Peer Review File

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Reviewer A

The paper titled “Efficacy and safety of durvalumab versus atezolizumab with chemotherapy in the treatment of small-cell lung cancer: a multicenter real-world study” is interesting. This was the first analysis comparing the efficacy and safety of PD-L1 inhibitors in combination with chemotherapy in patients with SCLC. This study showed that first-line durvalumab in combination with chemotherapy was more beneficial in terms of long-term survival and that there was no significant difference in the incidence of IRAEs between durvalumab and atezolizumab during its use. In addition, appropriate radiotherapy during treatment with immune checkpoint inhibitors in combination with chemotherapy may prolong survival, but the occurrence of immune-related pneumonitis should be vigilant. However, there are several minor issues that if addressed would significantly improve the manuscript.

1) What are the advantages of combination therapy? It is recommended to add relevant comparative analysis.

Reply: We feel great thanks for your professional review work on our article. Regarding the advantages of combination therapy, you asked about, I will give the following analysis: When the European Society of Internal Oncology (ESMO) Congress 2021 updated 3-year follow-up data from the CASPIAN study, the durvalumab plus chemotherapy group showed a significant improvement in median OS compared with chemotherapy alone (12.9 vs 10.5 months, p=0.0003). In addition, the 3-year OS rate in the immunochemotherapy group increased nearly three times, to 17.6% vs 5.8%, respectively. These data show a "long tail effect" of immunotherapy, with a significant advantage in long-term OS benefits in the immunochemotherapy group compared to the chemotherapy alone group.

Reference:

Paz-Ares L, Goldman JW. Durvalumab, with or without tremelimumab, plus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer: 3-year overall survival update from CASPIAN. ESMO Volume 7 Issue 2 2022.

2) In the introduction of the manuscript, it is necessary to clearly indicate the knowledge gaps and limitations of prior study and the clinical significance of this study.

Reply: Thank you for your suggestion. We have analysed the knowledge gaps and limitations of previous studies and the clinical implications of this study in the introduction section. The specific content is described below.

#Although data from clinical trials indicate comparable overall survival for atezolizumab and durvalumab (20, 22), clinical trials only recruit well-defined patients and do not reflect the heterogeneity of patients and diseases. Meanwhile, given the diverse efficacy and absence of head-to-head researches conducted to evaluate the efficacy among them, it might bring with confusion on selection in clinical practice. Real-world data are therefore needed to validate which immune checkpoint inhibitor is recommended in clinical practice for the treatment of patients with SCLC. We have briefly added this discussion in the last paragraph of the introduction (see Page 4, line 17-23).

Reference:

20. Horn L, Mansfield A S, Szczesna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer[J]. N Engl J Med, 2018,379(23):2220-2229.
22. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial[J]. Lancet, 2019,394(10212):1929-1939.

3) Is there a difference in the efficacy of immunotherapy for patients with different PD-1 expression levels? In the treatment plan, is there any difference in the efficacy of different immune checkpoint inhibitors? It is recommended that relevant information be added to the discussion.

Reply: Thank you for your comment. I give the following statement on the relationship between PD-1 expression levels and the efficacy of immunotherapy.

#As we know, PD-L1 expression refers to the proportion of tumor cells with PD-L1 protein expression in tumors and is an important biomarker for predicting the efficacy of immunotherapy (1). Several large clinical studies have shown a positive correlation between PD-L1 expression and the efficacy of treatment with ICIs, but a few studies have also shown that low levels of PD-L1 expression show better efficacy (2). Therefore, PD-L1 expression cannot be the only predictor of immunotherapy efficacy, as previous studies have shown that the efficacy of ICIs is still influenced by other factors, such as TMB, tumor infiltrating lymphocyte (TIL) density, driver mutations, and gut microbes (3).

Reference:

1. Pan Z K, Ye F, Wu X, et al. Clinicopathological and prognostic significance of programmed cell death ligand1 (PD-L1) expression in patients with non-small cell lung cancer: a meta-analysis[J]. J Thorac Dis, 2015,7(3):462-470.
2. Shen X, Zhao B. Efficacy of PD-1 or PD-L1 inhibitors and PD-L1 expression status in cancer: meta-analysis[J]. BMJ, 2018, 362: k3529.
3. Ren D, Hua Y, Yu B, et al. Predictive biomarkers and mechanisms underlying resistance to PD1/PD-L1 blockade cancer immunotherapy[J]. Mol Cancer, 2020,19(1):19.

#The efficacy of different immune checkpoint inhibitors is discussed below.

There are more studies on comparative efficacy analysis between PD-1 inhibitors, PD-L1 inhibitors and CTLA-4 inhibitors, while there is a lack of data on comparative efficacy between several PD-L1 inhibitors. According to the guideline of Chinese Society of Clinical Oncology (CSCO), atezolizumab + chemotherapy and durvalumab + chemotherapy had been recommended for treating ES-SCLC. The network meta-analysis by Jianxin Chen, et al revealed that there was no statistical difference observed in the indirect comparison of PFS or OS among agents of atezolizumab and durvalumab as first-line treatment in patients with extensive-stage SCLC. Besides, durvalumab was shown superiority on ORR when compared with atezolizumab, however, with a significantly higher risk of immune-related AEs when compared with atezolizumab (24). This study was a direct comparison between atezolizumab and durvalumab in first-line treatment of SCLC and the results of the study showed that first-line durvalumab is superior to atezolizumab. We have briefly added this discussion in paragraph 2 of the discussion (see Page 9, line 11-24).

Reference:

24. Chen J, Wang J, Xu H. Comparison of atezolizumab, durvalumab, pembrolizumab, and nivolumab as first-line treatment in patients with extensive-stage small cell lung cancer[J]. Medicine, 2021,100(15): e25180.

4) What is the tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors? It is recommended to add relevant content.

Reply: Thank you for your comments! As for this question, we give the following statement.

L. Khoja et al. have demonstrated that different tumor histologies (melanoma, renal cell and non-small cell lung cancer) have a different irAE profile when treated with PD-1 inhibitors (1). While intriguing, such a finding should not be a surprise given that antitumor immune responses differ across patients with different tumor types treated with the same ICI. Currently the reasons for this observation are not clear. The tumor microenvironment (TME), immune infiltrate, adaptive immune response and neoantigen formation may be influenced by histology and is thus one potential explanation for different toxicities (2,3).

Reference:

1. Pan Z K, Ye F, Wu X, et al. Clinicopathological and prognostic significance of programmed cell death ligand1 (PD-L1) expression in patients with non-small cell lung cancer: a meta-analysis[J]. J Thorac Dis, 2015,7(3):462-470.
2. Tumeh P C, Harview C L, Yearley J H, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance[J]. Nature, 2014,515(7528):568-571.
3. Khoja L, Kibiro M, Metser U, et al. Patterns of response to anti-PD-1 treatment: an exploratory comparison of four radiological response criteria and associations with overall survival in metastatic melanoma patients[J]. Br J Cancer, 2016,115(10):1186-1192.

5) The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as “Consecutive severe immune-related adverse events after PD-1 inhibitor induction and surgery in locally advanced non-small cell lung cancer: a case report, Transl Lung Cancer Res, PMID: 34584866”. It is recommended to quote this article.

Reply: Thank you for your kind reminding. We have carefully rewritten the introduction part of the article (see Page 4, line 17-31).

6) With the discovery of new drug targets and the continuous emergence of new combination treatment options, what breakthroughs will there be in the treatment of SCLC in the future? What inspiration can this study provide? It is recommended to add relevant content to the discussion.

Reply: We sincerely thank the reviewer for careful reading. For the discussion section, we added a discussion on the future development of SCLC treatment as follows.

#Recent breakthroughs in " immunotherapy in combination with chemotherapy " have changed the previous standard of care for SCLC and have shown signs of improving outcomes for SCLC patients (20, 22), as further validated by our real-world clinical data. In 2022, with the publication of data from clinical studies of our self-developed serplulimab and adebrelimab, which break through the previous magnitude of benefit of immune checkpoint inhibitors, a new record of OS for first-line treatment of ES-SCLC was set, providing more drug options for first-line treatment of SCLC (30, 31). SCLC must be firmly targeting precision therapy and immunotherapy. Although immune drugs have improved survival in SCLC patients to some extent, there is still huge room for improvement in their long-term survival rates. With the exploration and deeper understanding of the molecular typing and immune microenvironment of SCLC, the more rational use and combination of existing drugs and the development of more effective new drugs will drive the precision treatment of SCLC and improve patient survival faster. (see Page 10, line 31-33; Page 11, line 1-11).

Reference:

20. Horn L, Mansfield A S, Szczesna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer[J]. N Engl J Med, 2018,379(23):2220-2229.
22. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial[J]. Lancet, 2019,394(10212):1929-1939.
30. Cheng Y, Han L, Wu L, et al. Effect of First-Line Serplulimab vs Placebo Added to Chemotherapy on Survival in Patients with Extensive-Stage Small Cell Lung Cancer[J]. JAMA, 2022,328(12):1223.
31. Wang J, Zhou C, Yao W, et al. Adebrelimab or placebo plus carboplatin and etoposide as first-line treatment for extensive-stage small-cell lung cancer (CAPSTONE-1): a

multicentre, randomised, double-blind, placebo-controlled, phase 3 trial[J]. The Lancet Oncology, 2022,23(6):739-747.

Reviewer B

1) First, the title needs to indicate durvalumab + chemotherapy vs. atezolizumab + chemotherapy and the clinical research design of this study, i.e., a retrospective comparative cohort study.
Reply: We sincerely thank the reviewer for carefully reading. As suggested by the reviewer, we have corrected the title "Efficacy and safety of durvalumab versus atezolizumab with chemotherapy in the treatment of small-cell lung cancer: a multicenter real-world study" into "Efficacy and safety of durvalumab + chemotherapy vs. atezolizumab + chemotherapy in the treatment of small-cell lung cancer: a retrospective comparative cohort study" (see Page 1, line 3-5).

2) Second, the abstract is not adequate and needs further revisions. The background did not indicate the clinical needs for comparing the two treatments and what the knowledge gap is. The methods need to describe the inclusion of subjects, assessment of clinical factors and efficacy and safety outcomes, and follow up procedures. The results need to briefly summarize the clinical characteristics of the two groups and quantify "Baseline characteristics of the two groups were fundamentally balanced" by using statistics. The conclusion needs to have more detailed comments for the clinical implications of the findings and the limitations of this study.
Reply: We think this is an excellent suggestion. According to the reviewer's comments, we have revised the abstract clearly (see Page 1, line 29-33; Page 2, line 1-28).

3) Third, in the introduction of the main text, the authors need to analyze the clinical needs for comparing durvalumab with atezolizumab and have comments on their relative efficacy and safety. The authors need to describe the clinical questions that have not been answered in the published clinical trials to suggest the needs for real-world data.
Reply: Thank you so much for your careful review. Based on the reviewer's comments, we have added relevant content to the introduction below.
#Although data from clinical trials indicate comparable overall survival for atezolizumab and durvalumab (20, 22), clinical trials only recruit well-defined patients and do not reflect the heterogeneity of patients and diseases. Meanwhile, given the diverse efficacy and absence of head-to-head researches conducted to evaluate the efficacy among them, it might bring with confusion on selection in clinical practice. Real-world data are therefore needed to validate which immune checkpoint inhibitor is recommended in clinical practice for the treatment of patients with SCLC (see Page 4, line 17-31).

Reference:

20. Horn L, Mansfield A S, Szczesna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer[J]. N Engl J Med, 2018,379(23):2220-2229.
22. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial[J]. Lancet, 2019,394(10212):1929-1939.

4) Fourth, in the methodology of the main text, please accurately describe the clinical research design, sample size estimation, detailed baseline clinical data collected, and follow up procedures. In statistics, "This was a descriptive study for which no theoretical calculation of the number of patients to be included was made" is wrong since real-world study needs sample size estimation, in particular, a very large sample is needed for a real-world study but the current sample size is small. The authors need to explain why it can be a real-world study, which is often characterized by a large sample. Please describe the test of the baseline comparability of clinical characteristics and indicate the adjustment of potential confounders for comparing the two groups. Please ensure $P<0.05$ is two-sided.

Reply: Thank you for your suggestion. Based on the reviewer's comments, we have modified the method part below (see Page 5, line 1-33; Page 6, line 1-18).

 # Methods

Study population143 SCLC patients who met the inclusion criteria were collected from February 1, 2020 to April 30, 2022 in three provincial general hospitals in the capital of Anhui Province as outpatients or inpatients.

Inclusion criteria:

(1) Patients with histologically or cytologically confirmed SCLC as defined by the Veterans Administration Lung Study Group staging system.
(2) Age ≥ 18 years.
(3) Eastern cooperative oncology group (ECOG) score between 0 and 2.
(4) Receiving treatment with durvalumab or atezolizumab.

All conditions must be met to be included in this study.

Exclusion criteria:

(1) Patients with significant deficiencies in relevant medical records.
(2) Previous autoimmune disease or interstitial lung disease.
(3) Patients with previous use of PD-1 inhibitors.

##Data collection

Data included patients' demographics and baseline characteristics (sex, age, smoking status, background diseases, ECOG); disease characteristics (metastatic sites at diagnosis, stage at diagnosis) and follow up indicators (follow-up time, PFS, OS, IRAEs, interventions after the occurrence of IRAEs).

##Observed indicators

Clinical efficacy: Patients receiving durvalumab or atezolizumab in combination with chemotherapy were evaluated for efficacy every 2 courses of treatment. Clinical outcomes were assessed according to RECIST version 1.1 and were classified into the following states:

Complete response (CR), Partial response (PR), Stable disease (SD) and Progressive disease (PD). We sought to assess the OS (the time from the initiation of immunotherapy to the time of death from any cause) and PFS (the time from the initiation of immunotherapy to disease progression according to the RECIST or death from any cause) in the targeted population.

Immune-related adverse events: To investigate the safety of PD-L1 inhibitors in combination with chemotherapy regimens, we screened for all drug-related adverse events by reviewing all clinical records and laboratory tests during the use of durvalumab or atezolizumab. IRAEs were screened by reviewing clinical records, radiology reports and pathology during treatment with PD-L1 inhibitors and were based on the National Cancer Institute common terminology criteria for adverse events. IRAEs were graded on a scale of severity from 1-5, with grades 1-2 being considered low grade IRAEs and grades 3-5 being considered high grade IRAEs.

##Statistical analysis

This was a descriptive study for which no theoretical calculation of the number of patients to be included was made. Clinical characteristics, safety, and survival outcomes were compared using the Fisher's exact (descriptive analysis) and log-rank (Kaplan-Meier) tests. IBM SPSS Statistics version 26.0 (IBM SPSS Inc., Chicago, USA) was used for the statistical analysis. A P value<0.05 was set as the significance level.

##Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of The First Affiliated Hospital of USTC (AF/SC-12-2/04.0) and individual consent for this retrospective analysis was waived.