A retrospective study of ensartinib-treated *ALK*-positive locally advanced or metastatic NSCLC patients in China

Xiaobin Yuan[‡,1], Yang Wang[‡,1], Min Yang[1], Pengxiang Wu[1], Hui Chen[1], Yu Yun[1], Zhilin Shen[1], Dong Ji[1], Yongbin Ma*[,1] & Lieming Ding**[,1]

[1]Betta Pharmaceuticals Co., Ltd, Hangzhou, Zhejiang, 311100, China
*Author for correspondence: yongbin.ma@bettapharma.com
**Author for correspondence: lieming.ding@bettapharma.com
‡Authors contributed equally

Aim: This retrospective study aimed to assess the efficacy and safety of ensartinib in Chinese patients with *ALK*-positive advanced NSCLC in real-world clinical practice. **Methods:** Clinical data from *ALK*-positive NSCLC patients treated with ensartinib in China were collected and analyzed. Efficacy end points included objective response rate and progression-free survival. Safety profiles were also evaluated. **Results:** A total of 682 patients were included in this study. The study demonstrated promising efficacy with an objective response rate of 54.0%, and the median progression-free survival was not estimable. Ensartinib exhibited a manageable safety profile with treatment-related adverse events (TRAEs) consistent with prior clinical trials. The most common TRAE was rash (21.1%) and no TRAE led to death. **Conclusion:** Ensartinib is active and well tolerated for *ALK*-positive NSCLC patients in real-world clinical settings.

Plain language summary: Targeted therapies have significantly improved outcomes for patients with *ALK*-positive NSCLC. Ensartinib, a drug which blocks an enzyme in the body called *ALK* tyrosine kinase, has shown to be efficient and well tolerated in clinical trials. However, real-world evidence is crucial to confirm its effectiveness and safety in diverse patient populations. We analyzed the real-world outcomes of ensartinib treatment in 682 *ALK*-positive NSCLC patients in China, by looking at past records. The results showed that ensartinib demonstrated positive effects in most patients, meaning it helped in controlling their cancer progression. Side effects affected approximately one quarter of patients and most reported side effects were mild. Rash was the most reported side effect, accounting for about 21%. This study provides valuable insights into the real-world clinical performance of ensartinib, confirming its effectiveness and safety as a treatment option for *ALK*-positive NSCLC patients.

Lung cancer stands as one of the leading global causes of cancer-related high mortality and morbidity [1], and NSCLC accounts for approximately 80–85% of lung cancer cases [2]. Unfortunately, a majority of patients presented with advanced stage with local progression and distal metastasis at presentation. Although platinum-based chemotherapy regimen currently present the standard treatment approach for patients with advanced NSCLC, the therapeutic landscape has witnessed a remarkable transformation due to advancements in genetic testing technology and the emergence of targeted therapies. *ALK* gene was discovered as one of the most important driver oncogenes of NSCLC, with an incidence of positive *ALK* gene rearrangement at about 9% in advanced NSCLC patients [3]. Randomized trials have demonstrated that *ALK* inhibitors, such as crizotinib, ceritinib and alectinib, have successfully prolonged the median progression-free survival (PFS) and improved quality of life in advanced patients with *ALK*-positive NSCLC over conventional chemotherapy [4].

Ensartinib is an oral, highly selective, potent ALK–tyrosine kinase inhibitor (TKI), which has been approved by the National Medical Products Administration (NMPA) as the first-line treatment for the *ALK*-positive locally

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advanced or metastatic NSCLC patients in March 2022. Structurally, ensartinib represents a novel second-generation ALK–TKI, featuring an aminoquinazoline substitution for the aminopyridine found in the chemical structure of crizotinib. The phase I dose-escalation and expansion trials showed that ensartinib exhibited remarkable efficacy with maintain manageable toxicity [5–7]. The phase I trial showed that ensartinib exhibited remarkable efficacy with maintain manageable toxicity across four cohorts (150, 200, 225 and 250 mg per day) in 48 patients with advanced *ALK*- or *ROS*-positive NSCLC [7]. In this above study, ensartinib exhibited moderate absorption, with a median time to maximum concentration ranging from 3.00 to 4.00 h, with a mean half-life ($T_{1/2}$) ranging from 21.0 to 30.2 h. The area under the curve (AUC) of ensartinib approached saturation at doses between 200 and 225 mg. Two dose-limiting toxicities (DLTs) were observed in 250 mg, resulting in the determination of the maximum tolerated dose (MTD) and the recommended phase II dose (RP2D) as 225 mg per day. The phase II study of ensartinib conducted in 160 patients with crizotinib-resistant *ALK*-positive NSCLC, median PFS was 9.6 months (95% CI: 7.4–11.6), and the overall and intracranial objective response rate (ORR) was 52% (95% CI: 43–60) and 70% (95% CI: 53–83), respectively [8]. Of note, in the phase III eXalt3 study, ensartinib as the first-line treatment significantly extended median PFS with advanced *ALK*-positive NSCLC patients over crizotinib (25.8 months vs 12.7 months; HR: 0.51; 95% CI: 0.35–0.72; p < 0.001). The confirmed intracranial response rate, as confirmed by the independent review committee, demonstrated a substantial advantage with ensartinib at 63.6%, in stark contrast to the 21.1% observed with crizotinib [9].

Given that ensartinib is a novel and newly available second-generation ALK–TKI, its efficacy and safety in large-scale, real-world patient populations remain uncertain. To address this uncertainty, this retrospective study was conducted to assess the efficacy and safety of ensartinib in *ALK*-positive locally advanced or metastatic NSCLC patients in actual treatment practice.

Methods

Patients & study design

Data were obtained from the patient record from the hospital electronic database which was analyzed by the Betta Pharmaceuticals Co., Ltd. All patients with unresectable stage IIIB–IV *ALK*-positive locally advanced or metastatic NSCLC who were scheduled to be treat with ensartinib between 16 December 2020 and 16 December 2021 were eligible for the study. Eligible patients (age ≥18 years) were required to receive ensartinib (225 mg orally, once daily) until disease progression or intolerable toxicity. The primary objective was PFS. The second objective was ORR and safety. The Institutional Review Board (IRB) at China Pharmaceutical Industry Research and Development Association waived the need for approval or informed consent because of the anonymized and retrospectively analyzed data. The study was performed in accordance with the Helsinki Declaration and Good Clinical Practice Guidelines.

Assessment

For each patient, a comprehensive set of demographic and baseline data were collected, encompassing key factors such as age, sex, smoking history, Eastern Cooperative Oncology Group (ECOG) performance status (PS), tumor histology, tumor stage and line of therapy. Efficacy and safety data were recored at 1 month after the first dose of ensartinib, and then at least every 2 months. Physician-based tumor response was evaluated by computerized tomography (CT) imaging according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, which was recorded as complete remission (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Safety assessment was conducted in patients who had received at least one dose of ensartinib. All treatment-related adverse events (TRAEs) were coded following the Medical Dictionary for Regulatory Activities (MedDRA) version 12.1 and graded by the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Statistical Analysis

Analyses were conducted using Statistical Analysis Software version 9.4 (SAS Institute, Cary, NC) in the study. And analyses were performed using descriptive methods including frequency and percentage. All TRAEs occurred during medication period were coded and complied with MedDRA (version 12.1). Tumor response of ensartinib was correlated with both PFS and ORR. PFS was defined as the time from the start of ensartinib until objective disease progression, and ORR was defined as the percentage of patients achieving CR or PR. Univariate and multivariate Cox proportional hazard regression modeling was used for determining risk factors for PFS. ORR was

Table 1. Patient demographics and clinical characteristics.	
Characteristics	Total (n = 682), n (%)
Sex	
Male	306 (44.9%)
Female	376 (55.1%)
Age	
<65 years	515 (75.5%)
≥65 years	167 (24.5%)
Smoking history	
Yes	34 (5.0%)
No	607 (89.0%)
Others	41 (6.0%)
ECOG performance status	
0–1	587 (86.1%)
≥2	90 (13.2%)
Missing	5 (0.7%)
Tumor histology	
Adenocarcinoma	623 (91.3%)
Squamous cell carcinoma	32 (4.7%)
Others/missing	27 (4.0%)
Tumor stage	
IIIB–IIIC	74 (10.8%)
IV	585 (85.8%)
Others/missing	23 (3.4%)
Line of therapy	
First line	210 (30.8%)
Second line	306 (44.9%)
Third line or multiple lines	2 (0.3%)
Others/missing	164 (24.0%)
ECOG: Eastern Cooperative Oncology Group.	

subjected to a detailed analysis based on predefined subgroups, encompassing variables such as sex, age, smoking history, ECOG PS, tumor histology, tumor stage and line of therapy.

Results

Baseline characteristics

From 16 December 2020 to 16 December 2021, a total of 682 patients were enrolled in this study. All patients were assessable for the efficacy and safety analysis. The median follow-up time was 4.8 months. Baseline demographics were shown in Table 1. The median age was 57 years (range: 18–95 years). With regard to age, 515 patients (75.5%) were younger than 65 years and 167 patients (24.5%) were older than 65 years. The majority of patients had no smoking history (89.0%), and had adenocarcinoma (91.3%) and ECOG PS of 0–1 (86.1%). Most patients (85.8%) were diagnosed with stage IV disease. Ensartinib predominantly served as the second-line therapy for most patients (44.9%), while 30.8% and 0.3% of patients initiated treatment with ensartinib as their first-line therapy and third/multiple-line therapy, respectively.

Efficacy

As of the date of data cutoff, a total of 30 of 682 patients (4.4%) patients had PFS events. The overall median PFS was not estimable (NE; 95% CI: 8.1–NE) (Figure 1). Subgroup analysis showed that the median PFS with the first-line therapy and second-line therapy was NE (95% CI: 4.8–NE) and 8.1 months (95% CI: 6.4–NE), respectively (Figure 2). Univariate analysis identified that being male (HR: 2.23, 95% CI: 1.06–4.66; p = 0.0295) and having squamous cell carcinoma (HR: 6.95, 95% CI: 2.95–16.37; p < 0.001) were significant predictors with poorer PFS. By multivariate analysis, squamous cell carcinoma was related to a worse PFS (HR: 4.44, 95% CI: 1.75–11.26;
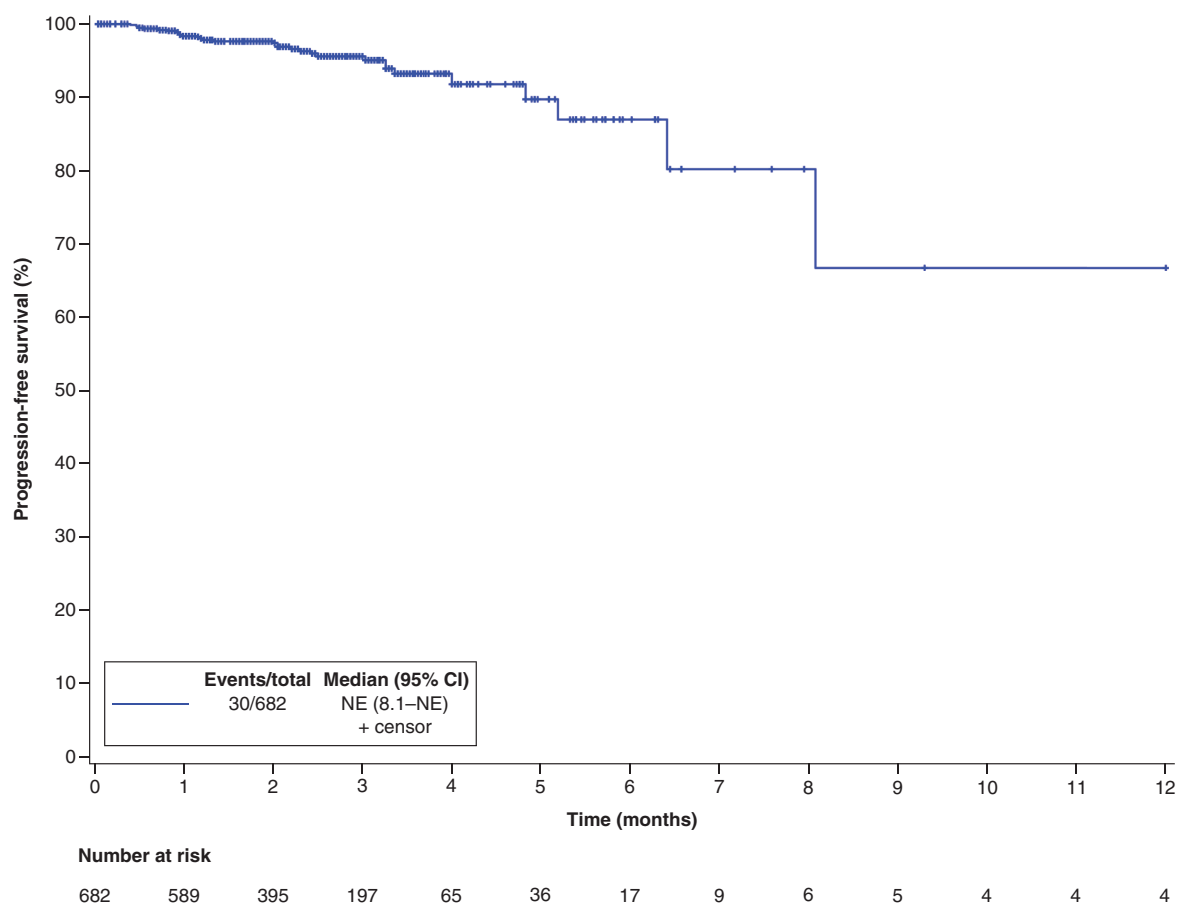
Figure 1.   Progression-free survival in all evaluable patients.
NE: Not estimable.

p = 0.0017) (Table 3). The ORR among the 682 efficacy-evaluable patients was 54.0% (95% CI: 50.1–57.8%) (Figure 3). In subgroup analysis, ORR was 50.0% (37/74) and 54.5% (331/607) in smoker and nonsmoker subgroups, 56.6% (332/587) and 35.6% (32/90) in ECOG PS of 0–1 and ≥2 subgroups, 53.0% (330/623) and 65.6% (21/32) in adenocarcinoma and squamous cell carcinoma subgroups, 68.9% (51/74) and 51.8% (303/585) in stage III and IV subgroups, 68.1% (143/210) and 48.0% (147/306) in first-line and second-line subgroups.

Safety

TRAEs were recorded in 162 (23.8%; 162/682) patients. The most frequently reported TRAE were rash (21.1%). Other TRAEs, each occurring in at least 1% of patients, including pruritus (3.8%), constipation (2.2%), facial edema (1.3%) and vomiting (1.0%). Grade 3 or higher TRAE was reported in 1.0% of patients. No treatment-related deaths were reported. One patient aged 68 years discontinued due to grade 2 interstitial lung disease (ILD) (Table 2). Instances of liver injury, characterized by elevated alanine aminotransferase, were observed in 4 patients (0.6%), while elevated aspartate aminotransferase was noted in two patients (0.3%). Grade 3 increases in alanine aminotransferase occurred in 2 (0.3%) of patients and no grade 3 or higher elevated aspartate aminotransferase reported. The complete TRAEs were summarized in Supplementary Table 1.

Discussion

In this retrospectively analysis, we examined the real-world efficacy and safety of ensartinib in routine clinical practice. Our findings revealed that ensartinib showed a satisfying efficacy and manageable safety profile in Chinese patients with *ALK*-positive NSCLC, as well as confirming the results of the phase III eXalt3 study.

At the time of analysis, 30 patients (4.4%) receiving ensartinib treatment had a PFS event, with an overall median PFS that could not be precisely estimated (NE; 95% CI: 8.1–NE). Subgroup analysis showed that the median PFS
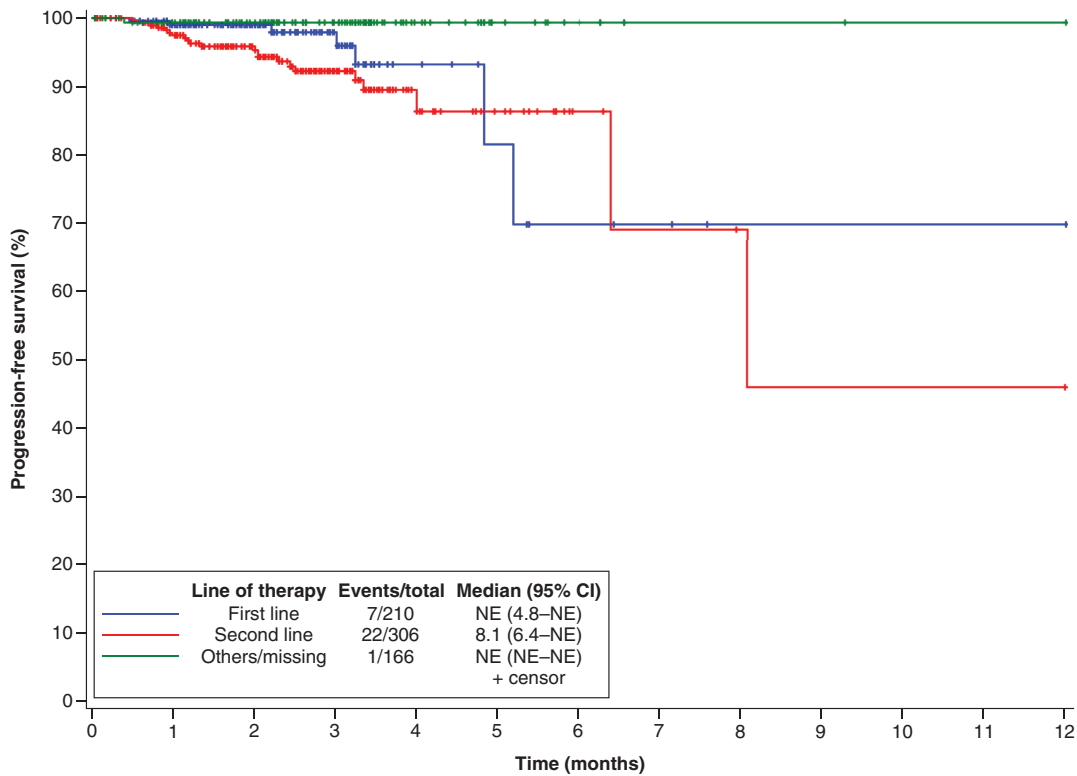
Figure 2. Progression-free survival curves according to line of treatment.
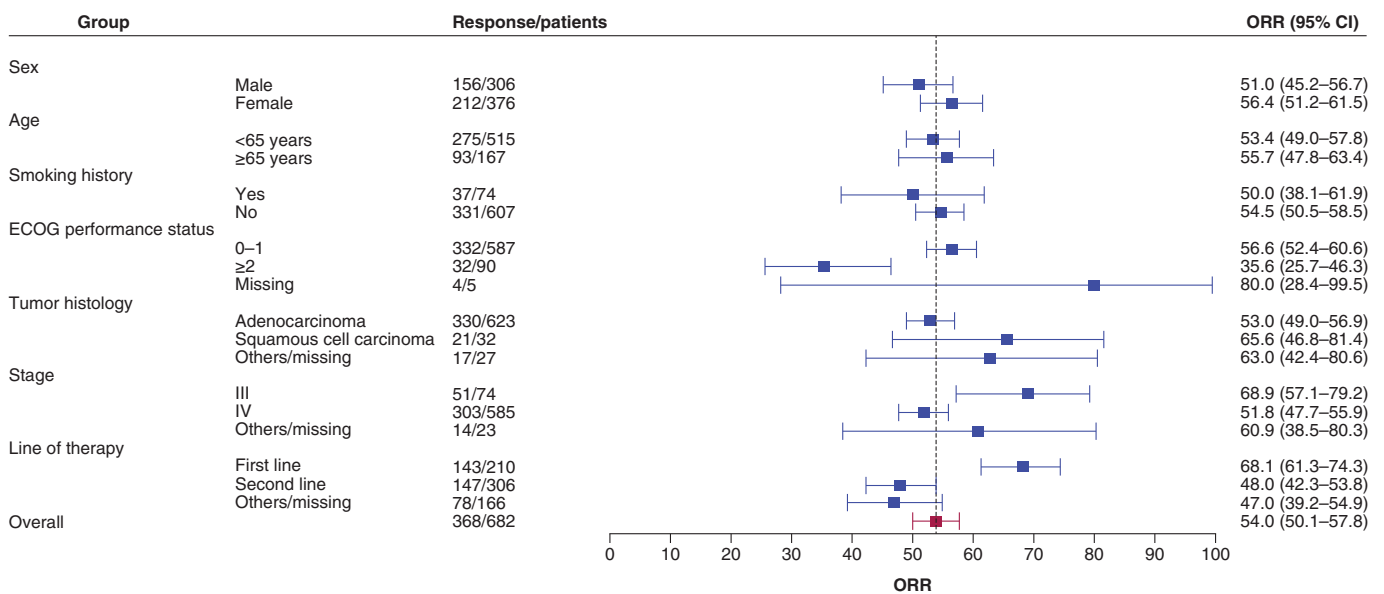NE: Not estimable.

Figure 3. Forest plots for subgroup analysis of objective response rate with respect to stratification factors.
ECOG: Eastern Cooperative Oncology Group; ORR: Objective response rate.

Table 2. Treatment-related adverse events reported in ≥1% patients.

	Grade 1, n (%)	Grade 2, n (%)	Grade ≥3, n (%)	Unknown, n (%)	Total, n (%)
TRAE	113 (16.6%)	40 (5.8%)	7 (1.0%)	2 (0.3%)	162 (23.8%)
Rash	100 (14.7%)	35 (5.1%)	7 (1.0%)	2 (0.3%)	144 (21.1%)
Pruritus	22 (3.2%)	3 (0.4%)	1 (0.2%)	0	26 (3.8%)
Constipation	10 (1.4%)	4 (0.6%)	0	1 (0.2%)	15 (2.2%)
Facial edema	9 (1.3%)	0	0	0	9 (1.3%)
Vomiting	6 (0.8%)	1 (0.2%)	0	0	7 (1.0%)
TRAE: Treatment-related adverse event.					

Table 3. Uni- and multivariate Cox regression analyses of independent prognostic factors for progression-free survival.

Variable	Progression-free survival (n = 30)			
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Sex				
Male	2.23 (1.06–4.66)	0.0295	1.78 (0.83–3.83)	0.1370
Female	1		1	
Age				
<65 years	1			
≥65 years	0.58 (0.22–1.52)	0.2645		
Smoking history				
Yes	0.58 (0.14–2.42)	0.4457		
No	1			
ECOG performance status				
0–1	1			
≥2	0.92 (0.32–2.66)	0.8798		
Tumor histology				
Adenocarcinoma	1		1	
Squamous cell carcinoma	6.95 (2.95–16.37)	<0.001	4.44 (1.75–11.26)	0.0017
Tumor stage				
III	0.56 (0.13–2.35)	0.4193		
IV	1			
Line of therapy				
First line	0.52 (0.22–1.23)	0.1326	0.71 (0.29–1.74)	0.4469
Second line	1		1	
Others/missing	0.08 (0.01–0.55)	0.0013	0.10 (0.01–0.77)	0.0272

HR was determined with univariate Cox regression analysis, and p-value in univariate analysis was assessed by the Log rank test. Variables with a p-value <0.05 in the univariate analysis were included in multivariate logistic regression analysis, and HR and p-value in multivariate analysis were evaluated by Cox regression analysis.
ECOG: Eastern Cooperative Oncology Group; HR: Hazard ratio.

was NE (95% CI: 4.8–NE) and 8.1 (95% CI: 6.4–NE) for patients receiving first-line or second-line treatment. In contrast, previous trials of ensartinib demonstrated the median PFS of 25.8 months (range: 0.03–44.0) and 9.6 months (95% CI: 7.4–11.6) for first-line and second-line treatments, respectively [8,9]. However, it's essential to recognize that our study is retrospective in nature and comes with inherent limitations. Unlike rigorous clinical setting, patients may benefit from combination with other therapeutic agents the alongside ensartinib, which should be more reflective of ensartinib efficacy in the real-world. To date, several ALK–TKIs has been developed, including first-generation ALK–TKI (e.g., crizotinib); second-generation ALK–TKIs (eg., alectinib, ceritinib, brigatinib, and ensartinib) third-generation ALK–TKI (e.g., lorlatinib). Among second-generation ALK inhibitor, ceritinib exhibited a median PFS of 16.6 months (95% CI: 12.6–27.2) and brigatinib reported 24 months (95% CI: 18.5–43.2) in the first-line setting [10,11]. Furthermore, median PFS for patients with ceritinib and brigatinib was 5.7 months (95% CI: 5.4–7.6) and 12.9 months (95% CI: 11.1–NE) for second-line studies, respectively [12,13].

Although across-trial comparisons are difficult and unreliable, the median PFS of current available second-generation ALK inhibitors were broadly similar.

In terms of another crucial efficacy parameter, ORR, our study reached an overall rate of 54.0% (95% CI: 50.1–57.8). The ORR in the *ALK*-positive patients receiving first-line and second-line ensartinib therapy was 68.1% (95% CI: 61.3–74.3) and 48.0% (42.3–53.8), respectively. These findings align similar to the data from previous phase II/III clinical study, where the ORR for ensartinib in first-line and second-line treatments was reported as 74% (95% CI, 66–81) and 52% (95% CI, 43–60), respectively [8,9]. Compared with other *ALK* inhibitors, ORR in the *ALK*-positive patients after first-line alectinib treatment was 82.9% (95% CI, 76.0–88.5) [14]. In the second-line setting, ORR with ceritinib and brigatinib was 38.6% (95% CI, 30.5–47.2) and 54% (97.5% CI, 43–65), respectively [12,13]. It's important to acknowledge that, due to the selection bias of retrospective studies and the relative insufficient follow-up time, our study data exhibited more variability compared with previous trials involving second-generation *ALK-TKIs*. Nonetheless, the overall ORR of 54% reaffirms the favorable efficacy of ensartinib in the real-world population.

The safety profile of ensartinib in this study remained consistent with previously reported data and exhibited no new safety signals [5–9]. The most common TRAE was rash (21.1%), mainly due to the concentrations of ensartinib in skin are nine-times than those in plasma [5]. The majority of rash was grade 1–2 in severity, with 1.0% of patients having grade 3–4 rash. This proportion was much lower than that of ensartinib in previous phase ii (56%) and phase III (67.8%) trials [8,9]. Importantly, no patients discontinued treatment due to rash, and there were no instances of treatment-related fatalities. In first-line studies [9,10,14,15], the most common AE for alectinib is anemia (20%), while for brigatinib, it is diarrhoea (52%), and for ceritinib, it is diarrhea (85%). In our current study, only 2 (0.3%) patients developed anemia and just 1 (0.2%) patient reported diarrhoea, with none of these cases reaching grade 3 or higher severity. Notably, these four drugs have displayed varying levels of hepatotoxicity in prior studies. While direct comparisons between these studies may be challenging, in the first-line settings, the incidence of grade 3 or higher elevated alanine aminotransferase and elevated alanine aminotransferase for alectinib is 15% and 14%, respectively [14], brigatinib reported rate of 21% and 26% [15], and ceritinib had an incidence of 31% and 17% [10]. In contrast, ensartinib has a low incidence, with only 4.2% and 0.7% for alanine aminotransferase and alanine aminotransferase elevation, respectively [9]. Here, the incidence of alanine aminotransferase and aspartate aminotransferase elevation was 0.6% (grade ≥3, 0.3%) and 0.3% (grade ≥3, 0). Consequently, ensartinib appears to be the least hepatotoxic option for the first-line treatment among *ALK*-positive NSCLC patients. Furthermore, this study recorded low incidences of other TRAEs, such as pruritus and constipation, which were reported at approximately 3.8% and 2.2%, respectively. In term of serious adverse events, only one patient had grade 2 ILD, and ILD was considered by the investigator to be related to the study medication. Fortunately, this patient showed improvement following the symptomatic treatment.

Some limitations exist in this study, such as the inherent selection bias, and the relatively short duration follow-up. Besides, data was not collected for the *ALK*-positive patients with brain metastases; the most frequently mutation types via next-generation sequencing were not distinguished, and stringent inclusion criteria were not used in this study. Finally, we cannot exclude that TRAEs were underreported in this study. Regarding the lower occurrence rate of TRAEs with ensartinib in real-world study compared with clinical trials, one such possibility is that clinical trials usually adhere to stricter monitoring and reporting procedures to ensure accurate recording and assessment of TRAEs. In the real world, these procedures may not be as rigorous, potentially resulting in lower reporting rates. In general, ensartinib was well tolerated with a manageable safety profile in the real-world population.

Conclusion

This retrospective study indicated favorable efficacy and safety of ensartinib in Chinese patients with *ALK*-positive NSCLC. On the practical side, ensartinib exhibits promising overall and intracranial efficacy. Furthermore, the safety profile of ensartinib is not identical to other second generation ALK–TKIs, which may lead to better tolerability in some patients. For those patients who cannot tolerate other ALK–TKIs, especially in liver injury patients, ensartinib may offer a viable alternative. Additionally, clinician formulate treatment plans based on the patient's specific circumstances and medical history. The choice of ensartinib may be influenced by the patient's genotype, clinical condition, and resistance mechanisms. In certain situations, ensartinib may be the more suitable treatment option.

Summary points

- This is a retrospective real-world study evaluating the efficacy and safety of ensartinib in Chinese patients with *ALK*-positive locally advanced or metastatic NSCLC.
- A total of 682 patients were included to evaluate the efficacy and safety of ensartinib and the majority of patients had adenocarcinoma (91.3%), Eastern Cooperative Oncology Group performance status of 0–1 (86.1%) and stage IV disease (85.8%).
- The median progression-free survival was not reached, and the median progression-free survival with the first-line therapy and second-line therapy was not estimable and 8.1 months.
- Overall, the objective response rate was 54.0%, and objective response rate for the first-line and second-line therapy was 68.1% and 48%, respectively.
- The most common treatment-related adverse event was rash (21.1%), and grade 3 or higher treatment-related adverse events were occurred in 1.0% of patients.
- One case of grade 2 interstitial lung disease, and no treatment-related deaths occurred.
- Ensartinib may be the least hepatotoxic ALK–tyrosine kinase inhibitors for first-line treatment in *ALK*-positive NSCLC patients.
- Ensartinib as a reliable treatment option for *ALK*-positive advanced NSCLC.

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