

Article information: <https://dx.doi.org/10.21037/tlcr-23-109>

Reviewer A

Comment 1 (from Reviewer A): 73- Central nervous system (CNS) metastases are a common poor prognostic factor in patients with advanced NSCLC with EGFR mutations (occurring in approximately 30% of patients during treatment with an EGFR-TKI) [1]. Osimertinib has shown excellent CNS penetration. In FLAURA study also revealed the high CNS efficacy of osimertinib in the first-line setting. Fewer patients in the osimertinib arm developed new brain lesions compared with the control arm(12% versus 30%) , supporting the protective role of osimertinib in the development of new CNS lesions [2].

Reply 1: We added the reviewer's comment to introduction section (we modified certain expressions or elements to fit the context).

Changes in the text: Please see line 88 to 93 highlighted with green marker.

Comment 2 (from Reviewer A): 90-Angiogenesis, the proces leading to the formation of new blood vessels, is one of the hallmarks of cancer. Studies established that vascular, endothelial growth factor (VEGF) is a key driver of sprouting angiogenesis, VEGF is overexpressed in NSCLC and inhibition of VEGF can suppress tumor growth.

Reply 2: We added the reviewer's comment to introduction section (we modified certain expressions or elements to fit the context).

Changes in the text: Please see line 68 to 70 highlighted with green marker.

Comment 3 (from Reviewer A): 93-Ramucirumab- antibodies that block signaling though VEGFR2. VEGF plays a key role in tumor angiogenesis, and dual blockade of the EGFR and VEGF receptor (VEGFR) pathways in EGFR mutation-positive NSCLC has demonstrated improved tumor control compared with EGFR inhibition alone.

Reply 3: We added the reviewer's comment to introduction section (we modified certain expressions or elements to fit the context).

Changes in the text: Please see line 71 to 75 highlighted with green marker.

Comment 4 (from Reviewer A): 114- exclusion criteria- point 16: sometimes patients having underlying disease and users rivaroxaban (Xarelto), apixaban (Eliquis), dabigatran (Pradaxa)

Reply 4: The exclusion criteria of our study mainly based on the RELAY study (Lancet Oncol 2019;20:1655-69.) and the study did not exclude patients given DOACs. We also perform screening through biochemical tests to exclude patients with coagulation abnormalities.

Reviewer B

Comment 5 (from Reviewer B): Reviewer B has commented on the clinical trial involving the combination of EGFR-TKIs and anti-angiogenic agents for EGFR-mutant NSCLC with brain metastasis, stating the need to clarify the positioning of osimertinib and erlotinib.

Reply 5: We appreciate Reviewer B for informing us the RAMOSE trial and we have restructured the introduction section, focusing on organizing the existing knowledge regarding the differences between Osimertinib and Erlotinib plus Ramucirumab. We have included some additional basic medical insights (see line 83 to 87 highlighted with yellow marker) and made changes to the order of sentences and slight modifications to expressions.

Changes in the text: Please see line 83 to 87 highlighted with yellow marker.