Peer Review File
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Reviewer A

General comment:
In this retrospective, multi-institutional study, the authors mainly report the effectiveness of ICI for NSCLC patients with driver mutation except EGFR mutation. It is a very important topic to distinguish whether driver mutation-positive patients respond before ICI treatment. Some of the observations are interesting, but there are several concerns that the authors should address.

Specific comments:
Comment 1: Many patients do not receive targeted therapy in the first line, for example, BRAF, MET, RET mutation, etc. Because the reviewer thinks that targeted therapies should be considered before immunotherapy, it isn't easy to accept the results well. How about explaining the background of the clinical practice guidelines for ICI treatment for driver mutation-positive patients in China?
Reply 1: Thanks for your comments. Taking the BRAF V600E mutation as an example, both the National Comprehensive Cancer Network (NCCN) guidelines in the United States and the European Society of Oncology (ESMO) guidelines recommend dalafinib+trametinib as the preferred treatment option for stage IV BRAF V600E mutation NSCLC. The Clinical Diagnosis and Treatment Guidelines for Lung Cancer of the Chinese Medical Association (2022 Edition) recommend dalafinib combined with trametinib as the only treatment option for stage IV BRAF V600 mutated NSCLC. The 2022 edition of the Chinese Society of Clinical Oncology (CSCO) guidelines recommends dalafinib combined with trametinib as a level II recommendation. However, it should be pointed out that at the time of guideline formulation (2022 edition), dalafinib+trametinib has not yet been approved in China as an indication for the treatment of BRAF V600 mutation advanced/metastatic NSCLC. The patient population included in our study was from May 2015 to October 2022. During this period, although targeted drugs were recommended as their first-line treatment at different levels of recommendation, some targeted drugs were not approved for use in these patient populations in China, so most patients were not able to use targeted drugs for first-line treatment.
Changes in the text：see Page 5, line 166-171.

Comment 2: Table 2 and Figure 4.
It is confusing to grasp the efficacy data, especially regarding the best response and PFS. These are mixed data with ICI monotherapy and ICI combination therapy. As adding chemotherapy usually results in better outcomes, the reviewer recommends modifying the Table and Figure

according to treatment (ICI monotherapy and ICI combination therapy) or remove from the main results.

Reply 2: Thanks for your comments. It indeed is unreasonable to ignore the number of treatment lines and treatment methods when comparing the efficacy between different subgroups. So, we have removed this part from the main results based on your suggestion. Meanwhile, a new efficacy chart has been added to display the efficacy of the total population on different treatment line and treatment methods. However, due to the small number of patients in different gene alteration groups, further analysis was not possible.

Changes in the text：see Page 9, line 303-318; Page 23-24, Figure 4, 5 and 6.

Comment 3: What kind of staining is used for PD-L1? What kind of methods are used for detecting driver mutations?

Reply 3: Thanks for your comments. We have added relevant information in the manuscript. All PD-L1 stain test use 22C3 antibodies. As for gene tests, parts used NGS and parts with PCR.

Changes in the text：see Page 7-8, line 261-264; Page 8, line 274.

Comment 4: Introduction.

This study excludes the EGFR mutation patients. The authors mention that ICI treatment is controversial for other driver mutations; what are the conclusions about the ICI treatment for EGFR mutation? Please indicate it in the introduction section.

Reply 4: Thanks for your comments. The probability of EGFR mutations occurring is higher compared to other genetic variations, so there is relatively more research on the application of immunotherapy in this population. The consensus for immunotherapy in advanced EGFR mutant NSCLC populations is mostly that it is not recommended to use it before targeted therapy, but in some prospective clinical studies targeting ICI plus chemotherapy after resistance to targeted therapy, it has not shown significant advantages compared to chemotherapy alone. There are some research data indicating that the combination of PD-1/PD-L1 inhibitors and angiogenesis inhibitors may prolong the progression free survival of such patients. For example, the Impower150 study used atezolizumab combined with bevacizumab and chemotherapy, while the ORIENT-31 study used sintilimab combined with bevacizumab analogues and chemotherapy. However, these studies did not show any improvement in OS. Therefore, in fact, further research is still needed on the immunotherapy of EGFR-mutated lung cancer. However given the rare incidence of other gene alterations, we plan to study them to supplement the immunotherapy experience of these patients with rare gene mutations. We have made modifications to the abstract section, so there are no further additions in the introduction section.

Changes in the text：see Page 2, line 66.

Comment 5: Fig 2A.
Please improve clearer.
Reply 5: Thanks for your comments. Because our research subjects contain too many types of genetic variations, only in this way can we better present all different types. We plan to keep this figure after careful consideration.

Reviewer B

The submitted paper represents a review describing the use of immunotherapy in Oncogene Addicted advanced non-small cell lung cancer. The aim of the review is clear in the abstract.
The introduction provides good background information, giving wide information on the oncogene-dependent disease, from the epidemiological aspects to the current treatments, and the current use of immunotherapy in NSCLC.
The results paragraph is divided into subgroups of analyses of gene alterations, which allows for a correct interpretation of the data found, as well as clinical outcomes were analyzed individually.
However, some limitations are evident in the results found:

Comment 1: The PDL1 value is not available in all patients, thus resulting in a possible incorrect interpretation of the data regarding responses to immunotherapy treatment.
Reply 1: Thanks for your comments. Some patients indeed do not have the data of PD-L1 expression. However, we analyzed in this way: for KRAS patients, we only included the population who have complete data in the Cox model analysis. In addition, in subgroup analysis, comparisons were made between populations who have available expression of PD-L1. We will interpret more cautiously in the results section.
Changes in the text：see Page 14, line 532-533.

Comment 2: A percentage of patients in all subgroups underwent second-line immunotherapy, in some of these (KRAS and HER2 paragraphs) the previous treatments are unknown, thus resulting in a possible incorrect interpretation of the results obtained.
Reply 2: Thanks for your comments. We have collected the treatment strategy of all patients before immunotherapy and after immunotherapy progression, but the main purpose of this study was to investigate the immunotherapy efficacy of these patients, so the previous treatment strategy of patients was not presented. We also realized that it is not appropriate to compare the efficacy without distinguishing between the number of immunotherapy lines and treatment strategy (ICI monotherapy or combined with chemotherapy). So, we have adjusted the interpretation of the results.
Changes in the text：see Page 9, line 303-318; Page 23-24, Figure 4, 5 and 6

Comment 3: No possible co-mutations are indicated.
Reply 3: Thanks for your comments. Our study is a retrospective study and does not involve further testing and analysis of past specimens from patients. Not all patients have received NGS testing, for example, some patients only use PCR to detect major genetic variations, so it is not possible to obtain co mutation information for all patients.

Comment 4: The methods by which the mutations were found are not specified.
Reply 4: Thanks for your comments. Our study is a retrospective study and does not involve additional processing of patient samples. The relevant data for genetic testing methods are derived from the patient's previous test results. We have added a detailed explanation of the methods of genetic testing in the results section.
Changes in the text：see Page 7-8, line 261-264.

Comment 5: Beyond that, the results of the study must also be interpreted from the perspective of a not-very-high number of patients. Therefore, the study does not confirm once and for all the ineffectiveness of immunotherapy in oncogene addiction, but it certainly adds a new small piece to this topic.
Reply 5: Thanks for your comments. The sample size of our study is indeed small, and the patients with different genetic variations varies in the situation of immunotherapy. We also separately described the different groups of patients with genetic changes when drawing conclusions. We have added at the end of the article about the need to interpret our conclusion with caution, as the sample size is limited.
Changes in the text：see Page 16, line 605-607.

Comment 6: The conclusions reiterate that the effectiveness of immunotherapy varies depending on the oncogenic driver and the need for and importance of expanding studies.
Reply 6: Thanks for your comments. We have rewritten the conclusion.
Changes in the text：see Page 16, line 612-613.

Reviewer C

The present study, Immunotherapy for patients with advanced non-small cell lung cancer and oncogenic driver alterations other than EGFR: a multicenter real-world analysis. is an interesting. However, several revisions are warranted before the considering the manuscript for publication. Please see my opinions below.

Comment 1: Was there a difference in efficacy between ICI monotherapy and ICI combined chemotherapy in the overall population? If ICI combined chemotherapy is highly effective, can

we not say that chemotherapy becomes an important treatment option for driver gene mutation positive patients?

Reply 1: Thanks for your comments. We conducted a supplementary analysis on the overall population, and the mPFS and mOS of ICI monotherapy was 2.8m and 16.2m, ICI+chemotherapy was 7.5m and 22.5m. The data mentioned above was not presented in the paper because the number of treatment lines had a certain impact on the efficacy of immunotherapy. The final supplementary modification presented in the paper shows that the mPFS and mOS for first-line immunotherapy in the overall population are 7.5m and 24.8m, respectively, while the mPFS and mOS for second-line and above are 4.7m and 17.1m, respectively. Among them, the mPFS and mOS of first-line ICI monotherapy were 4.9m and 20.9m, respectively. The mPFS and mOS of first-line ICI+chemotherapy were 7.8m and 25.8m, respectively. The mPFS and mOS of second-line and above ICI single drugs are 2m and 14.5m, respectively. The mPFS and mOS of second-line and above ICI+chemotherapy are 6m and 19.3m, respectively. The purpose of this study is to attempt to demonstrate the real-world situation of immune therapy in patients with driver gene positive non-small cell lung cancer. We did not include control group data that only received chemotherapy, but the article did not involve denying the effect of chemotherapy. From previously published research results, it can be seen that a multicenter cohort study in Asia showed that in cohort II with KRAS mutations, a total of 300 patients received first-line chemotherapy. The pemetrexed/platinum (PP) regimen resulted in a PFS of 6.4 vs 4.9 vs 5.6 months (HR=0.65, p=0.033, and HR=0.69, p=0.05) compared to gemcitabine/platinum (GP) or paclitaxel/platinum (TP) regimens, and the combination of ICI and chemotherapy did indeed improve the efficacy compared to ICI alone (mPFS，13.9 vs 5.2 months，HR = 0.59，p = 0.049）（DOI: 10.1016/j.jtocrr.2021.100261).

Changes in the text：see Page 9, line 306-318.

Comment 2: What was the percentage of stages IVA, IVB, and other in the 8th edition of TNM classification? Were cases of postoperative recurrence or recurrence after radiotherapy included? It should be considered to include in Table 1.

Reply 2: Thanks for your comments. The patients we studied were all in stage IV at initial diagnosis, and there was no recurrence or radiation therapy. The staging of IVa and IVb has been further distinguished and revised in the table1.

Changes in the text：see Page 25, table1.

Comment 3: Regarding KRAS-positive cases, it should be further discussed that although the IO combined chemotherapy significantly prolonged PFS compared to IO monotherapy, there was no significant difference in OS between the two groups.

Reply 3: Thanks for your comments. For the KRAS mutation population, we included the variable of treatment mode (ICI monotherapy vs ICI combined with others) for multivariate and univariate analysis. From the results, it can be seen that the upper limit of the OS confidence

interval exceeds 1. At the current follow-up deadline, we speculate that the reason why PFS benefits did not translate into OS benefits may be related to the small sample size. Further research is needed to expand the sample size in the future.
Changes in the text：see Page 14, line 523-524.

Comment 4: Regarding the subset analysis tableS1-S6, the table should indicate how many cases there were for each variable.
Reply 4: Thanks for your comments. We have added the cases of each variable in the tableS1-S6.
Changes in the text：see Page 25-30, table S1-S6.

Reviewer D

This study is the retrospective research, however the date is big.
The result is valuable.

Reviewer E

This is a well written and potentially informative study considering its global design.

Nevertheless, the incorporation in the same analysis of patients that received immunotherapy alone or in combination with other agents (not detailed) is a major issue, precluding the correct evaluation of the data proposed. Indeed, more that 2/3 of the patients received a combinatorial strategy (Table 1), and this highly influence the interpretation of the data: was the benefit generated by the treatment due to immunotherapy or by the "other agents"? Moreover, these latter were likely heterogeneous, adding another level of difficulty in the interpretation of the data.
Reply: Thanks for your comments. Our study is retrospective, and the uneven immunotherapy strategies treated within the included population is also one of its limitations, as the sample size is limited and unable to analyze further the efficacy of ICI combined with different drug groups to estimate its certain role. We are also quite careful in presenting the data. For the overall population, we did not directly compare ICI-based combination therapy vs ICI monotherapy. Instead, we compared the efficacy of ICI plus chemotherapy with ICI alone. Please refer to the details: In addition, we have reiterated in the discussion section the need for a cautious interpretation of the results, and further prospective research is needed.