

ORIGINAL ARTICLE

Efficacy and safety of ceritinib in anaplastic lymphoma kinase-rearranged non-small cell lung cancer: A systematic review and meta-analysis

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Abstract

What is known and objective: Ceritinib is a new, oral, potent and selective second-generation anaplastic lymphoma kinase (ALK) inhibitor approved by the Food and Drug Administration of the United States in April 2014. It is active in crizotinib-resistant patients, especially in patients with non-small cell lung cancer (NSCLC) and brain metastasis. The aim of this study was to analyse the effects and side effects of ceritinib in ALK-rearranged NSCLC.

Methods: We searched articles published from January 1980 to March 2019 in PubMed, EMBASE, Cochrane Library and Web of Science. The pooled estimate and 95% CI were calculated with DerSimonian-Laird method and the random effect model.

Results and discussion: From 15 articles, 2,598 patients were included in the meta-analysis. Eleven studies reported the ORR, and the DCR was presented in 10 studies. The ORR and DCR of ceritinib were 0.48 (95% CI, 0.39-0.57) and 0.76 (95% CI, 0.69-0.82), respectively. The PFS and OS were presented in nine and three eligible studies, respectively. The PFS and OS of ceritinib were 7.26 months (95% CI, 5.10-9.43) and 18.73 months (95% CI; 14.59-22.87). These results suggested that ceritinib can effectively treat patients with ALK-rearranged NSCLC. Diarrhoea, nausea and vomiting were the three most common AEs and occurred in 69% (95% CI 51.7-87.1%), 66% (95% CI 47.0-85.8%) and 51% (95% CI 35.9-66.8%) of patients, respectively. Considering serious gastrointestinal AEs, antiemetic and antidiarrhoeal drugs should be considered to improve a patient's tolerance to ceritinib.

What is new and conclusion: Ceritinib is effective in the treatment of patients with ALK-rearranged NSCLC with crizotinib resistance. The DCR was up to 76%, and PFS was extended to 7.6 months. The AEs were acceptable.

KEYWORDS

adverse events, anaplastic lymphoma kinase, ceritinib, non-small cell lung cancer

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1 | WHAT IS KNOWN AND OBJECTIVE

Lung cancer is the leading cause of cancer-related mortality worldwide.¹ Approximately 80-85% of lung cancer cases are diagnosed as non-small cell lung cancer (NSCLC).² Unfortunately, the prognosis of NSCLC is poor. The 5-year survival rate is 16%, and more than 50% of patients present with advanced disease. For patients with advanced NSCLC, platinum-based chemotherapy is the standard treatment, with an objective response rate of approximately 30%; however, this generally lasts only 4-5 months.³⁻⁵ Fortunately, with the increasing understanding of the pathogenesis of NSCLC in the last 10 years, the development of targeted drugs has improved the prognosis of patients.⁶⁻⁹ NSCLC with anaplastic lymphoma kinase (ALK) rearrangement accounts for approximately 5% of advanced adenocarcinomas.^{10,11} Most patients with NSCLC with ALK-rearrangement are younger, have never smoked or have a history of mild smoking, and have histological characteristics of adenocarcinoma.^{12,13} ALK fusion proteins promote the growth and survival of cancer cells by abnormally activating intracellular signals. Clinical studies have shown that the use of ALK inhibitors for the treatment of patients with ALK-rearranged NSCLC is better than that of chemotherapy drugs.

Crizotinib (LDK378; Novartis) was the first drug approved by the Food and Drug Administration of the United States (FDA) as a targeted therapeutic drug for patients with ALK-rearranged NSCLC.¹⁴ It has become a standard treatment in many countries. The use of ALK inhibitors in advanced patients significantly improves progression-free survival (PFS) and prolongs the lifespan of patients with late-stage ALK-rearranged NSCLC compared with that of chemotherapy. Crizotinib is a first-generation oral ALK inhibitor and a standard drug for ALK-rearranged NSCLC treatment.¹⁵ However, many patients treated with crizotinib experience disease progression within 12 months of treatment, the most common being brain metastasis.¹⁶⁻¹⁸ Ceritinib (LDK378, Novartis) is a new, oral, potent and selective second-generation ALK inhibitor approved by the FDA in April 2014. It has a stronger preclinical antitumour effect than crizotinib. Its efficacy is 20 times greater than that of crizotinib.¹⁹ In addition, ceritinib is active in crizotinib-resistant patients, especially in patients with brain metastases and NSCLC.^{20,21}

Despite the relevant studies on the efficacy of ceritinib in the treatment of ALK-rearranged NSCLC, the efficacy of ceritinib is still unknown. Therefore, we conducted a systematic review and meta-analysis of the efficacy and adverse events (AEs) of ceritinib on ALK-rearranged NSCLC to provide information for further scientific research and clinical applications.

2 | METHODS

2.1 | Search strategy

We searched articles published from January 1980 to March 2019 in PubMed (Medline), EMBASE (Excerpta Medica Database), Cochrane Library and Web of Science. We used keyword search terms

(‘ceritinib’) and (‘non-small cell lung cancer’ or ‘NSCLC’) in PubMed, Cochrane Library and Web of Science. In EMBASE, for the population, we used the keyword (‘non-small cell lung cancer’ or ‘NSCLC’); for the intervention, we used the keyword ‘ceritinib’; and for the study design, we used the keyword ‘clinical study’. In the search process, we not only used MeSH keywords to search but also a broader search term to collect all articles published that were relevant to this topic. We searched not only the original published articles but also the references cited in related review articles. In addition, we retrieved references from the search results.

2.2 | Selection criteria

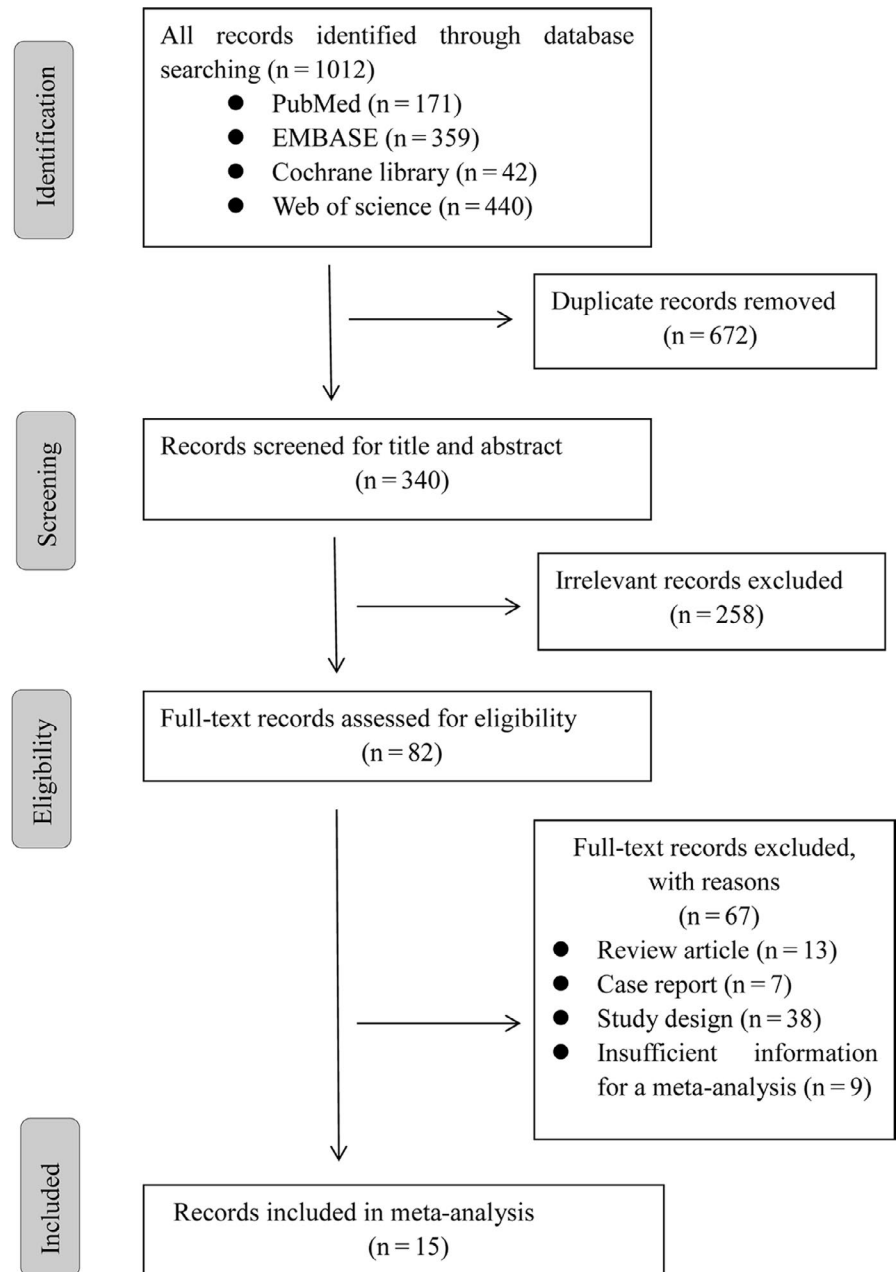
Eligible trials had to satisfy the following prespecified PICOS criteria. P (participants): ALK-rearranged NSCLC; I (intervention): oral ceritinib therapy treated; C (control): none; O (outcomes): objective response rate (ORR), disease control rate (DCR), overall survival (OS) and progression-free survival (PFS); S (study designs): phase I, II or III study prospective cohort study, or retrospective cohort study. Articles dealing with animal research or those not in English were excluded. We did not exclude studies involving patients pretreated with prior ALK inhibitors, nor did we exclude previous studies involving patients receiving chemotherapy. Where there were duplicate studies, articles published earlier or those that provided more detailed information were selected (Figure 1). Two researchers independently evaluated the literature according to the criteria to determine eligibility, and a third researcher was involved in resolving the differences between the two.

2.3 | Data extraction and analysis

This study conducted data analysis based on the PRISMA Statement.²² The following information was recorded in a pre-designed form: first authors, publication year, study design, population, age, male percentage, sample size, grouping and number of people in the group, data including counts and effect estimates, country, follow-up years, title, conclusion, PFS, OS, DCR, ORR and AEs. Most studies were single-arm studies, and a minority of studies included a chemotherapy control group. However, we only extracted data from the ceritinib-treated group. One researcher extracted the data independently, whereas another reviewed the data to ensure accuracy.

2.4 | Statistical methods

To evaluate the therapeutic effect of ceritinib in patients with ALK-rearranged NSCLC, we analysed the best responses. We extracted the ORR, DCR, PFS and OS from each ceritinib single-arm treatment group in each study. If, according to the ceritinib injection dosage/day, multiple sets of data were provided in a study, we extracted only the best response data from the 750 mg/d injection dosage.

FIGURE 1 Flow chart of study selection

The toxicities and AEs reported in each study were classified and merged, and the incidence of 11 common AEs was analysed.

We used Stata 14 for data merger analysis and heterogeneity tests between studies. The heterogeneity test between studies was evaluated by I^2 statistics and the Q test. At $P < .01$, heterogeneity was considered significant. A value of I^2 of 0% to 25% represented insignificant heterogeneity, more than 25% but less than or equal to 50% represented low heterogeneity, more than 50% but less than or equal to 75% represented moderate heterogeneity, and more than 75% represented high heterogeneity. We used the DerSimonian-Laird method and the random effect model to pool the effect size and draw forest plots. P values for all comparisons were two-tailed, and statistical significance was defined as $P < .05$ for all tests, except those for heterogeneity.

2.5 | Quality assessment

As most studies included were single-arm cohort studies, we used the CASP-Cohort-Study-Checklist to evaluate the quality of the studies. The CASP-Cohort List, a quality assessment tool, was proposed by the Oxford Evidence-based Medical Center in 2004 for cohort studies. It contains 12 questions and 3 sections to evaluate each study.

2.6 | Assessment of risk of bias

We used Stata 14 with meta-regression to analyse the sources of heterogeneity in the studies.

TABLE 1 Characteristics of included studies

Study	Study design	Population	Age	Male%	Sample size	Country	Follow-up (month)
Gainor et al (2015) ²¹	Retrospective analysis	ALK-positive patients (n = 73) were identified at four institutions: Massachusetts General Hospital (MGH; n = 40), National Cancer Center Singapore (n = 14), Istituto Europeo di Oncologia (n = 12), and Peter MacCallum Cancer Center (n = 7). Patients received crizotinib either as part of a clinical trial (N = 71; NCT01283516) or on a compassionate use basis (N = 2).	50 (22-72)	52.1%	73	Singapore	53.2
Nishio et al (2015) ²³	Phase I, multicentre, open-label study	Adult patients (18 yr) with locally advanced or metastatic malignancy harbouring genetic alterations in ALK, which had progressed despite standard therapy or for which no effective standard therapy exists, were included in this study.	44 (29-68)	45.0%	20	Japan	—
Crinò et al (2016) ²⁴	Single-arm, open-label, multicentre, phase II study	Patients Eligible patients had locally advanced/metastatic ALK-rearranged NSCLC. All patients must have received prior treatment with at least one platinum-based chemotherapy regimen and crizotinib. Prior treatment with any ALK inhibitor other than crizotinib was not permitted, and crizotinib must have been the last systemic antineoplastic therapy prior to crizotinib initiation.	51 (29-80)	50.0%	140	Italy	11.3
Kim et al (2016) ²⁵	Phase I, open-label	Briefly, eligible patients had ALK-rearranged NSCLC, were ≥ 18 years old, had locally advanced or metastatic NSCLC that had progressed despite standard therapy (including chemotherapy or ALK) or for which no effective standard therapy existed. Patients with untreated or locally treated asymptomatic and stable (>4 weeks) central nervous system (CNS) disease were eligible.	52 (24-80)	46.0%	246	USA	11.1
Tan et al (2016) ²⁶	Retrospective cohort	Individual patient data for crizotinib-treated patients were drawn from two single-arm trials (ASCEND-1, ASCEND-3); published summary data for crizotinib-treated patients were extracted from three trials (PROFILE 1001, PROFILE 1005, and PROFILE 1007)	52	46.0%	746	Singapore	11.1
Bendaly et al (2017) ²⁷	Chart Review Study	Each participating oncologist was invited to extract information from the medical records of the selected patients. This study did not collect any patient-identifying information and was exempted from review by the Western Institutional Review Board.	63.2 (55.3-69.2)	41.4%	58	USA	3.8
Cho et al (2017) ²⁸	Multicentre, randomized, open-label, phase 1 study.	Adult patients (aged 18 years) were eligible if they had histologically or cytologically confirmed diagnosis of stage IIIB or IV ALK + NSCLC	56.0 (25.0-86.0)	45.3%	137	Korea	4.1

(Continues)

TABLE 1 (Continued)

Study	Study design	Population	Age	Male%	Sample size	Country	Follow-up (month)
Oya et al (2017) ²⁹	Retrospective cohort	Between January 2007 and October 2016, four patients with advanced ALK-rearrangement-positive NSCLC were treated with crizotinib as the first ALK inhibitor, and eight patients with it as second ALK inhibitor after crizotinib failure. Among these 12 patients, we retrospectively reviewed eight patients who were treated with alectinib after crizotinib failure.	53 (29-71)	75.0%	8	Japan	—
Shaw et al (2017) ³⁰	Randomized, controlled, open-label, phase 3 trial	In this randomized, controlled, open-label, phase 3 trial (ASCEND-5), we recruited patients from 99 centres across 20 countries. Eligible patients (aged 18 years) had locally advanced or metastatic non-small cell lung cancer with a confirmed ALK-rearrangement. All patients had to have received one or two previous chemotherapy regimens (including a platinum doublet) for advanced disease, received previous crizotinib therapy for a minimum of 21 days, and subsequently had documented disease progression before study enrolment.	54.0 (44.0-63.0)	40.9%	231	USA	18.0
Soria et al (2017) ³¹	(ASCEND-4): a randomized, open-label, phase 3 study	Adult patients (aged 18 years) were eligible if they had histologically or cytologically confirmed locally advanced or metastatic non-squamous ALK-rearranged NSCLC, untreated with any systemic anticancer therapy (except neoadjuvant or adjuvant systemic therapy [if relapse had occurred > 12 months from the end of therapy])	55.0 (22-81)	46.0%	376	France	12.0
Cadranel et al (2018) ³²	Prospective cohort	The TAU programme included patients with advanced ALK + NSCLC, ROS1 + NSCLC, or other ALK + tumours. All patients were pretreated with crizotinib.	58 (19-90)	48.1%	214	France	12.0
Davies et al (2018) ³³	Two single-arm Phase II	The alectinib treatment arm was derived by pooling data from patients enrolled in two Phase II studies (Global study NP28673 [NCT01801111]. To derive the crizotinib arm, IPD were extracted by applying inclusion and exclusion criteria from the NP28673 and NP28761 clinical trials to the electronic health record derived database (Flatiron Health)	54.5 (± 11.7)	46.0%	250	UK	12.0
Hida et al (2018) ³⁴	Prospective phase II study	Adult patients were eligible if they had histologically or cytologically confirmed stage IIIB or IV ALK-positive NSCLC. Patients could have asymptomatic untreated or treated brain metastases with no steroid therapy within 2 weeks before study enrolment. From August 2015 to March 2017, a total of 20 patients were enrolled.	51.0 (29-79)	40.0%	20	Japan	11.6

(Continues)

TABLE 1 (Continued)

Study	Study design	Population	Age	Male%	Sample size	Country	Follow-up (month)
Metro et al (2018) ³⁵	Prospective cohort	The Italian ceritinib CUP was made available by Novartis Pharmaceuticals on 9 April 2015, and was intended for patients who were ineligible to participate in any of the accruing ceritinib clinical trials. Eligible patients had ALK-positive advanced NSCLC which had relapsed after a prior ALK TKI. The Italian centres who had an activated ceritinib CUP were contacted in order to provide the clinical data of enrolled patients. Out of 46 institutions, 25 centres took part in the study, for a total of 70 eligible patients who were treated with ceritinib as compassionate use.	56 (22-86)	48.6%	70	Italy	7.4
Yoshida et al (2018) ³⁶	Retrospective cohort	Patients with ALK-positive NSCLC treated at the Kyoto University Hospital from January 2012 to March 2017 were reviewed. There were 35 patients with ALK-positive NSCLC, nine of whom received ceritinib after alectinib	-	-	9	Japan	-
Total 15 studies							2598

3 | RESULTS

3.1 | Eligible studies

In the initial search, we retrieved 1,012 articles from 4 databases. After reading the title and abstract, excluding duplicate and irrelevant articles, we selected 340 articles. After manual reading of the full text, 67 papers were excluded because they were a review article (n = 13), case report (n = 7), or study design (n = 38) or there was insufficient information for a meta-analysis (n = 9). Finally, 15 articles with 2,598 patients were included in this meta-analysis (Figure 1).

3.2 | Description of studies

The meta-analysis included 15 studies that consisted of a total sample size of 2598. The 15 studies were first published in 2015 and most recently in 2018. The sample size ranged from 8 to 746, covering Asia, Europe, the Americas, Australia and other regions. Detailed features of each study are shown in Table 1.

3.3 | Meta-synthesis of results

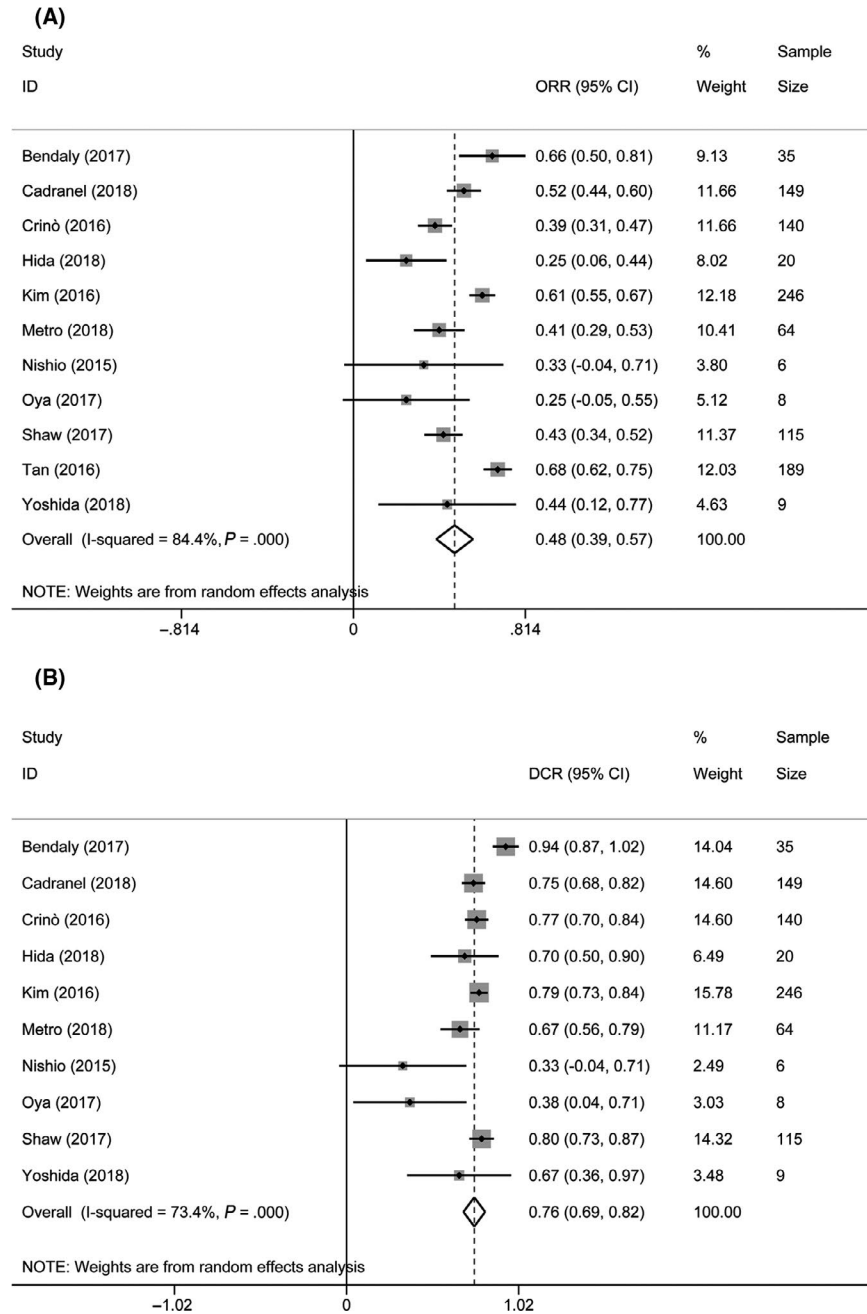
Eleven studies reported the ORR. The ORR in the combination group was 0.48 (95% CI, 0.39-0.57) but the heterogeneity of the overall ORR was significant ($I^2 = 92.6\%$) (Figure 2A).

The DCR was presented in 10 eligible studies. The number of studies included in the DCR merger was one less than that in the ORR merger, because Tan et al did not provide SD data. The pooled results suggested that ceritinib can effectively control ALK-rearranged NSCLC, with a statistically significant difference DCR = 0.76; (95% CI, 0.69-0.82; $P < .01$) (Figure 2B). In addition, we used the Chi-square test and I^2 statistic to verify the statistical heterogeneity ($I^2 = 73.4\%$), indicating moderate heterogeneity in the overall DCR. A random model was used according to a comprehensive analysis to examine the results.

Nine included studies reported the PFS. Nine studies did not overlap with the 11 studies included by the ORR. This is because some of the 15 studies we included provided both ORR and PFS, whereas others only provided the ORR or PFS. The pooled PFS was 7.26 months (95% CI, 5.10-9.43, $P < .01$) (Figure 3A). We selected Cochran's Q and I^2 statistics to verify the level of heterogeneity ($I^2 = 92.6\%$). A random effect model was adopted according to a comprehensive analysis to examine the results. These results suggested that the PFS has high heterogeneity.

The OS was presented in three eligible studies. The effects of ceritinib treatment on OS are shown in Figure 3B. The pooled OS was 18.73 months (95% CI: 14.59-22.87). Moreover, high heterogeneity was detected based on testing for included studies ($I^2 = 87.2\%$, $P < .01$) and a random effect model was selected to summarize effect size.

FIGURE 2 A, Forest plot of objective response rate (ORR). B, Forest plot of disease control rate (DCR)



3.4 | Assessment of AEs

We included all 10 studies that provided data on AEs, which mentioned 54 AEs. Because different studies may have different descriptions of the same AEs and the classification of AEs is different, we screened and reclassified 11 AEs, which were mentioned in at least five studies. The number of articles that mentioned each AE was not necessarily the same. We separated the incidence of the 11 AEs. After merging, we obtained 11 combined AEs (Table 2). The forest plot is shown in Figure 4. Diarrhoea, nausea and vomiting were the three most common AEs and occurred in 69% (95% CI 51.7-87.1%), 66% (95% CI 47.0-85.8%) and 51% (95% CI 35.9-66.8%) of patients, respectively.

3.5 | Assessment of publication bias

First, we performed a meta-regression analysis of the ORR group. Sample size was used as a covariate to perform single-factor meta-regression analysis ($P = .055$). It can be concluded that the sample size contributes to heterogeneity. Before meta-regression, $\tau^2 = 0.0153$ and $I^2 = 92.6\%$. After meta-regression, $\tau^2 = 0.01033$ and $I^2 = 75.31\%$. R^2 ($R^2 = 36.51\%$) showed that sample size could explain 36.51% of the heterogeneity (Figure 5). Subsequently, we used the baseline brain static percentage as a covariate to conduct univariate meta-regression analysis. Baseline brain metastatic percentage had no effect on heterogeneity (data not shown).

Meta-regression analysis was performed to identify the contributing factors of heterogeneity in the PFS group. We used sample size and baseline brain metastatic percentage as covariates to conduct univariate regression analysis, but these two covariates did not contribute to heterogeneity (data not shown). Because of incomplete data collection of other factors, it is difficult to identify the sources of heterogeneity.

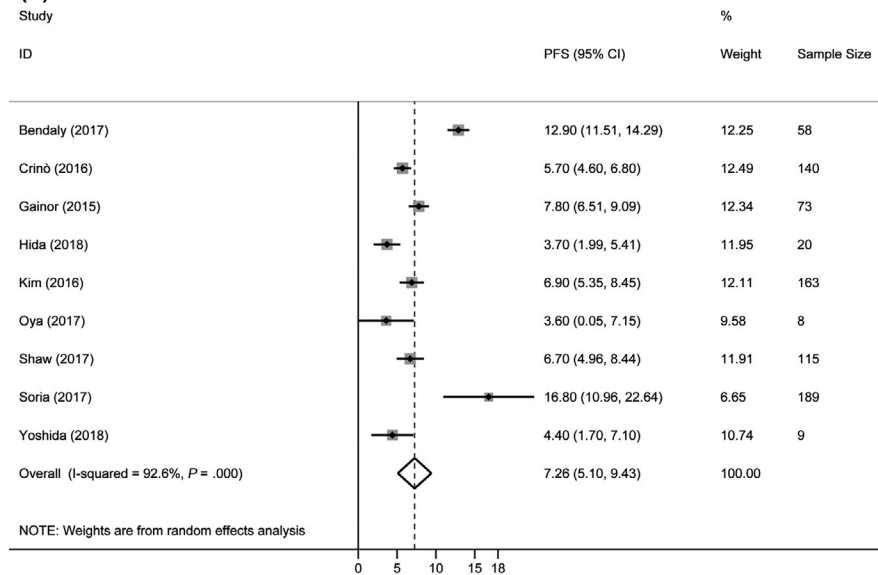
4 | DISCUSSION

We included 15 pieces of literature and 2,598 samples. The ORR and DCR of patients with NSCLC with ALK-rearrangement were 0.48 (95% CI, 0.39-0.57) and 0.76 (95% CI, 0.69-0.82), respectively, and the PFS and OS were 7.26 months (95% CI, 5.10-9.43) and 18.73 months (95% CI, 14.59-22.87), respectively. 'Diarrhoea', 'nausea' and 'vomiting' were the most common AEs. This suggested that

ceritinib effectively treats patients with ALK-rearranged NSCLC, and gastrointestinal reactions are the most common AEs.

Ceritinib is a new generation of selective oral ALK inhibitor, and its enzymatic activity is 20 times greater than that of crizotinib. In a rat model, the effective rate of ceritinib through the blood-brain barrier is 15%. In preclinical models, ceritinib effectively inhibits the activity of several crizotinib mutants, including Leu1196Met, Gly1269Ala, Ile1171Thr and Ser1206Tyr.¹⁹ Additionally, ceritinib is effective with and without crizotinib resistance mutations.³⁷ Based on these studies, ceritinib is expected to be used to treat patients with NSCLC whose disease has progressed or who are not crizotinib-tolerant.³⁸ A recent randomized, multicentre, open-label, phase III study (NCT01828112) compared ceritinib with chemotherapy in patients with advanced ALK-rearranged NSCLC who had previously received double-platinum chemotherapy and crizotinib. They showed that ceritinib treatment significantly prolongs the PFS (5.4 vs 1.6 months) and improves lung cancer-specific symptoms and

(A)



(B)

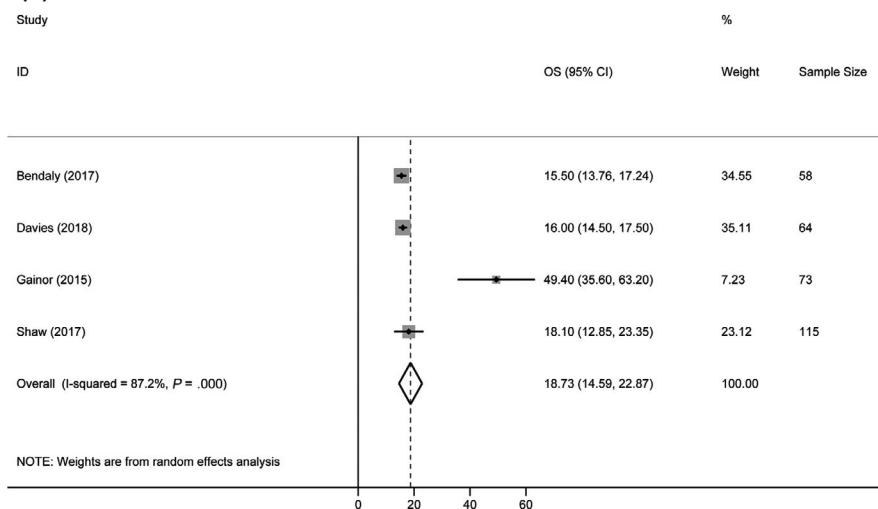
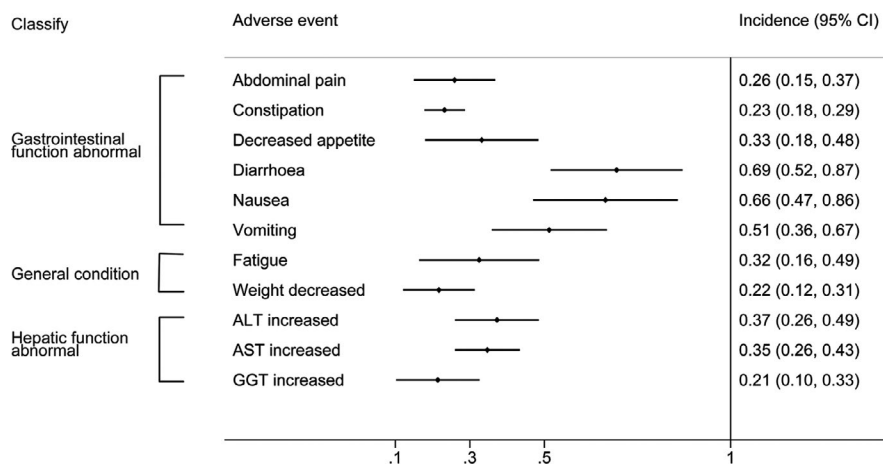


FIGURE 3 A, Forest plot of progression-free survival (PFS). B, Forest plot of overall survival (OS)

TABLE 2 Summary of toxicity

Toxicity	Classify	Incidence	95% CI	Studies included
Abdominal pain	gastrointestinal function abnormal	0.259	0.150-0.368	8
Constipation	gastrointestinal function abnormal	0.232	0.178-0.287	6
Decreased appetite	gastrointestinal function abnormal	0.332	0.180-0.484	8
Diarrhoea	gastrointestinal function abnormal	0.694	0.517-0.871	9
Nausea	gastrointestinal function abnormal	0.664	0.470-0.858	9
Vomiting	gastrointestinal function abnormal	0.513	0.359-0.668	9
Fatigue	general condition	0.325	0.164-0.486	8
Weight decreased	general condition	0.217	0.121-0.313	6
ALT increased	Hepatic function abnormal	0.373	0.260-0.485	9
AST increased	Hepatic function abnormal	0.347	0.260-0.434	8
GGT increased	Hepatic function abnormal	0.214	0.102-0.326	6

FIGURE 4 Forest plot of adverse events (AEs)

quality of life compared with chemotherapy.³⁹ In another randomized prospective study, patients with ALK-rearranged NSCLC received either ceritinib or platinum-pemetrexed chemotherapy. They observed that ceritinib significantly prolongs the PFS (16.6 months vs 8.1 months) and improves intracranial ORR³¹ (72.7% vs 27.3%) compared with chemotherapy. However, the improvement in survival and disease-related symptoms of ceritinib has not yet been confirmed and more trials are needed to validate and describe the clinical outcomes. As ceritinib begins to be routinely used for the treatment of ALK-rearranged NSCLC, an increasing amount of experience has been gained by using ceritinib. We need more precise descriptions to guide doctors in the use of ceritinib to obtain the best results. In our meta-analysis, we systematically reviewed the effect of ceritinib from the perspective of best responses. The ORR

and DCR of ceritinib were 0.48 (95% CI, 0.39-0.57) and 0.76 (95% CI, 0.69-0.82), respectively, and the PFS and OS were 7.26 months (95% CI, 5.10-9.43) and 18.73 months (95% CI, 14.59-22.87), respectively. These results suggest that ceritinib can effectively treat patients with ALK-rearranged NSCLC. Bendaly et al²⁷ showed that the DCR is as high as 94%. The reason for this difference may be that this was a retrospective study. There may have been some bias in choosing medical records, which ultimately led to an excessive DCR, or the criteria for judging the best responses may have been biased. Therefore, more studies should be conducted to examine the therapeutic effects of ceritinib.

Although ceritinib has a good clinical therapeutic effect, its use is still limited owing to serious gastrointestinal AEs. The most common AEs of ceritinib are nausea, vomiting and diarrhoea. Recent

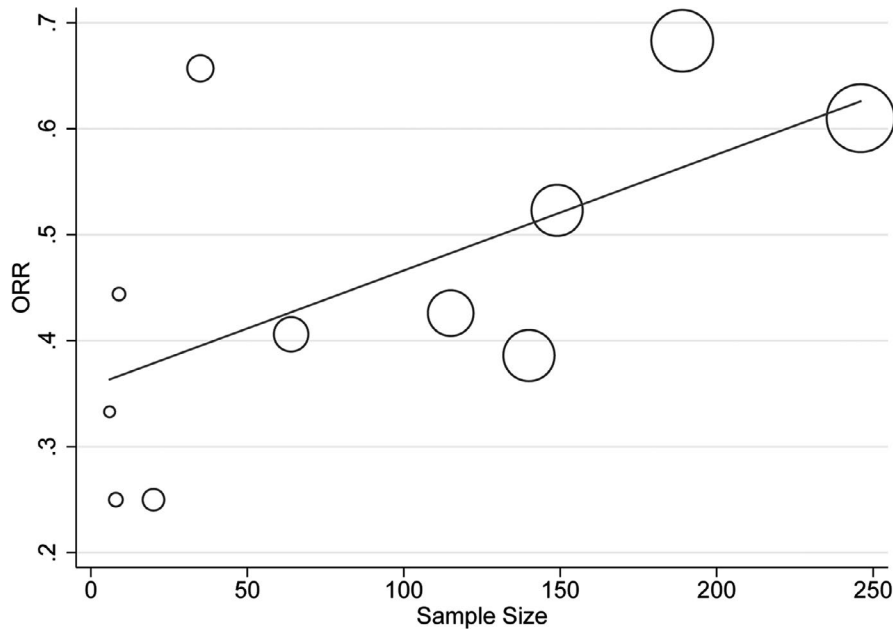


FIGURE 5 Meta-regression analysis for heterogeneity of objective response rate (ORR)

Meta-regression
REML estimate of between-study variance
 % residual variation due to heterogeneity
 Proportion of between-study variance explained
With Knapp-Hartung modification

Number of obs = 11
 tau2 = .01033
 I-squared_res = 75.31%
 Adj R-squared = 36.51%

ORR	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]
sample	.0010936	.0004966	2.20	0.055	-.0000297 .0022169
_cons	.3568672	.0696482	5.12	0.001	.1993121 .5144222

studies^{30,31} have reported diarrhoea (72-85%), nausea (66-69%) and vomiting (52-66%) in many patients after ceritinib treatment. Owing to severe gastrointestinal reactions, some patients must reduce their dosage or even stop using the drug. However, Lucio et al reported higher nausea (81.4%) and diarrhoea incidences (80.0%) than our study and a similar vomiting incidence (62.9%) to our study. In addition, other AEs such as fever, weight loss and liver dysfunction have been reported.^{34,35} In our meta-analysis, we categorized and merged the AEs of each study report and analysed the incidence of 11 common AEs. After the analysis, we included 10 studies. 'Diarrhoea', 'nausea' and 'vomiting' were the three most common AEs and occurred in 69% (95% CI 51.7-87.1%), 66% (95% CI 47.0-85.8%) and 51% (95% CI 35.9-66.8%), respectively. Considering these serious gastrointestinal AEs, we can further study antiemetic and antidiarrhoeal drugs to improve patient tolerance to ceritinib.⁴⁰ Although ceritinib induces obvious gastrointestinal reactions, it still has significant advantages in terms of other quality of life assessments, individual symptoms and overall quality of life.

This study had certain limitations. First, in all studies, the single-group rate was higher and there was a lack of control group data. The reason may be that ceritinib as a second-line and first-line drug has been used for only a short period and more large-scale controlled studies are to be expected in the future. Second, the

studies included had a short follow-up period, with the longest being 53.2 months, and most studies were 11 months. Therefore, OS and PFS data are incomplete.

5 | WHAT IS NEW AND CONCLUSION

Ceritinib effectively controlled the progress of ALK-rearranged NSCLC. Diarrhoea, nausea and vomiting were the most common AEs and the AEs were acceptable. This study should help to convey information to clinicians and patients on the rational use of ceritinib in the treatment of ALK-rearranged NSCLC.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

No conflicts of interest have been declared.

ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors.

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