prostate and pancreas. This would allow comparisons between different diseases and help to increase the sample of diseases that can be included in studies.

Reply 1: We appreciate your feedback and close attention to this text. A reference to the 2023 paper by Wildey et al. "Retinoblastoma expression and targeting by CDK4/6 inhibitors in small cell lung cancer. Mol Cancer Ther. 2023 Feb 01; 22(2) 264-273
DOI: 10.1158/1535-7163.MCT-22-0365" is included in this text.

We agree that the principles driving lineage plasticity in SCLC are also likely driving neuroendocrine differentiation in other cancer types and this is an important area for future exploration. This is mentioned in the final paragraph.

It should be emphasized that patients with SCLC are burdened with a performance status according to ECOG > 1. Identifying increasingly individualized therapies and administrations other than the intravenous route could help in the overall management of the patient.

Reply 2: We appreciate your feedback – this is a important point given so many patients have a poor performance status at presentation.

Changes in text: A sentence has been added highlighting the importance of finding alternatives to systemic chemotherapy given the poor performance status of many patients presenting with advanced SCLC.