

April 23, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: WJCO targeted therapies in NSCLC.doc).



Title: A review of the current targeted therapies for 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 improved according to the suggestions of the editor and reviewers.

1. The format has been updated.
2. Revisions have been made according to the suggestions of the reviewers.

Reviewer 1: this is a review article focused on the up-dated molecular targeted therapy for advanced non-small cell lung cancer. the authors comprehesively reviewed the latest results of molecular targeted therapy against EGFR, the mechanism of EGFR-TKI resistance, ALK, and other recently found targets. I think this review article is well-summarized including historical trials and background, and it thoroughly consists discussions of their points of molecular targeted therapy. therefore, it is beneficial to make it understood it for the reders in medical oncology, from thoracic oncologists to general oncologists. Basically, it is valuable to publish as it is at present, however, i recommend the authors to include some additional issues to improve this review article. minors: 1. pp 4. line 2. erlotinib is characterized by improvement of survival significantly for advanced non-small cell lung cancer without EGFR-mutation status in the BR. 21 trial although gefitinib did not show an improved survival in the ISEL trial. it is considered that erlotinib is approved at the relevalent dose as MTD whereas gefitinib is one-third of that dose. the SATURN trial also showed erlotinib to be effective for wild-type EGFR in early second-line setting (sequential maintenance therapy). Consider to include the above in the manuscript. 2. pp 10. line 21. as an important complication with crizotinib, cases of esophageal ulcer have recently been reported. You should consider introducing the reported case reports in your manuscript.

We thank the reviewer for the comments and agree that a summary of the major trials and historical background provides a useful context when discussing the current targeted therapies. In the section discussing the OS data from the BR.21 and ISEL trials, per the reviewer's suggestion, we now include a discussion of the doses of erlotinib and gefitinib relative to their MTDs. We choose not to include the SATURN trial in this review as using erlotinib as maintenance for wild-type EGFR is no longer routinely done, especially with the recent TAILOR trial showing superiority of docetaxel over erlotinib in wild-type EGFR patients in the second-line setting. We thank the reviewer for mentioning the rare but serious adverse event of esophageal ulceration associated with crizotinib and now include the appropriate reference in the review.

Reviewer 2: In general, this is a well written review which clearly reviewed the demonstrating efficacy of targeted therapies against EGFR as well as ALK and the challenge of acquired resistance to these small-molecular TKIs. The promising agents which may overcome the resistance and several other promising targeted therapies currently in development were also discussed. However, it still needs some minor revision before being published. 1. The abbreviations should be explained in detail when it firstly appeared whether they were widely known or not. For example, the 'OS' in line 4, third paragraph of page 3, the 'PFS' in line 5, third paragraph of page 4, the 'MET' in line 8, first paragraph of page 7, the 'ORR' in line 8 and 'AEs' in line 12, second paragraph of page 11,

the 'CRs' and 'PRs' in line 4, third paragraph of page 12 and the 'SD' in line 5, fourth paragraph of page 13. 2.

Some grammar and spelling mistakes should be checked and corrected. Some blank spaces were missing between words in several sentences and need to be corrected.

We appreciate the reviewer's comment and have made the appropriate typographical and grammatical changes.

Reviewer 3: Targeted therapies included small-molecular tyrosine kinase inhibitors and monoclonal antibodies: so, I think it is suitable to include monoclonal antibodies (EGFR Antibody) in the manuscript.

We thank the reviewer for raising the important question regarding cetuximab. While the FLEX trial showed an improvement in overall survival with the addition of cetuximab to cisplatin/vinorelbine in the first-line setting, there were significant toxicities with cetuximab. Other trials assessing cetuximab in the first- and second-line settings did not show a significant benefit for the addition of cetuximab to chemotherapy. Therefore, given the limit of our review, we decide not to discuss cetuximab, focusing on the small-molecular tyrosine kinase inhibitors instead. This monoclonal antibody continues to be studied in NSCLC, however, and we might have significant data to discuss in future reviews.

Reviewer 4: This is a review discussing the treatment of EGFR and ALK positive NSCLC including the challenges of overcoming acquired resistance to TKIs. The authors also comment on other potential but less frequent targets I have to make the following comments: 1. I believe that the trivial information regarding 1st generation EGFR TKIs should be substantially reduced. 2. The LUX lung trials should be summarized in a table 3. They should comment on the presence of T790M mutation pretreatment and combinational therapies upfront (Costa et al, CCR 2014) 4. They should include the recently published information about a very potent ALK inhibitor ASP3026, by Mori et al in Mol Cancer Ther. 5. Regarding ROS1, they should refer to the efficacy of foretinib for crizotinib resistant or naïve patients (Davare et al. PNAS, 2013)

We greatly appreciate the reviewer's thoughtful comments. As another reviewer has mentioned, the historical background on the first-generation EGFR TKIs provides a useful context to understand the current therapies in use, especially to the general oncologists. We think a table dedicated to afatinib and the LUX lung trials does not add much to what is already stated in the text. The recently published paper on the impact of pre-treatment T790M mutations on outcomes in the EURTAC trial is important and is now included in our review. We thank the reviewer for mentioning ASP3026 and foretinib, which are now also included in our review.

3. References and typesetting were corrected

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

Sincerely yours,

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