Peer Review File

Article information: https://dx.doi.org/10.21037/jtd-23-1399

Reviewer A

Although it is a well-planned study and a well-written manuscript, there are some concerns. The study's sample size is small. There are only 14 patients in the PD-L1 (+) group and only 6 in the PD-L1 (-) group when comparing the 2 groups according to the PD-L1 expression. Unfortunately, more than half of the study population comprises patients with 'not reported' PD-L1 levels. This should be explained by the authors.

Reply 1: Due to the retrospective setting, we have taken everything possible measure to obtain specimens from patients for testing.

In addition;

-Study design should be explained in detail in the material and method section.

Reply 2: We have modified our text as advised (see Page 4-5, line 108-143).

-There are 3 groups according to the treatment regimen. Can the authors give detailed information about PD-L1 levels in these groups?

Reply 3: We have modified our text as advised (see Page 6, line 170-173).

-Were there no shortcomings/limitations or strengths that need to be addressed in this study? Can the authors state them?

Reply 4: We have modified our text as advised (see Page 9, line 281-285).

-Line 212: 'esion' should be corrected.

Reply 5: We have modified our text as advised (see Page 8, line 242).

In conclusion, the authors may include more patients to increase the number of study population and the number of patients with known PD-L1 expression. Then the results of the study may be more significant.

Reply: Our research was a single-center retrospective study. To further evaluate the efficacy and safety of immunotherapy for the treatment of patients with locally advanced or metastatic EGFR-mutated NSCLC who had disease progression after receiving EGFR tyrosine-kinase inhibitor treatment and explore immunotherapy-related molecular markers and dominant populations, the prospective studies have been conducted in my team.

Changes in the text: none.

Reviewer B

In this retrospective, single-institutional study, the authors compared the efficacy and safety among the three different regimens in EGFR mutation-positive NSCLC patients who had progressed with EGFR-TKI. And they concluded that immunotherapy combined with

chemotherapy and immunotherapy combined with anti-angiogenic therapy have equivalent efficacy in the treatment of PD-L1 positive patients with advanced EGFR-TKI resistant LUAD. However, the reviewers think the results presented in the manuscript are overinterpreted because the number of patients is too small to compare the efficacy. For example, only six patients are analyzed for PFS in Fig 2D.
Increasing the number of eligible patients by extending the coverage period or collaborating with multiple institutions may strengthen your results.

Reply: Our research was a single-center retrospective study. Furthermore, immunotherapy after EGFR-TKIs resistance was not the standard treatment before the results of the ORIENT-31 study were disclosed. As a result, in real-world setting, the sample size was limited. However, our findings were consistent with those of the ORIENT-31 study. To further evaluate the efficacy and safety of immunotherapy for the treatment of patients with locally advanced or metastatic EGFR-mutated NSCLC who had disease progression after receiving EGFR tyrosine-kinase inhibitor treatment and explore immunotherapy-related molecular markers and dominant populations, the prospective studies have been conducted in my team.

Reviewer C

1) First, the title needs to indicate the clinical research design of this study, i.e., a retrospective cohort study. I also suggest the authors to indicate the comparisons across the three combination treatment groups.

   Reply 1: We have modified our text as advised (see Page 1, line 1-5). The comparisons across the three combination treatment groups have been indicated.

2) Second, the abstract is not adequate. The background did not explain the clinical needs for comparing the three combination treatment strategies and what the current knowledge gap is. The methods need to describe the inclusion of subjects, assessment of baseline characteristics, treatment administration, follow up procedures, and main statistical methods for comparing the three groups. The results need to briefly describe the clinical characteristics of the three groups and quantify the differences in treatment outcomes by reporting survival time and accurate P values. The current conclusion is misleading because of the small sample and no adjustment of potential confounders in the authors' analyses.

   Reply 2: This retrospective study has a low grade of evidence-based medicine, and there were different interpretations of the retrospective study data. To further evaluate the efficacy of immunotherapy for the treatment of patients with locally advanced or metastatic EGFR-mutated NSCLC who had received EGFR-TKI-resistant and explore immunotherapy-related molecular markers and dominant populations, the prospective studies have been conducted in my team.

3) Third, in the introduction, please review what has been known on the efficacy and safety of the combination treatment, particular differences between different combination strategies, and analyze the current knowledge gaps and limitations of the clinical evidence.

Reply 3: The differences between different combination strategies, analysis of the current knowledge gaps and limitations of the clinical evidence have been deeply stated in the section of discussion.

4) Fourth, in the methodology of the main text, please describe the clinical research design, sample size estimation, details of the administration of the three combination treatment, data collection of baseline factors, and follow up procedures. In statistics, the authors need to consider multiple regression analysis to exclude the confounding effects. The current results from univariate analysis are not convincing.

Reply 4: We have modified our text as advised (see Page 4-5, line 108-143). As for the statistics, due to the small sample size, there were no meaningful results in multiple regression analysis.

5) Finally, please consider to review and cite some related papers: 1. Shi J, Li J, Wang Q, Cheng X, Du H, Han R, Li X, Zhao C, Gao G, He Y, Chen X, Su C, Ren S, Wu F, Zhang Z, Zhou C. The safety and efficacy of immunotherapy with anti-programmed cell death 1 monoclonal antibody for lung cancer complicated with Mycobacterium tuberculosis infection. Transl Lung Cancer Res 2021;10(10):3929-3942. doi: 10.21037/tlcr-21-524. 2. Duan H, Wang T, Luo Z, Tong L, Dong X, Zhang Y, Afzal MZ, Correale P, Liu H, Jiang T, Yan X. Neoadjuvant programmed cell death protein 1 inhibitors combined with chemotherapy in resectable non-small cell lung cancer: an open-label, multicenter, single-arm study. Transl Lung Cancer Res 2021;10(2):1020-1028. doi: 10.21037/tlcr-21-130.

Reply 5: We have modified our text as advised (see Page 12-13, line 393-403).