Peer Review File

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Reviewer A

The Editorial Commentary focuses on the most recent therapeutic strategies for overcoming resistance to Osimertinib in patients with advanced EGFR-mutated NSCLC. The subject is very relevant, as no 2nd line therapy has officially been approved for patients progressing on Osimertinib. However, the MS is not easy to read and requires major revision of its structure and phrasing to be publishable. I tried to suggest some adjustments underneath, but further attention to the formulation of all paragraphs should be exercised by the Authors.
Re) Thank you for your generous comments. We are sorry that our paper is not easy to read, thus, we follow your advice point by point.

SPECIFIC POINTS

Occasionally, the Authors write the name of the EGFR gene in italics. All gene names, not only EGFR, should be in italics (according to international gene nomenclature). This is to be clearer (for not confusing gene and protein names in the text) and consistent.
Re) All gene names were in italics, according to reviewer's comments.

Line 28-30, "In a phase 3 study comparing osimertinib with gefitinib, osimertinib was identified as the standard of care in the first-line setting, regardless of EGFR mutation status": The sentence should be supported by a reference (I assume, the Authors refer to reference nr 4 here) and needs major revision. Indeed, "osimertinib was identified as the standard of care" does not make much sense when speaking about a drug. Furthermore, "regardless of EGFR mutation status" is unclear and ambiguous in this context, as it can be interpreted as if Osimertinib can be used also in NSCLC patients without EGFR mutations. Consider rephrasing, for example as "Based on the results of a phase 3 study comparing osimertinib with gefitinib (4), osimertinib is recommended as the standard of care in the first-line setting for NSCLC patients with EGFR mutations" or something similar.
Re) According to reviewer's comments, we referred as (4) and rephrased our sentences.

Line 30-33, "However, most patients who receive osimertinib experience acquired resistance, such as C797S, G724S, mesenchymal-epithelial transition (MET) amplification, or bypass mechanisms, and EGFR-TKIs are not effective after its recurrence (5-7).": The sentence is rather unclear, needs major revision. C797S and G724S should be defined as on-target EGFR-mutations, MET should be called gene or written in italics, and "EGFR-TKIs are not effective after its recurrence" is a cryptic statement that requires rephrasing (recurrence of what?).
Re) According to reviewer's comment, we rephrased our sentence.

Line 33-34, "Currently, the mechanism of resistance to EGFR-TKIs remains unelucidated":

This sentence should be modulated, for example as “the mechanisms of resistance to EGFR-TKIs remain incompletely elucidated”, as many mechanisms have been unveiled in the last decade and more are being discovered.
Re) According to reviewer’s comment, we rephrased our sentence.

Line 34-35, “Overcoming primary and acquired resistance by activating EGFR-mutant NSCLC cells is warranted”: Another unclear sentence that needs radical rephrasing. It sounds as if the EGFR-mutant NSCLC cells are the cause of drug-resistance (“by activating EGFR-mutant NSCLC cells”…).
Re) According to reviewer’s comment, we rephrased our sentence.

Line 36-37, “Recently, Elkrief et al. reported a phase 1/2 study of osimertinib and dacomitinib to mitigate primary and acquired resistance in EGFR-mutant lung adenocarcinoma (7)”: to avoid confusion between on- and off-target mechanisms of resistance, the authors should specify that the trial included patients with EGFR-mutant NSCLC progressing on osimertinib due to acquired secondary EGFR-mutations (i.e., on-target mechanism).
Re) According to reviewer’s comment, we added the following sentence; “and this trial included the patients with *EGFR*-mutant NSCLC progressing on osimertinib due to acquired secondary *EGFR* mutations.”.

Regarding reference 7 in the reference list: it is from 2023, not 2003.
Re) According to reviewer’s comment, we corrected 2003 to 2023.

Line 43-46, “2G EGFR TKIs, such as dacomitinib and afatinib, are pan-human EGFR (HER) inhibitors with superior efficacy compared with 1G EGFR-TKIs for the initial treatment of EGFR mutant NSCLC (2,3)”: This sentence should be placed at the beginning of the paragraph (line 36), as an explanation to readers not familiar with 1-3G EGFR-TKIs.
Re) The sentence was placed at the beginning of the paragraph of line 36.

Line 46-48, “Unfortunately, the additional administration of dacomitinib to osimertinib failed to reverse the resistance with acquired EGFR second mutations following osimertinib treatment.”: seems to be a repetition of the sentences above, especially the one on line 40 to 42. Thus, it can be conveniently deleted for clarity and shortening of the Editorial.
Re) This sentence was deleted according to reviewer’s suggestion.

It is peculiar that the Authors describe first (line 36-48) the attempts to overcome resistance to Osimertinib made in the past and then they list what the resistance mechanisms are (line 49-80). Moving the text in lines 49-80 before line 36 would be appropriate.
Re) We rephrased our sentence, according to reviewer’s suggestion.

Line 63-65, “Although our approach focuses on the resistance mechanism in first-line osimertinib, MET amplification as major resistance mechanisms involving bypass signaling was identified in 7%–15%”: What is the meaning of this statement? Please rephrase more clearly to make the point.

Re) We rephrased our sentence, according to reviewer's suggestion.

Line 65-70, "Other resistance mechanisms include 3.7% of rearranged during transfection (RET) rearrangements … (PIK3CA) mutations (9,10).": The phrasing should be corrected: "Other resistance mechanisms include in 3.7% of cases rearrangements of the rearranged during transfection (RET) gene … etc.
Re) We rephrased our sentence, according to reviewer's suggestion.

Line 81-82, "Tumors resistant to TKIs are biologically complex with multiple simultaneous resistances": Consider changing to the more proper the formulation "Tumors resistant to TKIs are biologically complex with multiple mechanisms of resistance".
Re) We rephrased our sentence, according to reviewer's suggestion.

Line 82-83, "An understanding of the mechanisms of resistance to osimertinib requires therapeutic approaches": It is unclear what the Authors mean here. In any case, understanding resistance mechanisms requires both pre-clinical and clinical studies.
Re) We rephrased our sentence, according to reviewer's suggestion.

Line 83-84, "however, no established treatment for disease progression after first-line osimertinib treatment has been identified": it should be changed to "… has been approved", as combination therapies for overcoming Osimertinib resistance with variable efficacy, are being tested worldwide (i.e., they have been "identified").
Re) We rephrased our sentence, according to reviewer's suggestion.

Line 86-87, "Investigated targeted therapies after Osimertinib include 1G or 2G EGFR-TKI, 1G plus 3G EGFR-TKI, brigatinib plus cetuximab": For clarity, the rationale for using Brigatinib plus Cetuximab should be specified and should be supported by a reference.
Re) Reference was added as the rationale for using Brigatinib plus Cetuximab

Lines 88-95: There should be some references supporting this description of the therapeutic approaches for overcoming off-target mechanisms of resistance to EGFR-TKIs.
Re) Some references were added.

Line 111-113, "Recently, promising novel agents include a HER3-directed antibody drug conjugate (ADC) and an EGFR-MET bispecific antibody in patients with osimertinib-resistance (17).": drug names should be used here for completeness (Patritumab Deruxtecan, Amivantamab).
Re) Drug names were used according to reviewer's comments.

Line 116-117, "… monoclonal antibody to HER3 binding to a topoisomerase I inhibitor": to avoid misunderstanding, it would be appropriate to use "monoclonal antibody to HER3 conjugated to a topoisomerase I inhibitor" instead of "binding to". Otherwise. it sounds like the mAb binds and targets the Topo I inhibitor, which is the payload.
Re) We rephrased our sentence, according to reviewer's suggestion.

Line 121-122, “respectively; data on previous osimertinib therapy showed similar outcomes (19)”: it is unclear what the Authors mean here (??).
Re) This sentence was deleted because of unclear.

Line 138-139: The sentence “Within the MET oncogene, MET amplification is a significant mechanism causing resistance to osimertinib” should be reformulated more properly and clearly.
Re) “Within the MET oncogene” was deleted for clear description.

Line 142-145, “Recently, the phase III MARIPOSA-2 study comparing amivantamab … osimertinib (22)”: shouldn't the phrasing be “Recently, the phase III MARIPOSA-2 study compared amivantamab … osimertinib (22)” to make sense? Otherwise, it reads as an incomplete sentence lacking a conclusion.
Re) This sentence was corrected.

Line 149-151, “Although amivantamab plus chemotherapy could be a potential second-line therapy after osimertinib disease progression, its survival benefit appears limited”: it would appropriate to mention that the toxicity of this combination is an issue too, as there were >70% grade 3+ AEs in the MARIPOSA-2.
Re) According to reviewer’s comments, this sentence was corrected.

The text from line 155 to 163 is just a repetition of what already written above. It can be eliminated to avoid redundancy.
Re) These sentences were deleted according to reviewer’s comments.

Line 171-172, “The combination of atezolizumab with carboplatin, paclitaxel, and bevacizumab (ABPC)”: the abbreviation ABPC used by the authors of reference 23 was for the combination of atezolizumab, bevacizumab, carboplatin, and paclitaxel. Thus, the drugs should be written in that order to make the abbreviation meaningful.
Re) According to reviewer’s comments, this sentence was corrected.

Line 173-174, “than those without atezolizumab (BCP)”: it should be “than the combination without atezolizumab (BCP)”.
Re) According to reviewer’s comments, this sentence was corrected.

Line 175-179, “However, updated exploratory OS demonstrated no significant difference between patients with ABPC and BCP (24). The question of whether the combination of ICI plus chemotherapy and antiangiogenic agents can overcome acquired resistance to osimertinib remains unanswered”: the Authors’ conclusion re. the combination of ICI+chemo+bevacizumab seems a bit too negative and categorical. Indeed, in the final exploratory analyses of the IMpower150 study, there were positive signals from subgroups of pts receiving atezolizumab-containing combi, in particular: A) patients with EGFR mutations in general, B) patients with sensitizing EGFR mutations, and C) patients with sensitizing EGFR mutations who had received previous TKI therapy, as they all showed longer mOS when treated

with ABCP than BCP [(A) mOS 26.1 vs 20.3 mo, HR = 0.74; B) mOS 29.4 vs 18.1 mo, HR = 0.60; C) 27.8 vs 18.1 mo, HR = 0.74)]. The cautious suggested conclusion (small cohorts) by Reck M et al. was that, as opposed to BCP, the ABCP combi improves OS in patients with sensitizing EGFR mutations that have progressed on TKI treatment.
Re) These sentences were deleted according to reviewer's comments.

Some typos to be corrected:

- Line 125: deruxecan should be deruxtecan;

- Line 128, "after progression to EGFR-TKIs" should be "after progression on EGFR-TKIs";

- Line 158 and Figure 1: "alternations" should be "alterations";

- Figure legend 1, "Mechanism of resistance to first-line osimertinib treatment" should be "Mechanisms of resistance to first-line osimertinib treatment" as they are multiple mechanisms.

- Text in reference 23, "of pateints" should be "of patients".
Re) According to reviewer's suggestions, some typos were corrected.

Reviewer B

This editorial commentary is highly relevant, comprehensive and written in a clear and logical way. Acquired resistance in EGFR-mutant NSCLC patients following progression on osimertinib treatment is a major clinical challenge and calls for carefully selected actions depending on the individual patient. The authors bring up the current different options available for these patients, and the corresponding results from clinical trials. I recommend this editorial commentary for publication.
Re) Thank you for your generous comments. We are so happy to hear acceptable comments from reviewer.