

ANSWERING REVIEWERS



July 16, 2021

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 67112-Revised Manuscript File).

Title: Recent advances and new insights in the management of early-stage EGFR-mutated non-small-cell lung cancer

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Name of Journal: *World Journal of Clinical Oncology*

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The manuscript has been modified according to the recently published evidence and the reviewer suggestions:

- 1) The manuscript has been updated
- 2) The language has been polished
- 3) Modifications were done according to the reviewer suggestions as follows:

Reviewer #1

Comment 1: Except OS analysis, PFS and ORR also should be discussed.

Response: In the article we discuss the results of disease-free survival and overall survival of the studies, since these are the parameters evaluated in the early stages, mainly in the adjuvant setting. Our review has as one of its main objectives to discuss whether the preliminary results of the ADAURA study are sufficient to be transferred to clinical practice. Progression-free survival and response rate are parameters mainly evaluated in metastatic disease.

Comment 2: I suggest authors add a figure to further describe how EGFR-mutated influence NSCLC.

Response: The pathophysiology of mutated EGFR NSCLC and the mechanism of action of EGFR TKIs are well known topics, which have been reviewed in multiple articles. We consider that this figure would not contribute to the topic under discussion, which is specifically the role of EGFR TKIs in early stages of mutated EGFR NSCLC. However, we present three informative tables that collect the most important data from the studies carried out in this setting. In addition, these tables have been updated with recently reported data (highlighted in yellow color).

Comment 3: Authors discuss that Adjuvant treatment with first- and second-generation EGFR TKIs, how about the later stages?

Response: The benefit of EGFR TKIs in late stages is briefly mentioned in the introduction and in the body of the manuscript. However, the issue under discussion is the role of these agents in the early stages. In early stages, most of the available data comes from studies performed with first-generation TKIs. The only third-generation TKI with data available in this setting is osimertinib with the ADAURA study, to which we make special mention in the manuscript. In the section "EGFR TKIs AS TREATMENT FOR RESECTABLE DISEASE", we have added the results of the IMPACT study, and in the section "EGFR TKIs AS TREATMENT FOR POTENTIALLY-RESECTABLE LOCALLY-ADVANCED DISEASE", we have added the final OS analysis of the EMERGING study -CTONG 1103. Both studies have recently been presented at ASCO (highlighted in yellow color).

Comment 4: The introduction is disordered, and Introduction should also briefly mention the purpose of the review.

Response: We have revised the introduction and improved it based on your suggestion. Furthermore, in the final paragraph of the introduction, we briefly mention the proposed revision to be carried out (highlighted in yellow color).

Comment 5: New insights should be more detail, and I think this part is vital. List the points are better.

Response: Most studies with published data have evaluated adjuvant treatment in resected disease. New perspectives in this review are "EGFR TKIs AS TREATMENT FOR POTENTIALLY-RESECTABLE LOCALLY-ADVANCED DISEASE" and "EGFR TKIs AS TREATMENT FOR UNRESECTABLE LOCALLY-ADVANCED DISEASE", as these are settings in which important clinical trials are being conducted. In the manuscript we briefly describe the design of the most important studies (ALCHEMIST, NeoADAURA, LAURA) that are currently underway.

Comment 6: The current obstruction for treating EGFR-mutated NSCLC also should be discussed.

Response: In the final paragraphs of the section "EGFR TKIs AS TREATMENT FOR RESECTABLE DISEASE", we discuss how high prices hinder access to drugs that have been shown to significantly prolong survival, such as EGFR TKIs. Likewise, we discuss the high cost of adjuvant treatment with osimertinib and the need to confirm a benefit in OS that justifies its use (highlighted in yellow color).

Overall, we would like to thank the reviewer remarks which have help us to improve substantially our manuscript.

4) References have been updated. We have added references 42, 49, 50 and 64 (all 2021) (highlighted in yellow color).

Thank you again for publishing our manuscript in *World Journal of Clinical Oncology*.

Sincerely yours,

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