Peer Review File

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Reviewer A:

I am not 100% convinced this piece is a valuable addition to the literature. ADAURA OS update is relatively old news by now.

The manuscript in its current form completely skips over the main points of ongoing discussion on ADAURA in the #LCSM community, e.g., what the flaws are in the ADAURA trial design which potentially invalidate the remarkable DFS/OS findings – Dr West and Dr Pennell have recently published a commentary on this.
https://acsjournals.onlinelibrary.wiley.com/doi/10.1002/cncr.35112?af=R

If you go ahead with revision could the piece, be restructured – there is a lot of detail on DFS/OS hazard ratios and little critical appraisal.

The discussion of financial modelling on adjuvant Osimertinib is probably the main interesting point raised here which I would be keen to see expanded – but other, distinct points need to be added for making this publishable.

The medical English in this piece is subpar – may I suggest the authors got a colleague fluent in medical English to proofread their draft next time they wish to submit a paper, or the relevant AI tools.

Suggested edits to the text

Being an invited article, we had length limits imposed by the editors and therefore could not go into other topics that could certainly increase interest in our work. However, we tried to follow your suggestions and modified the text. We hope you will find the final work better suitable for the journal.

Lines 32-39 – please clarify the study design – adjuvant chemotherapy was allowed in ADAURA before Osimertinib (vs. ALINA which has a different study design comparing ALK-targeting therapy AGAINST platinum-based chemotherapy).
We have added a sentence in the text. We have corrected the manuscript in red.
Change in the manuscript: lines 37-38.

Line 39 – remove the word ‘achievement’; use ‘rapid’, not ‘quick’
We have corrected the manuscript in red.
Change in the manuscript: line 45.

Lines 40-41 – I would just say ‘in resected EGFRm NSCLC’ – no need to reference stage here

We have corrected the manuscript in red.
Change in the manuscript: line 49.

Lines 42-43 – rephrase – let's just say 'platinum-ineligible patients could not benefit'
We have corrected the manuscript in red.
Change in the manuscript: line 50.

Lines 45-50 – the flow is off. What I presume you want to say is that (1) Osimertinib was approved in advanced disease (2), meanwhile, earlier-generation EGFR TKIs were being tested in the adjuvant setting with mixed results. Please elaborate on the results of trials of earlier EGFR TKIs as adjuvant therapy? why didn't they have practice-changing outcomes.
This sentence was not clear. We have rewritten it. We meant that all EGFR TKIs were initially evaluated and approved for the first line therapy. We have also added a paragraph on the main adjuvant studies with EGFR TKIs, supporting the data reported in Table 1.
We have corrected the manuscript in red.
Change in the manuscript: line 54 and lines 56-69.

Line 54. 'Primary report', not 'reporting'.
We have corrected the manuscript in red.
Change in the manuscript: line 79.

Lines 49-55 – references are missing
We have corrected the manuscript in red adding the references.
Change in the manuscript: lines 79, 80 and 83.

Line 55. 'Across all patient subgroups'
We have corrected the manuscript in red.
Change in the manuscript: line 81.

Lines 56 – could you make it painfully clear that 'type of EGFR mutation' in this context means ex19del vs. L858R – patients with other mutations were not included in this trial.
We have corrected the manuscript in red.
Change in the manuscript: line 82.

Line 57 – Rephrase – 'consistency' doesn't fit here? remarkable activity
We have corrected the manuscript in red.
Change in the manuscript: line 83.

Line 67-69 – interesting point – can you hypothesize why they did that?
Thank you for highlighting this point. The authors of ADAURA have updated their analysis according to the new TNM classification making it easier, in our opinion, to prescribe osimertinib in daily clinical practice. We hypothesized that the maintenance of the benefit of osimertinib is due to the substantially overlapping disease stages of the enrolled patients. We added a sentence in the text.

Change in the manuscript: lines 87-92 and 101-103.

Line 72 – 'superimposable'?????
We have corrected the manuscript in red.
Change in the manuscript: line 106.

Line 76 – 'for which' doesn't fit, please rephrase
We have corrected the manuscript in red.
Change in the manuscript: line 117-118.

Line 77-78 – I would be much more interested in rates of intracranial CR and intracranial PFS from FLAURA
Thank you so much for alerting us to this issue. We have corrected the manuscript in red.
Change in the manuscript: line 118-120.

Line 79 – remove 'a'
We have corrected the manuscript in red.
Change in the manuscript: line 120-122.

Line 81-83 – such studies are ongoing – discuss them. Use 'three' as opposed to '3' throughout the text please.
We have corrected the inaccuracy. Hope this modification is correct. We have corrected the manuscript in red.
Change in the manuscript: lines 125-127.

Line 84 – replace with either 'disease free survival rate' or 'likelihood of being alive and disease-free'
We have corrected the manuscript in red.
Change in the manuscript: lines 127-128.

Line 86 – I guess you mean the ADAURA investigators?
This sentence was not clear. We have rewritten it. We have corrected the manuscript in red.
Change in the manuscript: line 131-132.

Line 87 – this is phrased horribly, please try again.
We have rewritten the sentence. We have corrected the manuscript in red.
Change in the manuscript: lines 131-134.

Line 92 – add 'in the adjuvant setting'.
We have corrected the manuscript in red.
Change in the manuscript: line 140.

Lines 99-100 – I want to hear much more about toxicities and how they compare to FLAURA.

Thank you for the valuable suggestion. We have added a paragraph about this. We have corrected the manuscript in red.
Change in the manuscript: lines 149-154.

Line 101-103 – 'these data are not negligible', 'there are some toxicities involved', 'manage them properly' – poor phrasing, try again
We have corrected the manuscript in red.
Change in the manuscript: lines 154-156.

Line 113 – use 'needs to' here
We have corrected the manuscript in red.
Change in the manuscript: line 169.

Lines 117-119. I am intrigued by this perspective, and by the fact that different models yielded different outcomes. Please expand. Spell out QALY. The phrasing is poor – please try again. 'If it was willing'? Who? Established threshold? Established by whom?
Dear reviewer, thank you for appreciating our cue. We have expanded the discussion as requested. We have corrected the manuscript in red.
Change in the manuscript: lines 174-177 and 190-192.

Line 125-129 – this is still somewhat controversial. Are we truly curing patients, or just delaying relapse and death?
In our opinion, considering the initial positive survival data, osimertinib could cure a higher percentage of patients than post-operative chemotherapy or surgery alone. However, we still await the final results of the study with the long-term survival rates. We have corrected the manuscript in red, as you suggested.
Change in the manuscript: lines 186-190.

Line 130 – setting???
We have corrected the manuscript in red.
Change in the manuscript: line 193.

Lines 130-134. Do these trials have names? I imagine you are quoting TARGET as one of them. So much easier to go look them up afterwards if a trial name is available…
We have corrected the manuscript in red.
Change in the manuscript: lines 195-198.

Line 135 – financial toxicity, not 'economic burden'. Rephrase this sentence – very controversial as it is currently. Something like 'biomarkers predicting which patients do benefit from adjuvant osi and which patients can be safely spared three years of adjuvant treatment are needed'
Thank you for catching this. We have rewritten that statement, following your advice. We have corrected the manuscript in red.
Change in the manuscript: lines 198-201.

Line 138 – why this reference in particular? There are 100000 papers on ctDNA out there
we decided to report a reference summarising what is the "state of the art" in the use of ctDNA as a marker of minimal residual disease. The type of article and its intent (commentary letter) as well as the text length restrictions, do not allow us to extend the discussion/references.

Lines 139-144. Has ctDNA analysis from ADAURA not been presented at a conference yet? Please do some digging.
Dear reviewer, the ctDNA analysis of the ADAURA study is still ongoing, unfortunately we found no data presented. We have reported an ongoing trial that is evaluating treatment with another EGFR TKI (icotinib) based on MRD.
We have corrected the manuscript in red.
Change in the manuscript: lines 213-215.

Lines 148. Abrupt change of topic. Draw some conclusions? 'Adj osi is now firmly established as SOC in this setting …'
The conclusion was lacking. We have corrected the manuscript in red.
Change in the manuscript: lines 232-233.

Lines 151-152. ALINA has been presented – discuss. I am aware of a trial in progress ith adjuvant selpercatinib - ? LIBRETTO-432. Any others already in progress?
Dear reviewer, thank you for this suggestion. Considering the type of article and the limitation of the length of text, it was not possible to expand the discussion on the other ongoing studies of adjuvant with TKIs. However, we have added a sentence in the text to make our work more precise.
Change in the manuscript: lines 238-241.

Line 153. 'Healing'????? Please relace with 'cure'.
We have corrected the manuscript in red.
Change in the manuscript: line 243.

Lines 154 – rephrase. The role is clear – adj osi is SOC. The rest remains to be investigated.
We have modified the text as suggested. We have corrected the manuscript in red.
Change in the manuscript: line 244.

Line 155- 'predictive/prognostic'.
Thank you so much for pointing this out. We have modified the text as suggested. We have corrected the manuscript in red.
Change in the manuscript: line 248.

Line 172 – 'References', not 'bibliography'
We have corrected the manuscript in red.
Change in the manuscript: line 265.

Tables 1, 2 – not references in the text, please add reference.
the table references are reported in lines 60 and 69, respectively.

Table 2 – could you add trial names and add more details on treatments?
We have included more details on treatments in Table 2. We have corrected the table in red.

Line 181 – this reference is incomplete
We have corrected the manuscript in red.
Change in the manuscript: lines 273-275.

Reviewer B:

This is a brilliantly written editorial commentary on the updated results from the ADAURA trial. The authors reflect in depth on the efficacy and safety of osimertinib in the adjuvant setting in EGFR-mutant NSCLC patients following complete resection. In addition, the authors discuss possible financial limitations with the usage of osimertinib in the adjuvant setting as well as future scenarios for NSCLC patients with other oncogenic drivers. I recommend this editorial commentary for publication.

Dear reviewer, we appreciate your support of our work and are pleased to know that you have not requested any changes or additions to our work.

Reviewer C:

Thank you for submitting this interesting and informative manuscript to Chinese Clinical Oncology. I was pleased to receive it as a reviewer. While your manuscript provides valuable insights into an important clinical topic, there are some areas that could be refined to further augment the quality and impact of the work. Here are some respectful suggestions that could potentially improve the paper if you choose to implement them:

Dear reviewer, first of all we want to thank you for your suggestions, and for the time and efforts spent to revise our manuscript. We appreciate your support for our work and are pleased to know that you have provided minor comments and wise suggestions. We have tried to update our work following your advice and interesting insights. In some cases, in order not to weigh down the text, considering the intent of the article (commentary letter) and the limited length, we preferred not to edit it.

- You could provide more background on the mechanisms of action of osimertinib and how it differs from early generation EGFR inhibitors. This would give helpful context for readers less familiar with these medications.

Considering the word limit imposed by the journal and the specificity of the manuscript, we preferred not to do well on the differences of osimertinib compared to other EGFR TKIs. However, we thought it would be useful to include more information about the drug's mechanism of action. We have corrected the manuscript in blue, adding a paragraph.

Change in the manuscript: lines 38-41.

- You may consider expanding the discussion on cost-effectiveness and access barriers to osimertinib, as this context is important for real-world implementation. Elaborating on this aspect may better inform policy makers and stakeholders.

We have added a paragraph and some insights within the text.

We have corrected the manuscript in blue.

Change in the manuscript: 183-186.

- Additional limitations of the ADAURA trial and current evidence could be acknowledged. Discussing limitations transparently will add nuance and identify gaps to be addressed in future research.

We have corrected the manuscript in blue, adding a paragraph.

Change in the manuscript: line 216-231.

- You could further comment on whether 3 years should be the new standard duration based on these updated findings or if trials testing longer duration are still needed. This analysis would strengthen the clinical implications.

We have corrected the manuscript in blue, adding a paragraph. We have also cited an ongoing study (NCT05526755/TARGET) which is evaluating the continuation of treatment for 5 years.

We have corrected the manuscript in blue.

Change in the manuscript: line 123-126, line 196.

- The conclusion may benefit from explicitly stating the key next steps needed based on remaining questions around optimal therapy duration, predictive biomarkers, and long-term safety monitoring. This will orient readers towards implementation and advancing the field.
We have added a paragraph in the conclusion and some insights within the text. We have corrected the manuscript in blue.
Change in the manuscript: lines 245-249.

- Key terms such as “hazard ratio” could be defined the first time they are introduced for readers who may be less familiar with statistics terminology.
We have spelled 'hazard ratio'. We preferred not to include the definition because it seemed out of the scope of our manuscript. We have corrected the manuscript in blue.
Change in the manuscript: line 44.

Overall, these suggestions aim to enhance the manuscript's quality and impact for clinicians and researchers involved with the treatment of patients with EGFR-mutant NSCLC. I believe that implementing some of the above suggestions would make you important work even stronger.