META-ANALYSIS

Meta-Analysis of Atezolizumab vs Docetaxel in Non-Small Cell Lung Cancer Treatment Outcomes

Yingya Fu, MM; Guojuan Xue, MM

ABSTRACT

Objective • We aimed to investigate the clinical efficacy of atezolizumab and docetaxel in the treatment of non-small cell lung cancer (NSCLC) via meta-analysis and systematic review.

Methods • Publications were searched from China National Knowledge Infrastructure (CNKI), Chongqing Vipers Chinese Science and Technology Journal database (VIP), Wanfang database, PubMed database, Embase database, Cochrane Library and Web of Science. Randomized controlled trials (RCTs) of atezolizumab and docetaxel in the treatment of patients with NSCLC were collected. The retrieval period was from the establishment of the database to November 2021 and updated on 22 April 2023. According to the inclusion and exclusion criteria, the included studies were screened and quality evaluated. Meta-analysis was performed using RevMan 5.4.3 (Cochrane Training, Summertown, Oxford UK) software.

Results • A total of 6 RCTs were included in our analysis, including 6348 patients with NSCLC. Our results showed that the atezolizumab group had significantly longer overall survival (OS) than the docetaxel group (hazard ratio [HR] = 0.77; 95% CI, 0.73-0.81); $P < .00001$). In terms of progression-free survival (PFS) and objective response rate (ORR), the atezolizumab group was not significantly superior to the docetaxel group (HR = 0.96; 95% CI, 0.90-1.02; $P = .20$), (relative ratio [RR] = 1.10, 95% CI, 0.95-1.26; $P = .20$). In terms of treatment-related adverse events (TRAEs), after treatment, the number of patients with TRAEs in the atezolizumab group was significantly lower than in the docetaxel group (RR = 0.65; 95% CI, 0.54-0.79; $P < .00001$).

Conclusion • Compared with docetaxel, atezolizumab can significantly prolong OS in patients with NSCLC and reduce the occurrence of TRAEs, but there is no advantage in PFS or ORR remission rate. Due to some limitations in case numbers and quality of included studies, multicenter, large sample, high-quality RCTs are still needed for further validation. (*Altern Ther Health Med.* 2023;29(6):128-133).

Yingya Fu, MM; Guojuan Xue, MM; Pulmonary and Critical Care Medicine, The Seventh People's Hospital of Chongqing, Chongqing, China.

Corresponding author: Guojuan Xue, MM
E-mail: 990969498@qq.com

INTRODUCTION

Lung cancer still ranks first in cancer-related mortality and seriously threatens people's quality of life (QoL).[1] Approximately 85% of patients with lung cancer are classified as having non-small cell lung cancer (NSCLC).[2] Atezolizumab monotherapy is the preferred option in patients with a high expression of programmed death receptor 1 (PD-1).[3,4] Atezolizumab in combination with bevacizumab, carboplatin and paclitaxel is used as first-line therapy in patients with advanced non-squamous NSCLC and has been approved by the US Food and Drug Administration and the European Medicines Agency.[5] Docetaxel is the most widely used second-line agent when patients do not respond to first-line therapy. Clinical trials have confirmed that docetaxel can prolong the survival of patients with advanced NSCLC and serves as a reference standard for the efficacy of treatment in this patient population.[6]

Both atezolizumab and docetaxel have shown some efficacy in patients with advanced NSCLC, but a meta-analysis focusing specifically on their efficacy has not been done. To further compare the efficacy and safety of atezolizumab and docetaxel in the treatment of patients with NSCLC, our study performed a meta-analysis to systematically evaluate the existing relevant randomized controlled trials (RCTs).

MATERIALS AND METHODS

All procedures strictly followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Inclusion and Exclusion Criteria

Inclusion criteria. Randomized phase 2 or 3 studies comparing the efficacy and safety of atezolizumab with that of docetaxel in patients with locally advanced or metastatic NSCLC whose disease progressed after prior platinum therapy were included in the study. There were no restrictions on the dose, frequency or duration of treatment in the experimental or control groups. Study outcomes included overall survival (OS), progression-free survival (PFS), overall response rate (ORR) or treatment-related adverse events (TRAEs).

Exclusion criteria. (1) Retrospective studies, observational studies or non-prospective randomized controlled studies; (2) studies that did not contain outcome indicators needed for this study; (3) studies that were not published in Chinese or English; (4) duplicate literature, summaries of experiences, case reports, reviews, studies with too little or incomplete information, animal studies and conference proceedings; (5) studies with a total of <20 patients.

Study Definitions

NSCLC occurs when abnormal cells form and multiply in the lung tissues. It is the most common type of lung cancer, making up about 85% of all lung cancer cases.

Platinum-based therapies use a class of drugs called alkylating agents, which are usually most effective in treating slow-growing cancers. The platinum molecules in platinum-based drugs bind to the DNA of cancer cells; this binding is thought to induce DNA damage and cell death.

Per International Council for Harmonisation (ICH) Guidelines for Statistical Principles for Clinical Trials (E9), a TRAE is defined as an event that emerges during treatment that was absent pre-treatment, or worsens relative to the patient's pre-treatment state. Criteria for AEs were based on the National Cancer Institute common adverse events evaluation criteria (CTCAEV4.0).

Search Strategy

We searched the China Knowledge Network database (CNKI), Chongqing Vipers Chinese Science and Technology Journal database (VIP), Wanfang journal database (Wanfang database), Pubmed database, Web of Science, Embase database, and the Cochrane Library database by using the following key words: "non small cell lung cancer," "Carcinoma, Non-Small-Cell Lung," "Lung Neoplasms," "Lung cancer," "atezolizumab" and "docetaxel." The retrieval period was from the establishment of the database to November 2021 and updated on April 22, 2023. We also manually screened citations of relevant articles in order to identify additional studies.

Study Screening

A total of 2 researchers independently performed literature screening, review and acquisition of data and then checked the results. The researchers first excluded the studies that obviously did not meet the inclusion criteria after reading the title and abstract, screened the studies that did by reading the full text, and discussed the chosen studies in order to reach a final decision. If relevant data was missing or unclear, the researchers contacted the corresponding author in order to obtain accurate data, if possible, and if this was not available, the study was excluded.

Data Extraction

A total of 2 reviewers independently extracted data from the RCTs that met the inclusion criteria, and all the researchers discussed the results in the event of discrepancies. The following data were extracted from each study: (1) first author; (2) year of publication; (3) trial staging; (4) interventions of experimental and control groups, including drug, dosage, frequency, treatment duration; (5) number of participants; (6) main outcome: OS; (7) secondary outcomes: PFS, ORR and TRAEs.

Quality Assurance

The quality of the RCTs was assessed using the Jadad scale.[7] Studies were scored according to the presence of the 3 key methodological features of randomization, blinding and accountability of all patients, including withdrawals. It was decided that studies should be scored as high quality if they received a Jadad score of 4 or 5 (of a possible 5 points) and low quality if the score was ≤3.

Statistical Analysis

We used RevMan (Review Manager) 5.4.3, 2020 software 3 (Cochrane Training, Summertown, Oxford UK) for statistical analysis. Effect sizes related to time events (OS and PFS) were used for the hazard ratio (HR) and its 95% CI. For dichotomous data (ORR and TRAEs), we presented results as relative risk (RR) ratio with 95% CI; $P < .05$ was considered statistically significant.

The I^2 test was used to test for heterogeneity among the included studies. If there was no statistical heterogeneity between the results of the studies ($P > .10$; $I^2 \leq 50\%$), a fixed-effects model was used for the analysis; conversely, a random-effects model was used to analyze the sources of heterogeneity. Sensitivity analyses were performed by excluding a study and analyzing the remaining data for each round to test the robustness of our results. The meta-analysis results were represented by forest plots, and bias was examined via funnel plots.

RESULTS

Basic Data From the Included Studies

A total of 2200 relevant studies was obtained from the initial review. After screening the titles and abstracts according to the inclusion and exclusion criteria and further reading of the full text, 6 papers were finally included, and reported 8 RCTs.[8-13] A total of 6348 patients were included in this study, including 3187 in the atezolizumab group and 3161 in the docetaxel group. The literature screening process

Table 1. Basic Data From the Included Studies

Study	Trial Staging	Intervention					Outcomes							
							OS			PFS				
		Drug	Dosage	Frequency	Treatment duration (months)	Participants	Median (95% CI) [months]	HR (95% CI)	*P* value	Median (95% CI) [months]	HR (95%CI)	*P* value	ORR	TRAEs
Fehrenbacher, 2016	2 (POPLAR)	Atezolizumab	1200 mg	1× every 3 wk	3.7 (0-19)	144	12.6 (9.7-16.4)	0.73 (0.53-0.99)	.04	2.7 (2.0-4.1)	0.94 (0.72-1.23)	.68	14.6% (21/144)	67% (95/142)
		Docetaxel	75 mg/m²	1× every 3 wk	2.1 (0-17)	143	9.7 (8.6-12.0)			3.0 (2.8-4.1)			14.7% (21/143)	88% (119/135)
Rittmeyer, 2017	3 (OAK)	Atezolizumab	1200 mg	1× every 3 wk	3.4 (0-26)	425	13.8 (11.8-15.7)	0.73 (0.62-0.87)	.0003	2.8 (2.6-3.0)	0.95 (0.82-1.10)	.50	14% (58/425)	19% (80/425)
		Docetaxel	75 mg/m²	1× every 3 wk	2.1 (0-23)	425	9.6 (8·6-11·2)			4.0 (3·3-4·2)			13% (57/425)	
Fehrenbacher, 2018 (OAK1)	3 (OAK)	Atezolizumab	1200 mg	1× every 3 wk	NR	425	13.8 (11.8-15.7)	0.75 (0.64-0.89)	.0006	2.8 (2.6-3.0)	0.93 (0.80-1.08)	.3495	14.6% (62/425)	NR
		Docetaxel	75 mg/m²	1× every 3 wk	NR	425	9.6 (8.6-11.2)			4.0 (3.3-4.2)			13.4% (57/425)	NR
Fehrenbacher, 2018 (OAK2)	3 (OAK)	Atezolizumab	1200 mg	1× every 3 wk	3.4 (0-32)	613	13.3 (11.3-14.9)	0.80 (0.70-0.92)	.0012	2.7 (2.4-.9)	0.96 (0.85-1.08)	.4981	13.7 % (84/613)	64% (390/609)
		Docetaxel	75 mg/m²	1× every 3 wk	2.1 (0-30)	612	9.8 (8.8-11.3)			3.8 (3.3-4.1)			11.8% (72/612)	86.2% (498/578)
Pawel, 2019	3 (OAK)	Atezolizumab 1200 mg every 3 wk	1200 mg	1× every 3 wk	NR	398	13.8 (11.8-15.7)	0.73 (0.62-0.87)	.0003	11.3 (5.7, 14.8)	1.02 (0.88-1.88)	.80	15.1%(60/398)	NR
		Docetaxel 75 mg/m² every 3 wk	75 mg/m²	1× every 3 wk	NR	376	9.6 (8.6-11.2)			8.8 (7.0, 10.4)			13.8%(52/376)	NR
Gandara, 2018	3 (OAK)	Atezolizumab	1200 mg	1× every 3 wk	NR	425	12.7 (9.3-14.9)	0.83 (0.72-0.65)	.009	4.2 (3.9-4.6)	0.95 (0.82-1.10)	.50	16% (68/425)	NR
		Docetaxel	75 mg/m²	1× every 3 wk	NR	425	3.7 (2.7-4.0)			2.8 (2.6-3.0)			14% (60/425)	NR
Mazieres, 2021 (POPLAR)	2 (POPLAR)	Atezolizumab	1200 mg	1× every 3 wk	NR	144	12.6	0.76 (0.58-1.00)	.025	NR	NR	NR	NR	67% (95/142)
		Docetaxel	75 mg/m²	1× every 3 wk	NR	143	9.7			NR	NR	NR	NR	88% (119/135)
Mazieres, 2021 (OAK)	3 (OAK)	Atezolizumab	1200 mg	1× every 3 wk	NR	613	13.3	0.78 (0.68-0.89)	.000	NR	NR	NR	NR	65% (395/609)
		Docetaxel	75 mg/m²	1× every 3 wk	NR	612	9.8			NR	NR	NR	NR	86% (496/578)

NOTES: POPLAR = multicenter, randomized, open-label, all-comers phase 2 trial done at 61 academic medical centers and community oncology practices across 13 countries in Europe and North America to investigate the efficacy and safety of atezolizumab vs docetaxel in second- and third-line NSCLC treatment.
OAK = randomized phase 3 study comparing the efficacy and safety of atezolizumab with that of docetaxel in patients with locally advanced or metastatic NSCLC whose disease progressed after prior platinum therapy.

Abbreviations: NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TRAEs, treatment-related adverse events.

is shown in Figure 1, and basic data from the included studies are shown in Table 1.[8-13]

Results of Methodological Quality Evaluation

The 6 included studies were evaluated by the modified Jadad scale, and all 6 studies were found to be high quality, with a random randomized, double-blind and well-sampled study design. Details are shown in Table 2.[8-13]

Meta-Analysis Results

Overall survival. A total of 8 trials of 6 studies all reported on OS after atezolizumab or docetaxel treatment in 6348 patients with NSCLC.[8-13] There was no statistical heterogeneity among studies ($P = .89$; $I^2 = 0\%$), and the pooled effect size from the fixed effect model was used for the next analysis. The results showed that OS was significantly longer in the atezolizumab group compared with the docetaxel group (HR = 0.77; 95% CI, 0.73-0.81; $P < .00001$), as detailed in Figure 2.

Progression-free survival. A total of 6 trials in 5 studies reported on PFS after treatment with atezolizumab or docetaxel in 4836 patients with NSCLC.[8-12] There was no statistical heterogeneity among studies ($P = 0.97$; $I^2 = 0\%$), and the pooled effect size from the fixed effect model was used for the next analysis. After treatment, there was no statistically significant difference in PFS between the

Figure 1. Literature search procedure.

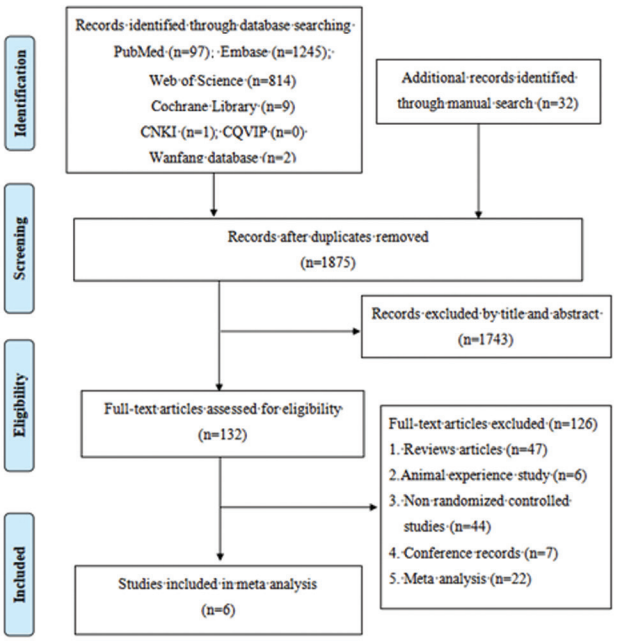


Table 2. Methodological Quality Assessment of Included Studies

Included studies	Randomization	Blinding	An account of all patients	Total Score
Fehrenbacher, 2016[9]	2	2	1	5
Fehrenbacher, 2018[12]	2	2	1	5
Pawel, 2019[11]	2	2	1	5
Gandara, 2018[8]	2	2	1	5
Rittmeyer, 2017[10]	2	2	1	5
Mazieres, 2021	2	2	1	5

Figure 2. Comparison of overall survival in the two groups.

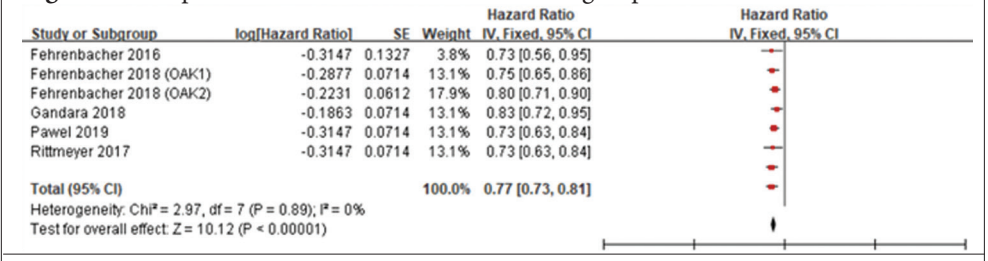


Figure 3. Comparison of progression-free survival in the two groups.

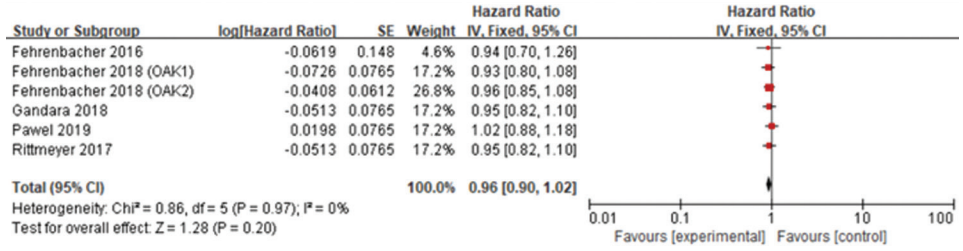


Figure 4. Comparison of objective response rate in the two groups.

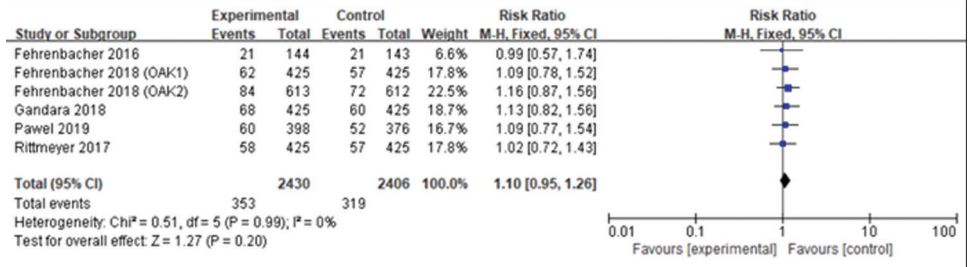


Figure 5. Comparison of treatment-related adverse events in the two groups.

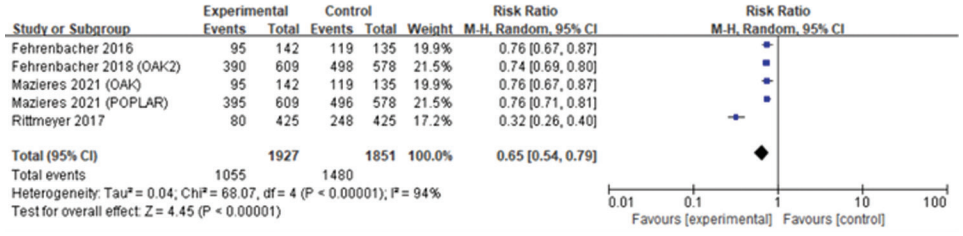
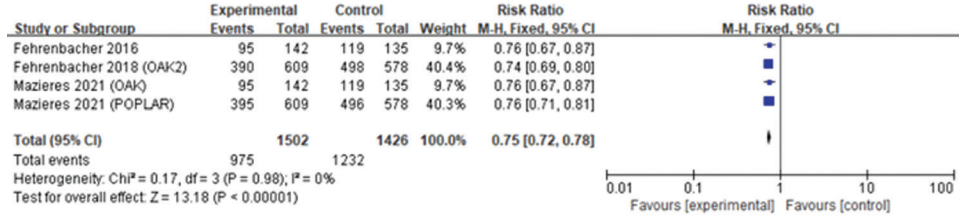


Figure 6. Sensitivity analysis by removing a study for comparison of treatment-related adverse events in the two groups.



atezolizumab group and the docetaxel group (HR = 0.96; 95% CI, 0.90-1.02; $P = .20$), as detailed in Figure 3.

Objective response rate. A total of 6 trials in 5 studies reported ORR after atezolizumab or docetaxel treatment in 4836 patients with NSCLC.[8-12] There was no statistical heterogeneity among studies ($P = .99$; $I^2 = 0\%$), and the pooled effect size from the fixed effect model was used for the next analysis. There was no statistical difference between the atezolizumab and the docetaxel groups in terms of ORR (RR = 1.10; 95% CI, 0.95-1.26; $P = .20$), as detailed in Figure 4.

Treatment-related adverse effects. A total of 5 trials in 4 studies reported TRAEs in 3778 patients with NSCLC treated with atezolizumab or docetaxel.[9,10,12,13] There was significant statistical heterogeneity among studies ($P < .0001$; $I^2 = 94\%$), and the pooled effect size of the random effect model was used for the next analysis. After treatment, the number of patients experiencing TRAEs in the atezolizumab group was significantly lower than in the docetaxel group (RR = 0.65; 95% CI, 0.54-0.79; $P < .00001$), as detailed in Figure 5. The heterogeneity test found that after excluding the study by Rittmeyer, 2017,[10] there was no statistical heterogeneity ($P = .98$; $I^2 = 0\%$), but the statistical results did not change, as shown in Figure 6.

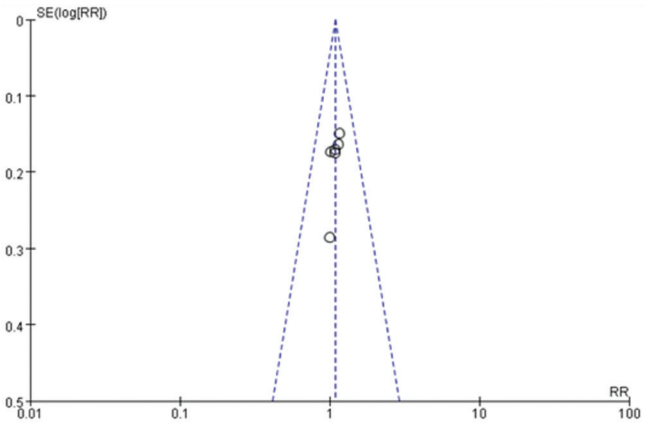
Publication bias

Publication bias analysis was performed using ORR as the index. As shown in Figure 7, the symmetry of the scattered distribution of the studies was reasonable, suggesting that the possibility of publication bias in this study was low.

DISCUSSION

Currently, the advent of programmed death receptor 1 (PD-1) and programmed death receptor 1 ligand (PD-L1) inhibitors has led to new options in the treatment of NSCLC. This study performed a meta-analysis of the results of the 6 included RCTs. We found that, in terms of OS, atezolizumab reduced the risk for death in progressive NSCLC compared with docetaxel; in terms of PFS, atezolizumab was not significantly superior to docetaxel ($P > .05$); in terms of ORR, atezolizumab also failed to improve the remission rate of progressive NSCLC compared with docetaxel ($P > .05$). However, atezolizumab had fewer adverse reactions, significantly less TRAEs than the docetaxel group and a better safety profile. Overall, the clinical efficacy of atezolizumab in the treatment of NSCLC was superior to that of docetaxel.

Figure 7. Funnel plot of publication bias analysis.



Our findings revealed a distinctive association between atezolizumab efficacy measures, including OS, PFS and ORR. Specifically, in the intent-to-treat population and PD-L1 expression subgroups defined by ≥1% and ≥5% tumor cell or tumor-infiltrating immune cell staining, atezolizumab treatment led to improved OS but not PFS or ORR. The significant improvement in OS, despite the absence of any progress in PFS or ORR in these populations, coupled with the observation that atezolizumab led to an increase in OS in both responsive and non-responsive patients, suggests that conventional radiographic endpoints may underestimate the therapeutic benefits of atezolizumab. These findings suggest that certain patients may experience benefits following Response Evaluation Criteria In Solid Tumors (RECIST)-defined progression, potentially due to delayed anticancer immune effects.

NSCLC cells can widely express PD-L1, activate PD-1 expressed by T cells, inhibit the immune response, promote tumor immune escape and enhance the resistance effect of the tumor microenvironment.[14,15] Combined with the available reports, immune-targeted therapy is believed to improve patients' immunity by enhancing the innate immune function, thereby inhibiting and killing tumor cells. PD-L1 and PD-1 are important immunoregulatory molecules and immunosuppressive factors. When this pathway is activated, TP53 is inactivated and the immune effect of T cells is reduced, inhibiting the formation of microenvironment, evading the body's immune surveillance and contributing to tumor growth.[16] Activation of the PD-1/PD-L1 signaling pathway promotes the formation of an immunosuppressive tumor microenvironment, and blocking the PD-1/PD-L1 signaling pathway can reverse the tumor immune microenvironment, thereby enhancing the killing effect of the body's immune system on tumor cells.[17]

Of note, PD-L1 expression in tumor cells and tumor-infiltrating immune cells independently predicted improved OS with atezolizumab. This finding contrasts with anti-PD-1 studies that showed an association with tumor cell PD-L1 expression only.[18-21] PD-L1 expression on tumor-infiltrating immune cells as a predictive biomarker is further supported by the association of T-effector and interferon γ gene signature with improved OS. These data are also consistent with the hypothesis that the benefit from checkpoint inhibition is pronounced in tumors with pre-existing immunity.

Taken together, these findings confirm the importance of assessing PD-L1 in tumor-infiltrating immune cells, in addition to tumor cells, as a predictive biomarker to identify patients most likely to benefit from atezolizumab. Neither PD-L1 immunohistochemistry nor T-effector and interferon-γ gene expression was associated with prognostic significance in OS in docetaxel-treated patients.

There have been numerous clinical studies affirming the efficacy of atezolizumab in metastatic urothelial carcinoma, nivolumab in renal cell carcinoma and melanoma and other anti-PD-1 agents in metastatic NSCLC and melanoma.[23-28] PD-1/PD-L1 will bring benefits to more patients with cancer, especially patients with advanced cancer. Atezolizumab is an artificially designed immunoglobulin G1 (IgG1) monoclonal antibody targeting PD-L1, and thus its mechanism of action is different from that of anti-PD-1 antibodies. In addition to blocking the interaction between PD-L1 and PD-1, it can reactivate suppressed immune cells and enable them to play a role in eliminating cancer cells.[17,29] Atezolizumab can also block the binding of PD-L1 and B7-1, which might further enhance the immune response.[30] Furthermore, direct targeting of atezolizumab to PD-L1 may leave the interaction of PD-L2 and PD-1 unaffected and possibly reduce autoimmunity to a minimum.[29, 31, 32]

Previous studies have shown that atezolizumab was well tolerated with significantly lower rates of TRAEs than docetaxel, which is consistent with the AEs observed in this study.[4,5] A previous study indicated that there was no OS benefit in the combination chemotherapy group compared with atezolizumab monotherapy, while ORR and PFS outcomes appeared to be better in the combination chemotherapy group, but the differences were not statistically significant.[33] These results all further support the National Comprehensive Cancer Network® NCCN® recommendation that patients with advanced NSCLC and high PD-L1 levels should be treated preferentially

with atezolizumab monotherapy rather than combination chemotherapy.[34] Of note, there was no significant advantage in PFS or ORR despite a significant prolongation of OS in the atezolizumab group. This discordance may be the result of increased immune infiltration, delayed antitumor activity or increased tumor size due to antitumor immune activity induced by subsequent treatment.[10,35] This also laterally reflected that patients with NSCLC treated with atezolizumab were equally able to benefit from PD-L1 therapy, although the effector mechanism of treatment after NSCLC progression was unclear.

From the overall quality of the included studies, our meta-analysis exhibited relatively satisfactory results according to strict criteria in terms of the inclusion and exclusion criteria because the included studies were all multicenter randomized controlled studies. However, even though the findings were highly consistent, we still need more research evidence to validate the results due to the small number of included studies.

Study Limitations

This study had some limitations. First, few articles were included in the study, and all of them came from Europe and the United States. Whether the findings of our study are applicable to Asian populations still needs to be confirmed by further relevant studies. Second, this meta-analysis was originally planned to conduct a subgroup analysis based on patients' PD-L1 expression to observe whether the treatment effect was related to PD-L1 expression, but relevant data from the included studies could not be obtained to complete this study. Third, only Chinese and English studies were retrieved for this meta-analysis, which may have resulted in a language bias. All of these factors may affect the accuracy of the conclusions of the meta-analysis. There are also limitations due to the number of articles and cases included in our study, which still need to be validated by future multicenter, high-quality, rigorous design and long-term follow-up RCTs with large samples.

CONCLUSIONS

Although atezolizumab did not have a significant advantage over docetaxel in terms of PFS and ORR, atezolizumab significantly prolonged OS in patients with NSCLC and was associated with fewer TRAEs. Due to some limitations in case numbers and the quality of included studies, multicenter, large sample, high-quality RCTs are still needed for further validation.

CONFLICT OF INTEREST

None.

FUNDING

None.

REFERENCES

1. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin*. 2016;66(2):115-132. doi:10.3322/caac.21338
2. Torre LA, Siegel RL, Ward EM, Jemal A. Global Cancer Incidence and Mortality Rates and Trends--An Update. *Cancer Epidemiol Biomarkers Prev*. 2016;25(1):16-27. doi:10.1158/1055-9965.EPI-15-0578
3. Reck M, Rodríguez-Abreu D, Robinson AG, et al; KEYNOTE-024 Investigators. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *N Engl J Med*. 2016;375(19):1823-1833. doi:10.1056/NEJMoa1606774
4. Herbst RS, Giaccone G, de Marinis F, et al. Atezolizumab for First-Line Treatment of PD-L1-Selected Patients with NSCLC. *N Engl J Med*. 2020;383(14):1328-1339. doi:10.1056/NEJMoa1917346
5. Socinski MA, Jotte RM, Cappuzzo F, et al; IMpower150 Study Group. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. *N Engl J Med*. 2018;378(24):2288-2301. doi:10.1056/NEJMoa1716948
6. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet*. 2014;384(9944):665-673. doi:10.1016/S0140-6736(14)60845-X
7. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17(1):1-12. doi:10.1016/0197-2456(95)00134-4
8. Gandara DR, von Pawel J, Mazieres J, et al. Atezolizumab Treatment Beyond Progression in Advanced non-small-cell lung cancer (NSCLC): Results From the Randomized, Phase III OAK Study. *J Thorac Oncol*. 2018;13(12):1906-1918. doi:10.1016/j.jtho.2018.08.2027
9. Fehrenbacher L, Spira A, Ballinger M, et al; POPLAR Study Group. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet*. 2016;387(10030):1837-1846. doi:10.1016/S0140-6736(16)00587-0
10. Rittmeyer A, Barlesi F, Waterkamp D, et al; OAK Study Group. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet*. 2017;389(10066):255-265. doi:10.1016/S0140-6736(16)32517-X
11. von Pawel J, Bordoni R, Satouchi M, et al. Long-term survival in patients with advanced non-small-cell lung cancer treated with atezolizumab versus docetaxel: Results from the randomised phase III OAK study. *Eur J Cancer*. 2019;107(124-132.
12. Fehrenbacher L, von Pawel J, Park K, et al. Updated Efficacy Analysis Including Secondary Population Results for OAK: A Randomized Phase III Study of Atezolizumab versus Docetaxel in Patients with Previously Treated Advanced Non-Small Cell Lung Cancer. *J Thorac Oncol*. 2018;13(8):1156-1170. doi:10.1016/j.jtho.2018.04.039
13. Mazieres J, Rittmeyer A, Gadgeel S, et al. Atezolizumab Versus Docetaxel in Pretreated Patients With NSCLC: Final Results From the Randomized Phase 2 POPLAR and Phase 3 OAK Clinical Trials. *J Thorac Oncol*. 2021;16(1):140-150. doi:10.1016/j.jtho.2020.09.022
14. Zhou C, Zhang J. Immunotherapy-based combination strategies for treatment of gastrointestinal cancers: current status and future prospects. *Front Med*. 2019;13(1):12-23. doi:10.1007/s11684-019-0685-9
15. Galluzzi L, Buqué A, Kepp O, Zitvogel L, Kroemer G. Immunogenic cell death in cancer and infectious disease. *Nat Rev Immunol*. 2017;17(2):97-111. doi:10.1038/nri.2016.107
16. Assoun S, Theou-Anton N, Nguenang M, et al; Association of TP53 mutations with response and longer survival under immune checkpoint inhibitors in advanced non-small-cell lung cancer. *Lung Cancer*. 2019;132(65-71. doi:10.1016/j.lungcan.2019.04.005
17. Herbst RS, Soria JC, Kowanetz M, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature*. 2014;515(7528):563-567. doi:10.1038/nature14011
18. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *N Engl J Med*. 2015;373(17):1627-1639. doi:10.1056/NEJMoa1507643
19. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. *N Engl J Med*. 2015;373(2):123-135. doi:10.1056/NEJMoa1504627
20. Garon EB, Rizvi NA, Hui R, et al; KEYNOTE-001 Investigators. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med*. 2015;372(21):2018-2028. doi:10.1056/NEJMoa1501824
21. Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet*. 2016;387(10027):1540-1550. doi:10.1016/S0140-6736(15)01281-7
22. Schild SE, Vokes EE. Pathways to improving combined modality therapy for stage III nonsmall-cell lung cancer. *Ann Oncol*. 2016;27(4):590-599. doi:10.1093/annonc/mdv621
23. Necchi A, Joseph RW, Loriot Y, et al. Atezolizumab in platinum-treated locally advanced or metastatic urothelial carcinoma: post-progression outcomes from the phase II IMvigor210 study. *Ann Oncol*. 2017;28(12):3044-3050. doi:10.1093/annonc/mdx518
24. George S, Motzer RJ, Hammers HJ, et al. Safety and Efficacy of Nivolumab in Patients With Metastatic Renal Cell Carcinoma Treated Beyond Progression: A Subgroup Analysis of a Randomized Clinical Trial. *JAMA Oncol*. 2016;2(9):1179-1186. doi:10.1001/jamaoncol.2016.0775
25. Escudier B, Motzer RJ, Sharma P, et al. Treatment Beyond Progression in Patients with Advanced Renal Cell Carcinoma Treated with Nivolumab in CheckMate 025. *Eur Urol*. 2017;72(3):368-376. doi:10.1016/j.eururo.2017.03.037
26. Long GV, Weber JS, Larkin J, et al. Nivolumab for Patients With Advanced Melanoma Treated Beyond Progression: Analysis of 2 Phase 3 Clinical Trials. *JAMA Oncol*. 2017;3(11):1511-1519. doi:10.1001/jamaoncol.2017.1588
27. Kazandjian D, Keegan P, Suzman DL, Pazdur R, Blumenthal GM. Characterization of outcomes in patients with metastatic non-small cell lung cancer treated with programmed cell death protein 1 inhibitors past RECIST version 1.1-defined disease progression in clinical trials. *Semin Oncol*. 2017;44(1):3-7. doi:10.1053/j.seminoncol.2017.01.001
28. Beaver JA, Hazarika M, Mulkey F, et al. Patients with melanoma treated with an anti-PD-1 antibody beyond RECIST progression: a US Food and Drug Administration pooled analysis. *Lancet Oncol*. 2018;19(2):229-239. doi:10.1016/S1470-2045(17)30846-X
29. Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy--inhibiting programmed death-ligand 1 and programmed death-1. *Clin Cancer Res*. 2012;18(24):6580-6587. doi:10.1158/1078-0432.CCR-12-1362
30. Butte MJ, Keir ME, Phamduy TB, Sharpe AH, Freeman GJ. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. *Immunity*. 2007;27(1):111-122. doi:10.1016/j.immuni.2007.05.016
31. Matsumoto K, Fukuyama S, Eguchi-Tsuda M, et al. B7-DC induced by IL-13 works as a feedback regulator in the effector phase of allergic asthma. *Biochem Biophys Res Commun*. 2008;365(1):170-175. doi:10.1016/j.bbrc.2007.10.156
32. Akbari O, Stock P, Singh AK, et al. PD-L1 and PD-L2 modulate airway inflammation and iNKT-cell-dependent airway hyperreactivity in opposing directions. *Mucosal Immunol*. 2010;3(1):81-91. doi:10.1038/mi.2009.112
33. Li DN, Lu WQ, Yang BW, et al. Atezolizumab Monotherapy or Plus Chemotherapy in First-Line Treatment for Advanced Non-Small Cell Lung Cancer Patients: A Meta-Analysis. *Front Immunol*. 2021;12:666909. doi:10.3389/fimmu.2021.666909
34. Peters S, Gettinger S, Johnson ML, et al. Phase II Trial of Atezolizumab As First-Line or Subsequent Therapy for Patients With Programmed Death-Ligand 1-Selected Advanced Non-Small-Cell Lung Cancer (BIRCH). *J Clin Oncol*. 2017;35(24):2781-2789. doi:10.1200/JCO.2016.71.9476
35. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res*. 2009;15(23):7412-7420. doi:10.1158/1078-0432.CCR-09-1624