Peer Review File

Article information: https://dx.doi.org/10.21037/tlcr-24-47

Reviewer A

The manuscript by Liu and colleagues describes a case report of the use of Aumolertinib, a third generation EGFR tyrosine kinase inhibitor, for use in a patient with Stage III EGFR mutant squamous cell lung cancer. The Authors describe the neoadjuvant use of this agent in a single patient who had radical surgery after neoadjuvant Aumolertinib for Stage IIIa squamous cell lung cancer. They report that this patient had no evidence of recurrence 14 months after treatment. They suggest that this therapy may have promise as an adjuvant treatment in advanced stage lung cancer patients. I have some questions and comments for the Authors to consider regarding this report.

The problem with a case report in a single patient is that there is no indication of the true risk benefit of the treatment rendered. It appears that the treatment with Aumolertinib was well tolerated without major complications. It is a leap of faith to assume that this will be the case in all patients who receive this treatment. Some discussion of possible side effects, both short-term and longer-term. of this treatment would help to present a more nuanced and accurate description of the possible treatment-related problems. The patient described seems to be in good health without a smoking history, but the clinical stage seems to be Stage IIIa with a positive mediastinal node and the average 5-year survival for this patient is 10-15%. Although the patient appears to be tumor-free at 2 years following treatment, it is very presumptive to assume that the 5-year survival will be improved with Aumolertinib. About the best that can be said is that the treatment regimen as described is well tolerated. Much more work needs to be done to prove the efficacy of this agent in prolonging life in patients with Stage III EGFR-positive NSCLC. Additionally, there does not seem to be much information about how long or what intensity is required when using Aumolertinib. So, about all that can be said about this treatment is that it seems to be well tolerated. Much more information is required to gain some insight into the effectiveness and safety of this agent.

Having raised these questions and concerns, I think that this brief report provides some provocative information that should trigger further research and patient treatment protocols. It is not acceptable to say that this drug is safe and effective for treatment of advanced stage NSCLC, and that should be clearly stated in the Authors' manuscript. Further, the patient risk factors that might impact response to Aumolertinib should be outlined. Anything the Authors can do to provide a more complete description of the possible complications and expected benefits of this drug would help Readers understand both the preliminary nature of this report and the possible factors that could impact any response to this agent.

Some indication of the availability of this agent should be included in the Authors' manuscript.

The drug manufacturer must have some preliminary clinical data to support the use of this drug and a brief description of this information should be included in this case report. Where, when, and how this drug is available should be clearly stated. I am unable to find any indication that this drug is available in the United States, so some description of where, when, and how this drug might be obtained and used for treatment of NSCLC should be included in this manuscript.

Q1: The true risk benefit of the treatment rendered.
A1: The risk-benefit of the treatment of Aumolertinib has been described in the APOLLO and AENEAS registration trials.
Changes in the text: we have modified our text as advised (see Page 3, line 45)

Q2: Discussion of possible side effects.
A2: A description of the side effects that occurred during treatment is provided.
Changes in the text: we have modified our text as advised (see Page 5, line 78)

Q3: The problem of prolonged survival time of patients.
A3: The patient has been followed up and is now doing well after 20 months. But it has not been shown to improve five-year survival, which is an ongoing concern with this drug and one that we will pursue in the future.
Changes in the text: we have modified our text as advised (see Page 5, line 76)

Q4: Drug dosage.
A4: The current approved standard dose of Aumolertinib is 110mg/d
Changes in the text: we have modified our text as advised (see Page 4, line 63)

Reviewer B

The authors present a case of lung squamous cell carcinoma that received neoadjuvant Aumolertinib and subsequent surgical resection. This manuscript might be helpful for clinicians, but the reviewer has concerns below.

Q1: According to the inclusion criteria of this trial (NCT04685070), only lung adenocarcinoma with EGFR-sensitive mutation was eligible for the trial. The authors should confirm and explain this.
A1: For trial NCT04685070, the eligibility criteria have been changed to stage III-IV, EGFR-positive NSCLC.
Changes in the text: we have modified our text as advised (see Page 4, line 49)

Q2: The basis for the diagnosis of LUSQ was unclear. The authors should show the pathologic findings and IHC results.
A2: We have added images of stained sections of pathological tissue to the text.
Changes in the text: we have modified our text as advised (see Page 4, line 59)

Q3: They should show the details of EGFR mutation (L858R, 19del, etc).
A3: The EGFR mutation of patient is 19del.
Changes in the text: we have modified our text as advised (see Page 4, line 61)

Q4: The authors mentioned that neoadjuvant Aumolertinib therapy for LUSQ was novel in their article. However, the novel point was not discussed. Neoadjuvant targeted therapy has been already reported in several papers. Discussion should focus specifically on "neoadjuvant Aumolertinib", "neoadjuvant targeted therapy for LUSQ", and "dramatic efficacy of EGFR-TKI for LUSQ".
A4: We have changed the focus of our article to neoadjuvant targeted therapy for LUSQm.
Changes in the text: we have modified our text as advised (see Page 5, line 91)

Q5: The authors showed the expression of PD-L1 in Figure 3 and mentioned it in the discussion. However, they only demonstrated the low PD-L1 expression in NSCLC with EGFR mutation, which are well-known fact, and it is unclear what they wanted to show and discuss and what was relevant to their case. Discussion should focus especially on issues that are relevant to their case.
A5: After our consideration, we decided to accept the opinion of the review experts and removed the discussion about PDL1 as well as the images.

Reviewer C

This study explores the feasibility of neoadjuvant EGFR-TKI therapy combined with radical surgery for stage III EGFR-mutant NSCLC, particularly focusing on lung squamous cell carcinoma (LUSQm), an area with limited research. This report presents a successful case of neoadjuvant target therapy using Aumolertinib, a third-generation EGFR-TKI, combined with radical surgery for stage IIIA LUSQm. The radiological partial response and pathological complete response provide valuable insights into the efficacy of this treatment approach.

Q1: The clinical stage before the administration of Aumolertinib is cN2, but is it a single or multi-station? If it is a multi-station, we should consider a regimen using durvalumab after CRT.
A1: The patient only had para-aortic lymph nodes metastases, which had resolved on postoperative pathology.
Changes in the text: we have modified our text as advised (see Page 4, line 55)

Q2: The patient was followed up for 14 months after surgery, but until when was Aumolertinib used?
A2: We currently believe that Aumolertinib should be continued for three years after surgery to prevent possible tumor recurrence.
Changes in the text: we have modified our text as advised (see Page 5, line 77)