



A comprehensive clinical evaluation of first-line drugs for ALK-positive advanced non-small cell lung cancer

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Background: Anaplastic lymphoma kinase-tyrosine kinase inhibitors (ALK-TKIs) are mainly used in the treatment of ALK-positive advanced non-small cell lung cancer (NSCLC), but a comprehensive clinical evaluation of ALK-TKIs is lacking. Hence, a comparison of ALK-TKIs for first-line treatment of ALK-positive advanced NSCLC is essential to provide rational drug use and a basis for improving national policies and systems.

Methods: According to the Guideline for the Administration of Clinical Comprehensive Evaluation of Drugs (2021) and the Technical Guideline for the Clinical Comprehensive Evaluation of Antitumor Drugs (2022), a comprehensive clinical evaluation index system of first-line treatment drugs for ALK-positive advanced NSCLC was established by literature review and expert interviews. We conducted a systematic literature review, meta-analysis, and other relevant data analyses, combined with an indicator system, to establish a quantitative and qualitative integration analysis for each indicator and each dimension of crizotinib, ceritinib, alectinib, ensartinib, brigatinib, and lorlatinib.

Results: The comprehensive clinical evaluation results of all dimensions were as follows: in terms of safety, alectinib had a lower incidence of grade 3 and above adverse reactions; for effectiveness, alectinib, brigatinib, ensartinib, and lorlatinib showed better clinical efficacy, and alectinib and brigatinib have been recommended by several clinical guidelines; in terms of economy, second-generation ALK-TKIs have more cost-utility advantages, and both alectinib and ceritinib have been recommended by the UK and Canadian Health Technology Assessment (HTA) agencies; for suitability, accessibility, and innovation, alectinib has a higher degree of physician recommendations and patient compliance. Except for brigatinib and lorlatinib, all other ALK-TKIs have been admitted to the medical insurance directory; the accessibility of crizotinib, ceritinib, and alectinib is good, meeting the needs of patients. Second- and third-generation ALK-TKIs have higher blood-brain barrier permeability, stronger inhibition ability, and innovation than first-generation ALK-TKIs.

Conclusions: Compared with other ALK-TKIs, alectinib performs better across six dimensions and has a higher comprehensive clinical value. The results provide better drug choice and rational use for patients with ALK-positive advanced NSCLC.

Keywords: Anaplastic lymphoma kinase-tyrosine kinase inhibitor (ALK-TKI); advanced non-small cell lung cancer (advanced NSCLC); comprehensive clinical evaluation of drugs

Submitted Feb 01, 2023. Accepted for publication Apr 06, 2023. Published online Apr 27, 2023.

doi: 10.21037/jtd-23-380

View this article at: <https://dx.doi.org/10.21037/jtd-23-380>

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Introduction

Lung cancer ranks first in incidence and mortality of all malignant tumors in China (1). Non-small cell lung cancer (NSCLC) accounts for about 85% of lung cancers. The onset of NSCLC is insidious, and the disease is often at an advanced stage by the time of diagnosis, with a poor prognosis (2). The anaplastic lymphoma kinase (*ALK*) gene rearrangement is caused by a chromosomal inversion in NSCLC patients. Echinoderm microtubule-associated protein-like 4 (*EML4*) and *ALK* gene rearrangement formed fusion gene (*EML4-ALK*) are also known as *ALK* gene positive. *EML4-ALK* is an important tumor driver gene that promotes the occurrence and progression of NSCLC, with an incidence of 3–5% (3). Targeted therapy for advanced *ALK*-positive NSCLC can effectively prolong the survival time of patients with significant curative effects (4–8). Various *ALK* tyrosine kinase inhibitors (*ALK*-TKIs) have been used to treat *EML4-ALK*-positive NSCLC patients. Crizotinib was the first drug approved by the Food and Drug Administration (FDA) to treat patients with *ALK*-positive NSCLC (9). Subsequent second-generation inhibitors, like ceritinib, alectinib, ensartinib, and brigatinib, and a third-generation inhibitor, lorlatinib, have shown stronger inhibition and higher blood-brain barrier permeability (10–12). These drugs are already on the market in China.

Although *ALK*-TKIs have made breakthrough progress,

the evidence level and basis for rapid drug approval are lower than for conventional drugs, thus potentially increasing the risks associated with *ALK*-TKI drug use. Additionally, *ALK*-TKIs are expensive, and the treatment duration is long, creating a heavy economic burden on the government and patients. The Chinese government has admitted some *ALK*-TKIs into the medical insurance scheme through price negotiation and other means, which provides more choices for *ALK*-positive NSCLC patients, but the disease burden remains high for most patients. The 2018 edition of the National Essential Medicine List has not covered *ALK*-positive therapeutic drugs. Therefore, it is essential to select accessible and affordable *ALK*-positive therapeutic drugs. A comprehensive clinical evaluation of drugs is the basis for the selection and dynamic adjustment of essential drugs and the promotion of a rational drug use in clinic. By carrying out a complete comprehensive clinical evaluation, a multi-dimensional decision-making basis can be provided for drug selection and clinical use. At present, a comprehensive clinical evaluation of antitumor drugs has been listed as one of the four major evaluation areas of national interest. There is no comprehensive clinical evaluation of *ALK*-TKIs in *ALK*-positive patients with advanced NSCLC. Therefore, this study aimed to combine the clinical application practice of antitumor drugs with the drug supply guarantee policy to integrate and analyze evidence-based medical data. The comprehensive clinical value of six *ALK*-TKIs was compared in terms of safety, effectiveness, economy, suitability, accessibility, and innovation. In this study, a comprehensive clinical evaluation system consistent with advanced *ALK*-positive NSCLC was established. This study provides a comprehensive clinical evaluation of antitumor drugs that is scientific, homogeneous, and standardized to establish a reference for clinical drug use and catalog access in hospitals and provides a basis for improving national policies and systems.

Highlight box

Key findings

- By comparing first-line drugs for *ALK*-positive advanced NSCLC using a comprehensive clinical evaluation of *ALK*-TKIs, we found that alectinib had the best comprehensive clinical value.

What is known and what is new?

- Studies evaluating the clinical value of *ALK*-TKIs based on one to two dimensions have already been conducted.
- This study focused on six dimensions of *ALK*-TKIs in treating *ALK*-positive advanced NSCLC patients and covered the safety, effectiveness, economy, suitability, accessibility, and innovation of *ALK*-TKIs.

What is the implication, and what should change now?

- This study's comprehensive clinical evaluation of *ALK*-TKIs for patients with *ALK*-positive advanced NSCLC provides rational drug use in clinic and a basis for relevant policy formulation and decision-making.
- Real-world studies are needed to explore the clinical use of *ALK*-TKIs, and the system established remains to be further verified in clinical practice.

Methods

Selection of experts and establishment of an expert opinion interview consulting group

An expert opinion interview team was established, expert at senior associate levels and above with extensive experience in related work and research were selected to form an expert advisory group. They were recruited from level II or III medical institutions from five major regions (eastern, western, southern, northern, and central regions) of China, and each

Table 1 Comprehensive clinical evaluation indicators of first-line drugs for ALK-positive advanced NSCLC

Index	Indicators					
	1	2	3	4	5	6
Primary index	Safety	Effectiveness	Economy	Suitability	Accessibility	Innovation
Secondary index	Grade 3 and above adverse event incidence, monitoring by drug supervisory and administrative departments	Clinical efficacy, quality of life, guideline recommendation	Cost-utility analysis, international HTA recommendation	Physician recommendation, patient compliance, health insurance directory, indication	Price, availability, affordability	Mechanism of drug, urgent clinical need, patent value, localization of technology
Tertiary index	–	OS, PFS, ORR	–	–	Market shares, urban affordability, rural affordability	–

ALK, anaplastic lymphoma kinase; NSCLC, non-small-cell lung cancer; HTA, Health Technology Assessment; OS, overall survival; PFS, progression-free survival; ORR, objective response rate.

expert comes from a different medical institution. The team consisted of 24 experts, including five experts in oncology medicine, five in pharmacy, five in medical insurance, three in health economics, three in health administration, and three in drug bidding and purchasing.

Determination of the focus of evaluation and construction of the comprehensive clinical evaluation index system

According to the Guideline for the Management of Comprehensive Clinical Evaluation of Pharmaceutical Products (in 2021) (13) and the Technical Guideline for the Comprehensive Clinical Evaluation of Antitumor Drugs (in 2022) (14), we constructed a comprehensive clinical evaluation system for six ALK-TKI drugs (crizotinib, ceritinib, alectinib, ensartinib, brigatinib, and lorlatinib) in the first-line treatment of advanced NSCLC. Using a literature review and expert survey and opinion, six dimensions and key evaluation indicators of each dimension were determined, including safety, effectiveness, economy, suitability, accessibility, and innovation (*Table 1*). Regarding safety, effectiveness, and economy, we used a systematic literature review and meta-analysis to conduct a quantitative analysis. We also conducted a qualitative analysis using supplementary reports, such as the health technology assessment reports (HTA reports) and the adverse drug reaction monitoring reports. Regarding suitability, accessibility, and innovation, domestic and foreign drug price data and other related data were quantitatively

analyzed. A qualitative analysis was conducted based on drug instructions and multidisciplinary expert interviews.

Comprehensive clinical evaluation of antitumor drugs in all dimensions

Safety evaluation

We evaluated the quality of antitumor drugs and the risks that may arise after marketing. The comprehensive clinical evaluation of all antitumor drugs required the evaluation of safety in clinical use (except in certain circumstances). Relative safety comparison is the comparison of the safety difference of the control drug with the same pharmacological classification or with the same indications (14). ALK-TKIs belong to the same pharmacological classification and indications. The selected indicators were the incidence of grade 3 and above adverse events (\geq grade 3 AEs). The post-marketing safety information includes the announcement issued by the State Medical Products Administration, the warning issued by the National Drug Administration of the United States and the European Union, and the withdrawal from the market (14). The selected indicators were the monitoring results of the drug supervision and administration departments. In this study, the incidence of \geq grade 3 AEs and monitoring by drug regulatory authorities were selected as the two secondary indicators. A meta-analysis and systematic review was conducted to determine the incidence of \geq grade 3 AEs. The incidence of \geq grade 3 AEs was systematically

compared between six ALK-TKI first-line drugs for ALK-positive advanced NSCLC. Clinical randomized controlled trials were included, excluding single-arm and unavailable full-text studies. The study population was ALK-positive patients with advanced NSCLC. The databases searched included PubMed, Web of Science, and the ClinicalTrial website. The retrieval period was from the establishment of the databases until June 30, 2022. Finally, nine studies were included (15-23) with a total of 2,508 patients.

Effectiveness evaluation

The effectiveness evaluation of antitumor drugs was based on the actual efficacy for patients after taking the drugs, including primary clinical outcome, secondary clinical outcome, and patient-reported outcome (PRO) (14). Indicators were measured based on the best available evidence and were optimized from clinical efficacy or actual effectiveness indicators. The primary clinical outcome reflects the long-term benefits for patients and the disease outcomes over the whole life course after medication, including overall survival (OS) and progression-free survival (PFS). Secondary clinical outcomes refer to other measurable clinical indicators, including disease control rate (DCR) and objective response rate (ORR). PRO was derived directly from patient reports on their health-related quality of life (HRQOL). In this study, three secondary indicators (clinical efficacy, quality of life, and guideline recommendation) were selected, and three tertiary indexes (OS, PFS, and ORR) were selected. The clinical efficacy of six ALK-TKIs in the first-line treatment of ALK-positive advanced NSCLC patients was compared and analyzed using a meta-analysis and systematic review. Clinical randomized controlled trials were included in the meta-analysis, excluding studies with incomplete data and one-arm studies. The study population was ALK-positive patients with advanced NSCLC. The databases searched included PubMed, Web of Science, and the ClinicalTrial website. The retrieval period was from the establishment of the databases to June 30, 2022. Finally, 10 studies (15-24) were included, with a total of 2,715 patients.

The Cochrane risk bias assessment tool was used to evaluate the quality of 10 studies included in the safety and effectiveness studies.

Economy evaluation

Economic evaluation refers to the identification, measurement, comparison, and analysis of the cost, benefit, effect, and utility of different drug treatment regimens using basic health economics or pharmacoeconomics methods.

The clinical input-output ratio of drugs was evaluated comprehensively, and the economics of the clinical use of drugs was measured (14). It is recommended that cost-utility analysis (CUA) and cost-benefit analysis (CBA) be given priority. In this study, two secondary indicators of CUA and HTA recommendations were selected, and a systematic literature review was conducted.

Suitability assessment

Drug suitability refers to the precise application of a drug to the target population in an appropriate way under the guidance of an appropriate prescription (14). Since the course of antitumor treatment is generally long, drug suitability plays a vital role in improving patients' long-term medication compliance. In this study, four secondary indicators, including physician recommendation, patient compliance, medical insurance directory, and indications were selected. We used expert interviews and access to the website of regulatory authorities to obtain the data. The CUA of the six ALK-TKIs were compared and analyzed using a systematic literature review to evaluate their economic benefits. The literature review included economic researches but excluded studies that lacked relevant data. The search databases included PubMed and Web of Science.

Accessibility evaluation

Accessibility assessment is a comprehensive and scientific assessment of drug supply capacity and patient burden using pharmacoeconomics and pharmacoepidemiology. Availability and affordability are recommended to evaluate the clinical accessibility of antitumor drugs (14). Availability refers to the potential opportunities for tumor patients to obtain targeted drugs, the types and quantities of marketed drugs, and the equipping capacity of medical institutions/drug retailers, etc. Affordability refers to the affordability of treatment costs for urban and rural patients' families. In this study, three secondary indicators (price, availability, and affordability) and three tertiary indexes (market share, urban affordability, and rural affordability) were selected using the data retrieval method on the official website.

Innovation evaluation

The innovative evaluation of antitumor drugs is a professional, multi-tiered, multi-perspective gathering and analysis of information. Based on domestic and foreign literature and the actual situation in China, the guide recommends evaluation from three dimensions: clinical innovation, service innovation, and industrial

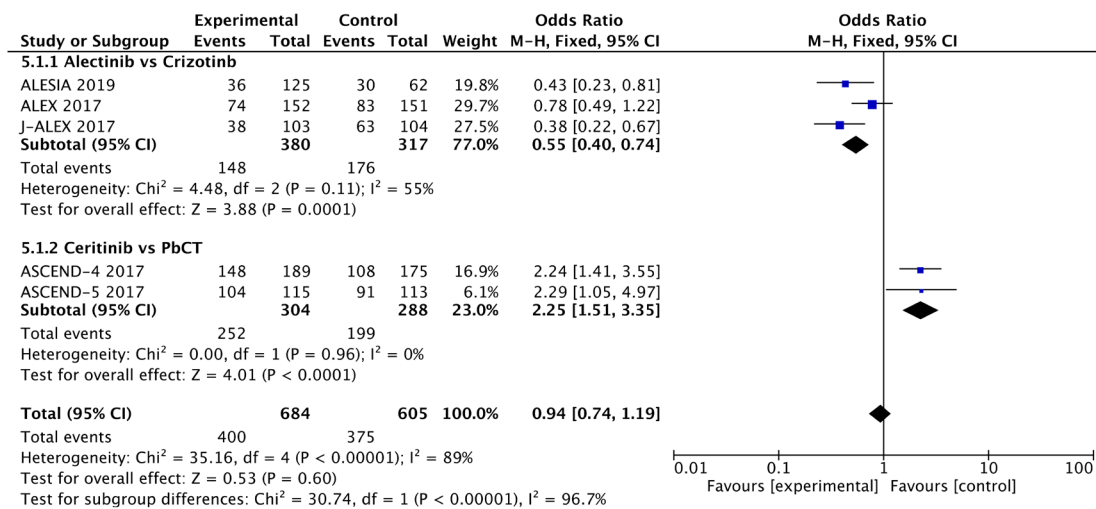


Figure 1 Forest map of direct comparison of the incidence of \geq grade 3 AEs in different first-line drugs for ALK-positive advanced NSCLC. AEs, adverse events; ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer.

innovation (14). Clinical innovation evaluates the degree to which antitumor drugs meet patients' drug needs. Service innovation assesses the impact of drug use on health service systems. Industrial innovation assesses the production capacity of innovation and research and development. In this study, four secondary indicators, including drug action mechanism, urgent clinical need, patent value, and technology localization, were selected, and a systematic literature review was used.

Statistical analysis

Meta-analysis and systematic review were conducted. Indicators of relative risk ratio (RR), hazard ratio (HR) and 95% confidence interval (CI) were used.

Results

Evidence from the comprehensive clinical evaluation of ALK-TKI drugs in all dimensions

Safety

Meta-analysis showed that the incidence of \geq grade 3 AEs was lower in alectinib than in crizotinib (OR =0.55, 95% CI: 0.40–0.74) (15–17), whereas the incidence of \geq grade 3 AEs with ceritinib was higher than in Platinum-based chemotherapy regimens (OR =2.25, 95% CI: 1.51–3.35, $P < 0.05$, Figure 1) (19,20). In addition to meta-analysis, clinical trials of brigatinib, ensartinib, lorlatinib, and crizotinib were

reviewed. Grade 3 and above AEs were higher in brigatinib (78% vs. 64%), ensartinib (50.4% vs. 42.4%), and lorlatinib (72% vs. 56%) than in crizotinib (21–23).

Regarding the monitoring reports from drug regulatory authorities, the United Kingdom and Japan suggested that crizotinib had safety risks of heart failure, and Europe suggested that crizotinib had safety risks of visual impairment in children.

Effectiveness

The results of the meta-analysis found that in terms of OS, alectinib was associated with a lower risk of death than crizotinib (HR 0.64, 95% CI: 0.44–0.92, $P < 0.05$) (15–17). Crizotinib (HR 0.80, 95% CI: 0.61–1.05) (18,24) and ceritinib (HR 0.85, 95% CI: 0.64–1.11) (19,20) showed no significant difference in the risk of death compared with Platinum-based chemotherapy ($P > 0.05$). In terms of PFS, alectinib was better than crizotinib (HR 0.40, 95% CI: 0.32–0.49) (15–17), and both crizotinib (HR 0.43, 95% CI: 0.35–0.53) (18,24) and ceritinib (HR 0.52, 95% CI: 0.43–0.64) (19,20) had longer PFS than Platinum-based chemotherapy regimens ($P < 0.05$, respectively, Figure 2A,2B). In addition to the meta-analysis, a review of clinical trials (21–23) found that the PFS of brigatinib (30.8 months), ensartinib (25.8 months), and lorlatinib (PFS not reached) was significantly better than crizotinib (less than 13 months) ($P < 0.05$, respectively). The OS was still changing at the data cutoff, but there was no statistical difference in OS between brigatinib and crizotinib,

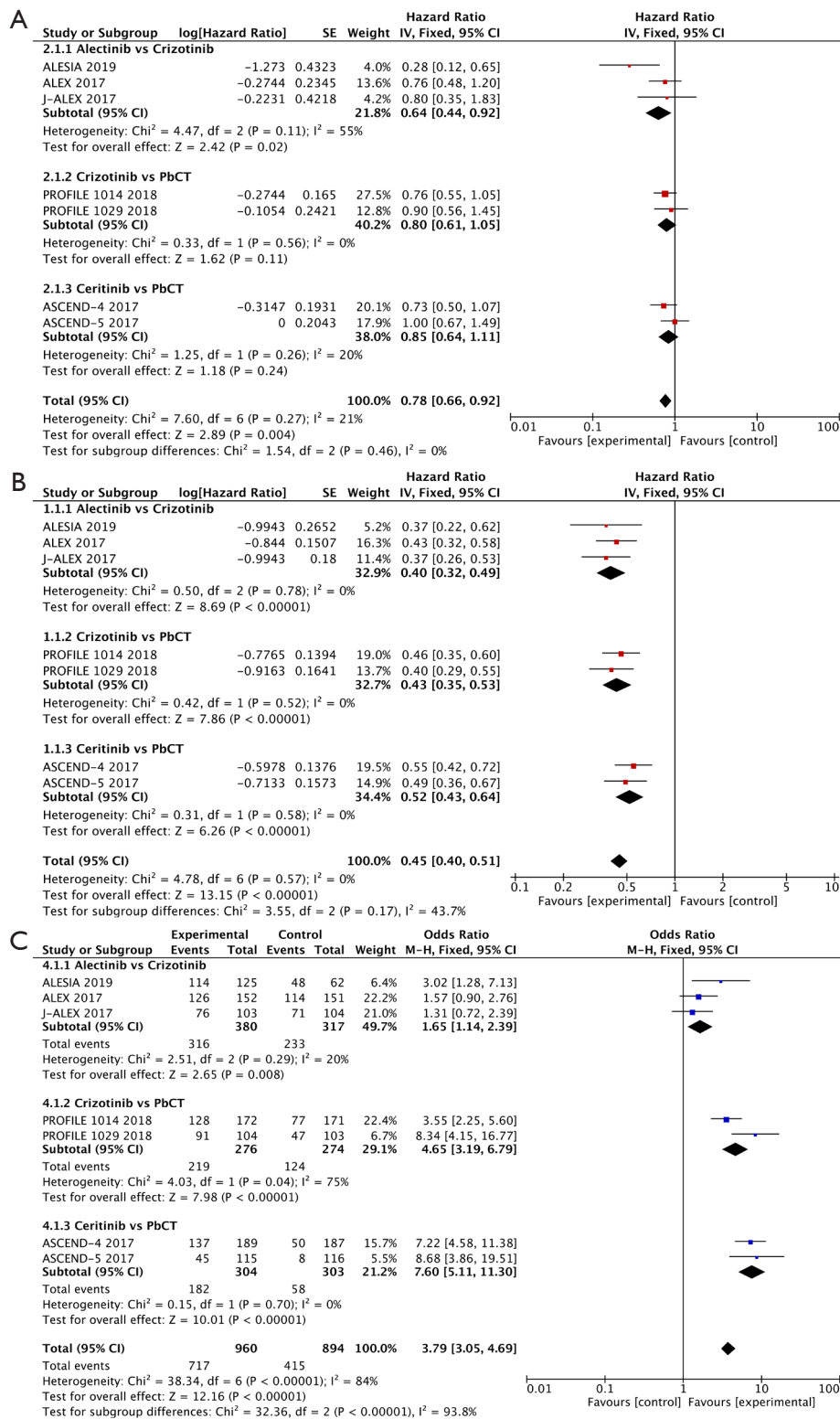


Figure 2 Forest map of direct comparisons between different first-line drugs for ALK-positive advanced NSCLC. (A) OS; (B) PFS; (C) ORR. ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; ORR, objective response rate.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
ALESIA 2019	+	+	+	+	+	+	+
ALEX 2017	+	+	+	+	+	+	+
ALTA-1L 2021	+	?	+	+	+	+	+
ASCEND-4 2017	+	+	+	+	+	+	+
ASCEND-5 2017	+	+	+	+	+	+	+
CROWN 2020	+	+	+	+	+	+	+
EXALT3 2021	+	+	+	+	+	+	+
J-ALEX 2017	+	+	+	+	+	+	+
PROFILE 1014 2018	+	?	+	+	+	+	+
PROFILE 1029 2018	+	?	?	+	+	+	+

Figure 3 Cochrane risk of bias instrument assessment. Green: low risk; red: high risk; yellow: unclear risk.

ensartinib and crizotinib, lorlatinib and crizotinib, respectively ($P>0.05$).

In terms of ORR, alectinib was superior to crizotinib (OR =1.65, 95% CI: 1.14–2.39) (15–17), and both crizotinib (OR =4.65, 95% CI: 3.19–6.79) (18,19) and ceritinib (OR =7.60, 95% CI: 5.11–11.30) were superior to Platinum-based chemotherapy ($P<0.05$, respectively, *Figure 2C*). In addition to the meta-analysis, our review of clinical trials (22,23) found no significant difference in ORR between ensartinib and crizotinib ($P>0.05$), while the ORR of lorlatinib was significantly better than that of crizotinib (76% vs. 58%, $P<0.05$).

The Cochrane risk bias assessment results showed that most of the included studies had a low risk of bias, and the literature quality was good (*Figure 3*).

For quality of life, we used a literature review to

summarize and analyze the effects of six first-line ALK-TKI drugs on quality of life in patients with ALK-positive advanced NSCLC. The retrieval databases were PubMed and Web of Science, and studies related to crizotinib, brigatinib, ceritinib, alectinib, and lorlatinib were retrieved (19,25–28). The results showed that lorlatinib significantly improved patients' quality of life compared with crizotinib ($P<0.05$) (19). Compared with crizotinib and chemotherapy, brigatinib significantly improved patients' quality of life ($P<0.05$, respectively) (25,26). Crizotinib and ceritinib improved patients' quality of life better than chemotherapy ($P<0.05$, respectively) (10,27). There was no significant difference between alectinib and crizotinib in improving life quality ($P>0.05$) (28).

Regarding guideline recommendations, we retrieved the authoritative NSCLC treatment guidelines issued by authoritative institutions and industrial associations in China, the United States, Europe, and other countries (9,11,29–32). The NCCN Guidelines for Non-Small Cell Lung Cancer (2022 v3) recommend brigatinib, alectinib, and lorlatinib as first-line treatments for ALK-positive advanced NSCLC (9). The American Society of Clinical Oncology (ASCO) Dynamic Guidelines 2021 recommend alectinib and brigatinib for patients with ALK rearrangement, PS 0–2, and previously untreated NSCLC (29). The European Society of Oncology (ESMO) Guidelines (in 2020) recommend crizotinib for first-line drug treatment of ALK-positive advanced NSCLC. Alectinib and brigatinib are recommended as class IA for patients with central nervous system metastasis (30). The Chinese Society of Clinical Oncology (CSCO) Guidelines for the Diagnosis and Treatment of Non-small Cell Lung Cancer (in 2022) recommend alectinib (priority recommendation), crizotinib, and ceritinib for first-line treatment of stage IV ALK-fused NSCLC. Brigatinib and lorlatinib are recommended for third-line treatment (11). The Chinese guidelines for the diagnosis and treatment of anaplastic lymphoma kinase positive and ROS1 positive non-small cell lung cancer (in 2018) recommend crizotinib as the first-line drug for patients newly diagnosed with ALK-positive advanced NSCLC (Class I recommendation) (3). The Guidelines for the Clinical Diagnosis and Treatment of Lung Cancer of the Chinese Medical Association Oncology Society (in 2021) recommend crizotinib, alectinib, and ceritinib as first-line treatments for ALK-rearranged NSCLC (31). The Chinese Guidelines for the Treatment of Brain Metastases in Lung Cancer (in 2021) recommend second-generation ALK-TKIs to treat ALK-rearranged advanced NSCLC with brain metastases (32).

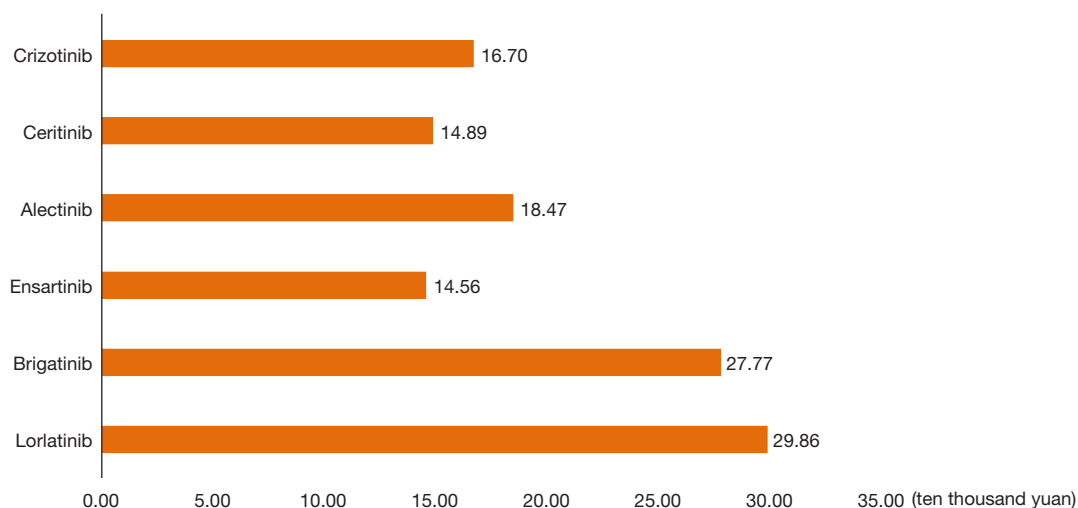


Figure 4 Annual cost of NSCLC treatment with crizotinib, ceritinib, alectinib, ensartinib, brigatinib, and lorlatinib (ten thousand Yuan). NSCLC, non-small cell lung cancer.

Economical efficiency

The results showed that for first-line drug treatment of ALK-positive advanced NSCLC patients, second-generation ALK-TKIs (ceritinib, alectinib, and ensartinib) have a cost-utility advantage over first-generation crizotinib (33-35). Among second-generation ALK-TKI drugs, the cost-utility value of ceritinib was superior to that of alectinib (35). Compared with crizotinib, the current price of lorlatinib in China is not economical (36). Regarding HTA recommendations, the National Institute for Health and Clinical Excellence (NICE) recommended brigatinib, alectinib, ceritinib, crizotinib, and Platinum-containing two-drug chemotherapy as first-line drug treatments for ALK-positive advanced NSCLC (37). Based on relevant clinical studies and guidelines, Canada's Drug and Health Technology Agency (CADTH) recommended alectinib and ceritinib as first-line drugs for treating ALK-positive advanced NSCLC due to better cost-effectiveness than crizotinib (38).

Suitability

In terms of physician recommendations and patient compliance, data were collected through interviews with five clinical experts from Shanghai Municipality, Jiangsu, Anhui, Sichuan, and Zhejiang provinces. The interview results showed that physicians highly recommended alectinib, and they reported high levels of patient compliance with this drug. Regarding the medical insurance list and indications, crizotinib, ceritinib, alectinib, and ensartinib are all on the

current Medicare list. All six indications for ALK-TKIs covered locally advanced or metastatic NSCLC.

Accessibility

In terms of price, crizotinib, ceritinib, and alectinib have all been approved for first-line treatment of ALK-positive advanced NSCLC and entered the national medical insurance directory, and their prices are much lower than international prices. Ensartinib was approved for second-line treatment of ALK-positive advanced NSCLC in the medical insurance directory. Brigatinib and lorlatinib are not currently covered by the medical insurance directory and are relatively expensive. In terms of affordability, the annual cost of the six ALK-TKIs for advanced ALK-positive NSCLC is shown in *Figure 4* (it was assumed that ensartinib 100 mg and 25 mg were used together, and brigatinib was administered at a 90 mg dose for the first 7 days and 180 mg dose after 7 days).

In terms of affordability for urban and rural residents, after being reimbursed by insurance, the annual cost of crizotinib, ceritinib, and alectinib in the treatment of ALK-positive advanced NSCLC was 50,100, 44,700 and 55,400 yuan, respectively. The proportion of the six ALK-TKIs in the per capita disposable income of urban and rural residents in 2021 is shown in *Figure 5*.

Innovation

In this study, the six ALK-TKIs evaluated are small molecule targeted drugs. Compared with chemotherapy,

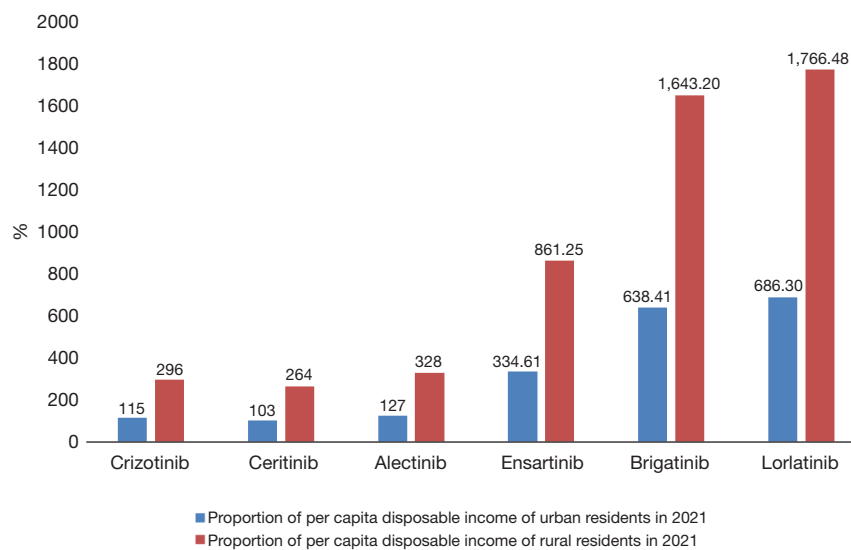


Figure 5 The annual treatment costs of crizotinib, ceritinib, alectinib, ensartinib, brigatinib, and lorlatinib accounting for the per capita disposable income of urban and rural residents in 2021.

they can significantly improve treatment outcomes in ALK-positive advanced NSCLC patients. Crizotinib, the first generation of ALK-TKIs, significantly improves patients' quality of life compared with standard chemotherapy, but with the extension of medication time, drug resistance and disease progression will inevitably occur (39). Compared with crizotinib, the second- and third-generation ALK-TKIs demonstrate stronger inhibitory capacity, better blood-brain barrier permeability, and more innovative drug mechanisms of action. In terms of clinical urgency, the data on clinical use and demand were collected by expert interviews (refer to method: "Suitability"). The results of the clinical expert interviews showed that ALK-TKIs are urgently required for tumor prevention and treatment, and the degree of urgent clinical need was high. Regarding patent value and technology localization, none of the six drugs have reached the patent expiry date, and the patent value is high. Among them, ensartinib is China's first highly selective and efficient ALK-TKI with fully independent intellectual property rights. Among ALK-targeted drugs, there are still four new domestic drugs in phase III clinical trials (CT-707, TQ-B3139, XZP-3621, and SAF-189). It is vitally important to promote the localization of technology.

Discussion

Policies have been issued successively in China to guide and

standardize the technical work and comprehensive clinical evaluation related to antitumor drugs for the prevention and control of major national diseases (13,14). As antitumor drugs, it is vitally important to comprehensively evaluate the clinical value of ALK-TKIs, which have high clinical demand and good targeted therapeutic effects in treating ALK-positive advanced NSCLC. Previous studies have mainly considered the clinical value of ALK-TKIs based on one or two dimensions, such as safety, efficacy (40), or economy (33,34). In addition, the study subjects included patients treated with ALK-TKIs in both first-line and later treatments. This study focused on patients receiving first-line treatment for ALK-positive advanced NSCLC and included patients in the Asian population. This study covered not only the safety, efficacy, and economics but also the suitability, accessibility, and innovation. Therefore, this study started from national policy and clinical practice needs and investigated the clinical value of six ALK-TKIs. We aimed to provide a reference for a rational use of antitumor drugs and medical insurance admission decision-making in hospitals.

Owing to the possibility of experiencing adverse reactions, patients are more likely to adjust, skip or discontinue medication after antitumor treatment. Ensuring the safety of medication is the premise of long-term treatment. Safety evaluation results showed that the incidence of \geq grade 3 AEs was lower in alectinib than in crizotinib, and the incidence of \geq grade 3 AEs in both crizotinib and ceritinib was higher than in Platinum-based

chemotherapy, and the incidence of \geq grade 3 AEs with brigatinib, ensartinib, and lorlatinib was higher than in crizotinib. The second and third-generation ALK-TKIs showed better safety than the first generation ALK-TKIs. A meta-analysis also showed that alectinib and brigatinib had less discontinuation due to adverse reactions than ceritinib and crizotinib, and lorlatinib had the lowest discontinuation rate (40). The common adverse reactions to ALK-TKIs include gastrointestinal adverse reactions and hepatotoxicity (10,15,17-19,21-23). However, some ALK-TKIs may cause specific adverse reactions. For example, the related AEs of crizotinib include visual impairment, prolonged QT interval, and neutropenia. In addition, crizotinib also has a high incidence of gastrointestinal events (diarrhea, etc.), and elevated aminotransferase. These AEs limit its application to some extent. Besides, ceritinib related AEs include gastrointestinal side effects, hyperglycemia, elevated amylase, and lipase. Alectinib related AEs include elevated blood creatine phosphokinase, photosensitive dermatitis, and elevated total bilirubin. Ensartinib associated AEs include rash and elevated serum creatinine. Lorlatinib related AEs of hyperlipidemia and central nervous system function related toxicity. Brigatinib associated AEs include hypertension and elevated blood creatine phosphokinase. Specific adverse reactions of different ALK-TKIs may limit their application in some populations. It is necessary to conduct further studies on the safety of different ALK-TKIs since the proportion of patients who decreased their dose or stopped medication due to adverse reactions was not explained in the relevant studies.

Effectiveness evaluation showed that compared with first-generation ALK-TKIs, second- and third-generation ALK-TKIs significantly prolonged PFS. PFS, ORR, and OS were significantly better with alectinib than with crizotinib. The central nervous system permeability and inhibition ability of second- and third-generation ALK-TKIs are better, and thus the curative effect is better. A review of literature related with quality-of-life of ALK-TKIs found that brigatinib and lorlatinib significantly improved quality of life in comparison to crizotinib and chemotherapy. Patients often face a burden of symptoms and side effects during antitumor therapy, which greatly reduces their quality of life and affects their treatment compliance. Therefore, adverse reaction management is essential in improving medication compliance and optimizing HRQOL (41). It is necessary to conduct whole-process management of patients on the occurrence of adverse reactions and their quality of life. With changes to the function of pharmacists,

pharmacists can play a positive role in the medication process. In addition, as far as the guidelines for ALK-TKI usage are concerned, alectinib (9,29,11,31,32) and crizotinib (3,11,30,31) have been recommended as first-line treatments by more clinical guidelines.

Generally, antitumor drugs are expensive, especially small-molecule targeted drugs and monoclonal antibodies, and are a major component of patient treatment costs. Reasonable price has a significant influence on whether patients will choose such drugs for treatment. For the economic evaluation, ceritinib, alectinib, and ensartinib have been recommended by more economic evaluation studies. At present, crizotinib, ceritinib, and alectinib have all been approved as first-line treatments of ALK-positive advanced NSCLC (11) and have been entered into the national medical insurance directory. Their cost is far lower than the international price, and their accessibility and affordability are good, which will largely affect the choice of medication for patients. Crizotinib, ceritinib, and alectinib, when used as first-line treatments for ALK-positive advanced NSCLC, accounted for a much lower proportion of the income of urban and rural residents in 2021 than ensartinib, brigatinib, and lorlatinib. This further reduced the economic burden on patients. The indication for ensartinib to enter the national medical insurance is already second-line treatment, but it is not economical for its first-line treatment. Although the clinical efficacy of brigatinib and lorlatinib is significantly better than crizotinib, their short time on the market and lack of inclusion in the national insurance directory mean their economic efficiency and accessibility are poor. Based on the current prices of brigatinib and lorlatinib in our country, they are not economical (in dollar terms, annual cost of NSCLC treatment with crizotinib, ceritinib, alectinib, ensartinib, brigatinib, and lorlatinib are \$24,829, \$22,138, \$27,460, \$21,647, \$41,287, \$44,394 respectively). A reasonable reduction in drug prices in the future will improve their economic viability. In terms of innovation, all six drugs are ALK-targeted therapeutic drugs and demonstrate better mechanistic innovation than chemotherapy drugs. Studies (10,31,32) have shown that the median PFS of the patients treated with crizotinib is less than 1 year, and more than 40% of patients are prone to brain metastasis. The control and prevention of brain metastasis are insufficient, resulting in worse prognosis. It is one of the most common reasons for treatment failure. The mechanism action of second- and third-generation ALK-TKIs are significantly more innovative. According to the six evaluation dimensions,

alectinib performed better in the first-line treatment of ALK-positive advanced NSCLC.

Comprehensive clinical evaluations of drugs have been increasingly applied in rational drug use in clinic and for improving essential drug list systems and other research fields. This study followed the standard procedures and evaluation methods of the clinical evaluation guidelines (13,14) and combined with various disciplinary tools, such as HTA, to comprehensively evaluate the clinical value of six ALK-TKIs, and the results were reliable with a high level of evidence. This study also had some limitations: it mainly integrated and analyzed literature data from published clinical trials. Real-world studies of ALK-TKIs have been conducted in Caucasians (42). There may be some differences in the application practices of ALK-TKIs in different countries. Besides, the marketing time of ALK-TKIs in domestic and foreign countries is different, and the use of ALK-TKIs in various countries is also different. For example, brigatinib was launched abroad in 2017, and lorlatinib was launched abroad in 2018. However, they were not launched in China until 2022. Therefore, the actual application of these drugs in the real world in China is worth exploring. Besides, whether the comprehensive clinical evaluation index system established in this study truly reflects clinical practice usage remains to be further verified.

Conclusions

In conclusion, this study initially explored the clinical value of ALK-TKIs, and alectinib proved to have higher comprehensive clinical value. The results provide better drug choice for patients with ALK-positive advanced NSCLC. Besides, the results provide evaluation procedures and methods for the comprehensive evaluation of other types of antitumor drugs (cytotoxic drugs, novel antitumor drugs, etc.) in the future, and ensure rational drug use in clinic and offer a basis for decision-making and improvement of the national antitumor drug supply security system and relevant policy formulation.

Acknowledgments

Funding: The study was supported by Suzhou science and technology development plan (Medical and health science and technology innovation - Applied Basic Research) project (SKJYD2021160) and Hospital Pharmaceutical Research Fund of Chia Tai Tianqing, Jiangsu Pharmaceutical Association in 2022 (Q202230).

Footnote

Peer Review File: Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-380/prf>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-380/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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(English Language Editor: D. Fitzgerald)

Cite this article as: Wang WQ, Xu T, Zhang JJ, Wang Y, Wang Y, Zhang W, Zhu JG. A comprehensive clinical evaluation of first-line drugs for ALK-positive advanced non-small cell lung cancer. *J Thorac Dis* 2023;15(4):1935-1947. doi: 10.21037/jtd-23-380