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Peer Review File

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Review Comments

Anlotinib is a novel multi-target TKI for tumor angiogenesis and tumor cell proliferation, which is approved as a third-line or beyond treatment for advanced NSCLC. In the manuscript “Anlotinib or Platinum–Pemetrexed as second-line therapy in EGFR T790M–Negative Lung Cancer”, the authors investigated the efficacy of anlotinib and platinum–pemetrexed chemotherapy in T790M–negative NSCLC patients after first-line EGFR-TKI therapy.

A number of improvements need to be made before the manuscript can be accepted.

- (1) What progress has been made with treatment for advanced NSCLC? Relevant content should be included in the introduction.

Reply 1: We have updated recent progress in the revised manuscript.

Changes in the text: Please see Page 3, line 57.

- (2) Up to now, what has been the general treatment for patients with T790M-negative NSCLC after first-line EGFR-TKi has failed?

Reply 2: For patients with T790M-negative at the time of progression after EGFR-TKI failed, platinum-based chemotherapy is the general treatment. There are few approved treatment options for patients without the T790M-mutation who are refractory to EGFR-TKIs, except chemotherapy. The combination of chemotherapy, immunotherapy, and antiangiogenesis shows efficacy in T790M-negative patients as observed in IMPOWER150. However, the number of patients in that study was relatively small.

Changes in the text: We have clarified the content in the introduction section. (see Page 3, line 61 and Page 4, line 73)

- (3) The possible mechanism analysis should be increased. This will better support the

ANNALS OF PALLIATIVE MEDICINE

conclusions of the study.

Reply 3: In T790M–negative patients after EGFR-TKIs failed, bypass resistance mechanisms include using alternative cellular pathways and activating downstream signal transduction, which facilitate tumor cell growth and survival. *MET* gene amplification, *HER2* gene amplification, and *PI3KCA* gene mutations are the most frequently observed changes. Changes in tumor phenotypes at disease progression have also been reported showing up to 10% of EGFR-TKI resistant tumors contain transformation to SCLC. Rarely, epithelial-to-mesenchymal transition can occur. Other rare mechanisms of resistance to EGFR-TKIs include acquired receptor tyrosine kinase fusions, and BRAF kinase fusions. So the non-selective use of multi-target TKI, e.g. anlotinib as a second-line treatment may lead to failure. Changes in the text: We have modified our text as advised (see Page 10, line 218).

(4) The results are too simple. What are your plans for further study? Please elaborate on this in detail in the discussion.

Reply 4: In recent studies, multi-TKI for tumor angiogenesis and tumor cell proliferation, with the combination of ICI, could optimize the immunosuppressive tumor-associated macrophages, and potentially increase the therapeutic response to immunotherapy as shown in lung cancer in vivo models and by preliminary clinical data in NSCLC. So in the further study, we will try to combine anlotinib plus ICI in T790M–negative patients to determine the antitumor effect. Changes in the text: We have modified our text as advised (see Page12, line 256).

(5) What does the future look like for the application of anlotinib in other cancers? Please include relevant content in the discussion.

Reply 5: The relevant content has been added in the “discussion” section.

Changes in the text: We have modified our text as advised (see Page 10, line 207).