Clinical Data From the Real World: Efficacy Analysis of Ceritinib (450mg) in ALK-Rearrangement Non-Small Cell Lung Cancer Patients with Brain Metastases in China

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Abstract

Objectives: The real-world intracranial efficacy data of ceritinib at a dose of 450mg quaque die (QD, once a day) are still unavailable, thus this study aims to explore the intracranial efficacy of ceritinib (450mg QD) in anaplastic lymphoma kinase (ALK)-rearrangement non-small cell lung cancer (NSCLC) patients in China.

Materials and Methods: The intracranial efficacy [objective response rate (ORR) and disease control rate (DCR)] was evaluated according to the Response Assessment in Neuro-Oncology (RANO) standard, along with progression-free survival (PFS) and adverse events (AEs) obtained through follow-ups.

Results: A total of 57 ALK-rearrangement NSCLC patients with brain metastases (BM) were enrolled in this study. Among them, 53 patients experienced progression at baseline during or after prior crizotinib, and 24 patients received prior brain radiotherapy. The intracranial ORR and DCR were 73.7% and 93.0%, respectively. The median intracranial PFS in patients reaching the endpoint was 8.75 months; while that in all patients was not reached and predicted to be not evaluable (NE) (95% CI: 12.9-NE). The estimated 12-month event-free probability (EFP) of intracranial lesions was 68.1%. Subgroup analysis showed the estimated 12-month EFP of intracranial lesions was relatively higher in patients with prior brain radiotherapy (93.8% vs 47.1%, *P*=0.0006). Additionally, we reported a 74-year-old female ALK-rearrangement NSCLC patient with BM achieved continuous response (intracranial PFS: 12.9 months) to ceritinib reduced to 150mg QD due to intolerable AE and administered for 7.5 months.

Conclusion: Ceritinib administered at a dose of 450mg QD to ALK-rearrangement NSCLC patients with BM in China demonstrates superior ORR and DCR, as well as PFS and EFP that are expected to be improved. Especially the estimated 12-month EFP of intracranial lesions was improved in patients with prior brain radiotherapy.

Background

Lung cancer is the neoplasm with the highest prevalence and mortality rates in the world, of which approximately 85% are non-small cell lung cancer (NSCLC). Due to the lack of effective approaches for early diagnosis, 70–80% of patients have lost the chance of surgery when they were diagnosed [1]. At present, chemotherapy, targeted therapy and immunotherapy are used as the main non-surgical systemic therapies for NSCLC.

Since the concept of precision medicine was first proposed in 2011, targeted therapy has become a new hope for the treatment of advanced NSCLC patients with positive driver genes. The rearrangement of anaplastic lymphoma kinase (ALK), a molecular subtype and major driver gene of lung cancer, has been observed in approximately 5% of NSCLCs [2]. The efficacy of the first-generation ALK tyrosine kinase inhibitor (TKI) crizotinib in the treatment of advanced ALK-rearrangement NSCLC has been confirmed in a series of PROFILE trails [3, 4]. However, all patients inevitably develop drug resistance, which encourages the second-generation TKIs such as ceritinib and alectinib. Ceritinib, an oral TKI with high selectivity, has obvious inhibitory effect on the growth of crizotinib-resistant tumor cells, shown by preclinical studies [5]. The Phase I/II clinical studies (ASCEND-1 and ASCEND-2) have preliminarily confirmed that ceritinib administered at the maximum tolerated dose of 750 mg quaque die (QD, once a day) under fasted condition achieves a good efficacy in the treatment of ALK-rearrangement NSCLC [6, 7]. According to the ASCEND-4 and ASCEND-5 studies, in comparison with conventional chemotherapy, ceritinib significantly prolongs progression-free survival (PFS) (ASCEND-4: 1.6 months vs 5.4 months and ASCEND-5: 8.1 months vs 16.6 months) after crizotinib failure or in first-line treatment [8, 9]. Its efficacy in lung cancer patients with brain metastases (BM) is also a key concern of clinicians. About 30–50% of ALK-rearrangement NSCLC patients have BM which portend a poor prognosis [1–3]. Besides, BM detected in the ALK-rearrangement NSCLC patients 1–2 year after crizotinib treatment are a common manifestation of acquired resistance to crizotinib [4–8]. Another focus of clinical practice is its safety which can affect patients' compliance with treatment, thus affecting its efficacy. In previous studies, a high proportion of gastrointestinal (GI) disturbances such as diarrhea, nausea and vomiting have been noted when ceritinib was administered at a dose of 750 mg QD under fasted condition. Due to these side effects, 69.3%-80% of patients' treatment have to be adjusted, delayed or even interrupted. In order to improve patients' compliance with treatment, ASCEND-8 study made a new exploration on the administration mode of ceritinib. As a result, the doses of 750 mg QD under fasted condition and 450 mg QD under fed condition are similar in pharmacokinetics; while the latter can both improve efficacy and significantly enhance GI tolerability (ORR: 78.1% vs 75.7%, DOR: not reached vs 15.4 months, and PFS: not reached vs 12.2 months) [10, 11]. However, all of the above studies were performed on the basis of Korean and Caucasian patients, and the impact of ethnic differences is still unknown.

On May 31, 2018, China granted approval to ceritinib for the treatment of advanced ALK-rearrangement NSCLC patients who are intolerant of or experience disease progression during the treatment with crizotinib. With the widespread use of ceritinib, the real-world data concerning its efficacy in Chinese patients deserve attention. Although the ASCEND-7 has reported its intracranial efficacy data at 750 mg QD under fasted condition, those at 450 mg QD under fed condition are still unavailable. Therefore, this study aims to observe the intracranial efficacy of ceritinib (450 mg QD under fed condition) in Chinese patients, and make an analysis of the data recently observed.

Methods

Patient Information

A total of 57 ALK-rearrangement NSCLC patients with BM visiting West China Hospital from October 2018 to May 2020 were reviewed retrospectively in this study. All patients have received a targeted therapy with ceritinib 450mg QD.

Through the electronic medical record system, the patients' basic clinical characteristics and prior treatment data, such as gender, age, Eastern Cooperative Oncology Group (ECOG) performance status score, smoking history, pathological type, TNM stage, metastasis site and gene status, were

collected completely. The efficacy and adverse events (AEs) during ceritinib treatment were collected by means of outpatient and inpatient medical records, outpatient follow-up and phone call.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) a NSCLC diagnosed histopathologically or cytologically; (2) complete clinical staging according to the 8th edition of the AJCC Staging System; (3) an ALK rearrangement detected by reverse transcription-polymerase chain reaction (RT-PCR), ventana immunohistochemistry (IHC), fluorescence in situ hybridization (FISH) or next-generation sequencing (NGS); (4) receiving at least one dose (450mg) of ceritinib under fed condition; and (5) complete medical records.

Exclusion criteria: (1) receiving ceritinib targeted therapy and any other systemic anti-tumor therapy at the same time or (2) follow-up cannot be completed safely.

Dosage and Administration

All patients received at least one dose (450mg) of ceritinib under fed condition. Among them, a patient suffered from vomiting caused by an intolerance (AE grade 2) three months after receiving ceritinib at a dose of 450mg QD under fed condition, thus the dose was reduced to 300mg QD by the clinician after evaluation. Another patient suffered from severe diarrhea (AE grade 3) three months after receiving ceritinib at a dose of 450mg QD under fed condition, thus the dose was reduced to 300mg QD by the clinician after evaluation, and then 150mg QD so as to ensure tolerability. All patients took ceritinib orally until disease progression, drug intolerance, or patient's refusal or death.

Efficacy Evaluation

All patients' data were collected by means of electronic medical records, phone call and outpatient follow-up. The whole body efficacy was evaluated according to the version 1.1 of the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). The evaluation of intracranial efficacy was divided into complete response (CR), partial response (PR), stable disease (SD) and progression disease (PD) in the light of the Response Assessment in Neuro-Oncology (RANO) Working Group Criteria. Objective response rate (ORR) = (CR + PR) / total cases × 100% and disease control rate (DCR) = (CR + PR + SD) / total cases × 100%. The last follow-up was on May 15, 2020.

Statistical Analysis

Frequency (%) and median (interquartile range) were used to describe qualitative and quantitative data, respectively. Chi-square test or Fisher extract test was used to compare the ORR and DCR between patients with different characteristics. Kaplan-Meier was used to estimate survival curve, median progression-free survival (PFS), as well as 6-month and 12-month event-free probabilities. The normal approximation method for the difference between two proportions was used to compare the estimated 6-month and 12-month event-free probabilities between patients with different characteristics. R-3.6.2 was introduced as the data analysis software in this study.

Results

Patients' Baseline

A total of 57 (26 males and 31 females) ALK-rearrangement NSCLC patients with BM were enrolled in this study, with a median age of 50.0 years (range, 44.0–57.0 years). All patients were diagnosed ALK rearrangement by FDA-approved tests. The numbers of patients with an ECOG PS score from 1 to 4 were 26, 17, 8 and 6, respectively. Four patients (incl. 2 cases of secondary malignant bone tumor, 1 case of secondary adrenal tumor, and 1 case of secondary high-grade neuroendocrine tumor) had a family history of tumor, in which one father suffered from lung cancer. Seventeen patients had a history of smoking. All patients suffered from stage IV lung adenocarcinoma. A variety of methods for detecting ALK rearrangements were performed in this group, including IHC in 30 cases, NGS in 17 cases, RT-PCR in 7 cases and FISH in 3 cases, where ALK + V-raf murine sacoma viral oncogene homolog B1 (BRAF) was detected in one case. Two patients developed intracranial + meningeal metastases and 13 patients developed liver metastases. Fifty-three patients received prior crizotinib and 1 patient received prior alectinib. Twenty-one patients received at least one cycle of platinum-based doublet chemotherapy after experiencing disease progression during first-line TKI therapy. Besides, 24 patients received brain radiotherapy and 5 patients underwent intracranial lesion resection. Ceritinib was administered to 21 patients in the first or second line setting and 36 patients in the third, fourth or fifth line setting. The last follow-up was on May 15, 2020. The average duration of ceritinib exposure was 9.38 months. (Table 1 *and Supplementary Material 1*)

Table 1
Patients' Baseline

Variables	N(%) / median (P_{25}-P_{75})
Age	50.0 (44.0–57.0)
Gender	
Male	26 (45.6)
Female	31 (54.4)
Smoking	
Yes	17 (29.8)
No	40 (70.2)
ECOG PS. score	
1	26 (45.6)
2	17 (29.8)
3	8 (14)
4	6 (10.5)
Family cancer history (Yes)	4 (7)
Pathology	
ADC	57 (100)
TNM stage	
IV stage	57 (100)
Gene status	
ALK	56 (98.2)
ALK + BRAF	1 (1.8)
Meningeal metastasis (Yes)	2 (3.5)
Liver metastasis (Yes)	13 (22.8)
Crizotinib treatment history	53 (92.3)
Alectinib treatment history	1 (1.8)
Chemotherapy (Yes)	21 (36.8)
Brain radiotherapy	24 (42.1)
Brain surgery	5 (8.8)
Ceritinib treatment lines	
1–2 lines	21 (36.8)
3–5 lines	36 (63.2)
Adverse effects	
Diarrhea	11 (19.3)
Nausea	6 (10.5)
Vomiting	6 (10.5)
Anorexia	5 (8.8)

ADC, adenocacinoma

ALK, anaplastic lymphoma kinase.

BRAF,V-raf murine sacoma viral oncogene homolog B1.

ALT, alanine amiotransferase.

AST, aspartate transaminase.

Variables	N(%) / median (P_{25}-P_{75})
Fatigue	2 (3.5)
High ALT	3 (5.3)
High AST	1 (1.8)
Others	4 (7.0)
None	13 (22.8)
ADC, adenocacinoma	
ALK, anaplastic lymphoma kinase.	
BRAF,V-raf murine sacoma viral oncogene homolog B1.	
ALT, alanine amiotransferase.	
AST, aspartate transaminase.	

Intracranial and Whole Body Efficacy Analysis

By the end of the last follow-up, the intracranial efficacy evaluation in the 57 patients showed that best response to ceritinib was CR in 1 patients, PR in 41 patients, SD in 11 patients and PD in 4 patients (Supplementary Table 1). The intracranial ORR and DCR were 73.7% (95% CI: 62.3–85.1) and 93.0% (95% CI: 86.3–99.6), respectively. Comparative analyses were made in various subgroups (gender, smoking, chemotherapy, brain radiotherapy, ceritinib treatment line, and prior TKI), and the results showed no statistical difference. As for the whole body efficacy evaluation, best response to ceritinib was CR in 1 patient, PR in 49 patients, SD in 6 patients and PD in 1 patient (*Supplementary Table 1*). The whole body ORR and DCR were 87.7% (95% CI: 79.2–96.2) and 98.2% (95% CI: 94.8–100.0), respectively. Comparative analysis in various subgroups found that the ORR of patients with prior brain radiotherapy was relatively higher (P = 0.044) (Table 2).

Table 2
Intracranial and Whole Body Efficacy Evaluation Results

Variables	Intracranial efficacy evaluation						Whole body efficacy evaluation					
	ORR			DCR			ORR			DCR		
	N (%)	95% CI	*P value*	N (%)	95% CI	*P value*	N (%)	95% CI	*P value*	N (%)	95% CI	*P value*
Total (n = 57)	42 (73.7)	62.3–85.1	NA	53 (93.0)	86.3–99.6	NA	50 (87.7)	79.2–96.2	NA	56 (98.2)	94.8–100.0	NA
Gender												
Male (n = 26)	17 (65.4)	47.1–83.7	0.193*	23 (88.5)	76.2–100.0	0.322	23 (88.5)	76.2–100.0	1.000	25 (96.2)	88.8–100	0.456
Female (n = 31)	25 (80.6)	66.7–94.6		30 (96.8)	66.7–94.5		27 (87.1)	75.3–98.9		31 (100.0)	100.0-100.0	
Smoking												
No smoking (n = 40)	32 (80.0)	67.6–92.4	0.112	38 (95.0)	88.3–100.0	0.575	34 (85.0)	73.9–96.1	0.662	40 (100.0)	100.0-100.0	0.298
Smoking (n = 17)	10 (58.8)	35.4–82.2		15 (88.2)	72.9–100.0		16 (94.1)	82.9–100.0		16 (94.1)	82.9–100.0	
Chemotherapy												
No history of chemotherapy (n = 36)	28 (77.8)	64.2–91.4	0.358*	33 (95.2)	82.6–100.0	1.000	32 (88.9)	78.6–99.2	0.701	36 (100.0)	100.0-100.0	0.368
With history of chemotherapy (n = 21)	14 (66.7)	46.5–86.8		20 (95.2)	86.1–100.0		18 (85.7)	70.7–100.0		20 (95.2)	86.1–100	
Brain radiotherapy												
No history of brain radiotherapy (n = 33)	23 (69.7)	54.0-85.4	0.423*	29 (87.9)	76.7–99.0	0.104	27 (81.8)	68.7–95.0	0.220	32(97.0)	91.2–100	1.000
With history of brain radiotherapy (n = 24)	19 (79.2)	62.9–95.4		24 (100.0)	100.0-100.0		23 (95.8)	97.8–100.0		24(100)	100.0-100.0	
Ceritinib treatment lines												
Ceritinib 1–2 lines (n = 21)	18 (85.7)	70.8–100.0	0.115*	19 (90.5)	77.9–100.0	0.620	18 (85.7)	70.8–100.0	0.701	21 (100.0)	100.0-100.0	1.000
Ceritinib 3–5 lines (n = 36)	24 (66.7)	51.3–82.1		34 (94.4)	87.0-100.0		32 (88.9)	78.6–99.2		35 (97.2)	91.8–100.0	
Brain radiotherapy and TKI												
No brain radiotherapy + No TKI (n = 3)	2 (66.7)	13.3–100.0	0.852	3 (100.0)	100.0-100.0	0.274	1 (33.3)	0.0-86.7	0.044	3 (100.0)	100.0-100.0	1.000
No brain radiotherapy + TKI (n = 30)	21 (70.0)	53.6–86.4		26 (86.7)	74.5–98.8		26 (86.7)	74.5–98.8		29 (96.7)	90.2–100.0	

ORR, overall response rate

DCR, disease control rate

TKI, tyrosine kinase inhibitor

*Chi-square test was used, the other used Fisher-exact test.

NA, not available

Variables	Intracranial efficacy evaluation						Whole body efficacy evaluation					
	ORR			DCR			ORR			DCR		
	N (%)	95% CI	*P value*	N (%)	95% CI	*P value*	N (%)	95% CI	*P value*	N (%)	95% CI	*P value*
Brain radiotherapy + No TKI (n = 1)	1 (100.0)	100.0-100.0		1 (100.0)	100.0-100.0		1 (100.0)	NA		1 (100.0)	100.0-100.0	
Brain radiotherapy + TKI (n = 23)	18 (78.3)	61.4–95.1		23 (100.0)	100.0-100.0		22 (95.6)	87.3–100.0		23 (100.0)	100.0-100.0	
ORR, overall response rate												
DCR, disease control rate												
TKI, tyrosine kinase inhibitor												
*Chi-square test was used, the other used Fisher-exact test.												
NA, not available												

In addition, an analysis on the intracranial and whole body PFSs was performed in this group. By the end of the last follow-up, 15 patients had an intracranial PFS and 12 patients had a whole body PFS, reaching the endpoint. Among these patients, the median intracranial PFS was 8.75 months (95% CI: 6.4–12.9) and the median whole body PFS was 7.6 months (95% CI: 6.1-NE) (Fig. 1). Although the median intracranial PFS and median whole body PFS of all patients were not reached (Fig. 2), the prediction results suggested the median intracranial PFS was non-evaluable (95% CI: 12.9-NE) and the median whole body PFS was non-evaluable (95% CI: 15.2-NE). Therefore, we further estimated the 6-month event-free probability and the 12-month event-free probability of all patients. The estimated 6-month and 12-month event-free probabilities of intracranial lesions were 94.1% (95% CI: 87.8-100.1) and 68.1% (95% CI: 54.1–85.7), respectively, and those of whole body lesions were 94.1% (95% CI: 87.9-100.1) and 74.7% (95% CI: 61.8–90.3), respectively. Further subgroup analysis showed that the estimated 12-month event-free probability of intracranial lesions was relatively higher in patients with prior brain radiotherapy (93.8% vs 47.1%, $P = 0.0006$). (Table 3 *and Supplementary Table 1*)

Table 3
Estimated 6-month and 12-month Event-free Probabilities in Terms of Intracranial and Whole Body Lesions

Variables	Intracranial lesions						Whole body lesions					
	Estimated 6-month event-free probability			Estimated 12-month event-free probability			Estimated 6-month event-free probability			Estimated 12-month event-free probability		
	Rate(%)	95% CI	*P* value	Rate(%)	95% CI	*P* value	Rate(%)	95% CI	*P* value	Rate(%)	95% CI	*P* value
All	94.1	87.8–100.0		68.1	54.1–85.7	-	94.1	87.9–100.0	-	74.7	61.8–90.3	-
Gender												
Male	92.1	82.3–100.0	0.561	67.7	48.6–94.3	0.944	92.3	82.6–100.0	0.572	73.5	54.9–98.2	0.879
Female	96.0	88.6–100.0		68.8	50.3–94.2		96.0	88.6–100.0		75.7	58.8–97.4	
Smoking												
Yes	94.1	83.6–100.0	0.982	62.7	38.9–100.0	0.642	88.2	74.2–100.0	0.296	67.2	44.2–100.0	0.485
No	94.3	86.9–100.0		71.0	55.2–91.3		97.0	91.3–100.0		78.7	64.6–95.8	
Chemotherapy												
Yes	100.0	100.0-100.0	0.069	61.4	40.9–92.0	0.463	95.0	85.9–100.0	0.821	65.6	46.4–92.9	0.264
No	93.9	91.3–100.0		73.3	55.9–96.2		93.5	85.2–100.0		82.0	66.3–100.0	
Brain radiotherapy												
Yes	100.0	100.0-100.0	0.069	93.8	82.6–100.0	0.0006	100.0	100.0-100.0	0.069	93.8	82.6–100	0.008
No	89.7	79.3–100.0		47.1	28.4–78.1		89.8	79.5–100.0		59.6	41.0-86.6	
Ceritinib treatment lines												
1–2 lines	84.0	68.8–100.0	0.061	64.6	41.7–100.0	0.715	88.7	74.9–100.0	0.311	68.2	44.6–100.0	0.581
3–5 lines	100.0	100.0-100.0		70.9	54.6–92.2		97.0	91.3–100.0		77.6	62.9–95.7	
Brain radiotherapy and TKI												
No brain radiotherapy + No TKI (n = 3)	66.7	30.0-100.0	/	NE	NE	/	66.7	30.0-100.0	/	NE	NE	/
No brain radiotherapy + TKI (n = 30)	92.7	83.5–100.0		50.7	30.9–83.2		92.9	83.4–100.0		64.2	44.8–91.9	
Brain radiotherapy + No TKI (n = 1)	100.0	100.0-100.0		NE	NE		100.0	100.0-100.0		NE	NE	
Brain radiotherapy + TKI (n = 23)	100.0	100.0-100.0		93.3	81.5–100.0		100.0	100.0-100.0		93.3	81.5–100.0	
PFS, progression-free survival												
TKI, tyrosine kinase inhibitor												
NE, not evaluable												

Side Effects

Of the 57 patients, 77.2% had adverse drug reactions. The most common AEs were diarrhea (11, 19.3%), nausea (6, 10.5%), vomiting (6, 10.5%) and anorexia (5, 8.8%). Besides, ALT increased in 3 patients and AST increased in 1 patient. Among these patients, a patient suffered from vomiting caused by an intolerance (AE grade 2) three months after receiving ceritinib at a dose of 450 mg QD under fed condition, thus the dose was reduced to 300 mg QD by the clinician after evaluation. Another patient suffered from severe diarrhea (AE grade 3) three months after receiving ceritinib at a dose of 450 mg QD

under fed condition, thus the dose was reduced to 300 mg QD by the clinician after evaluation, and then 150 mg QD so as to ensure tolerability. (Table 1 *and Supplementary Material 1*).

Case

A 74-year-old female patient was admitted to the hospital due to “dyspnea for more than two months”. After admission, contrast-enhanced CT of the chest revealed a 40×28mm lobulated mass in the right lower lobe, pleural thickening, irregular enhancement after contrast injection, enlarged right hilar lymph nodes, and slightly increased bilateral axillary lymph nodes, suggesting the high possibility of lung cancer with hilar lymph node metastases. On March 29, 2017, the patient underwent “video-assisted thoracoscopic right lower lobectomy + systematic lymph node dissection + pleural adhesion cauterization”. Postoperative pathologic examination showed that the right lower lobe > ~ poorly differentiated adenocarcinoma (micropapillary component + solid component), invading the pleura. Immunohistochemistry analysis of adenocarcinoma components revealed ALK-V (+), ROS-1 (-), PDL1 (+, 10%), TTF-1 (+). Starting from May 6, 2017, 4 cycles of AC chemotherapy (propranolol 750mg + nedaplatin 100mg) and 25 times of radiotherapy were completed. On May 15, 2018, chest CT revealed lung cancer recurrence with double pulmonary metastases. Crizotinib was administered orally for more than 10 months. Dizziness, fatigue and discomfort occurred during the treatment. On April 18, 2019, the patient developed headache. Head MRI revealed multiple intracranial metastases. Crizotinib was stopped and ceritinib was administered at a dose of 450mg QD under fed condition for more than 3 months. Headache was obviously relieved during the treatment. Head MRI showed that the multiple intracranial metastases were smaller than before. The efficacy was evaluated as PR. Due to intolerable diarrhea (AE grade 3), the dose was reduced to 300mg QD. Diarrhea and discomfort (AE grade 2) still occurred over the next 2 months, thus the dose was further reduced to 150mg QD, lasting 7.5 months. Head MRI showed that the multiple intracranial metastases continued to shrink, and headache disappeared. The efficacy was evaluated as PR. Blood abnormalities during the treatment included alanine aminotransferase (ALT, 128 IU/L), aspartate aminotransferase (AST, 87 IU/L) and serum carbohydrate antigen 125 (CA125, 81.16 U/ml). (Figure 3)

Discussion

Ceritinib has been put on the market in China for over 2 years. It is the first time to report the preliminary efficacy data of ceritinib administered at a dose of 450 mg QD under fed condition in the treatment of the intracranial metastases of ALK-rearrangement NSCLC patients in China.

By the end of the last follow-up, based on the efficacy statistics of ceritinib (450 mg QD under fed condition) in the treatment of intracranial metastases we observed, the intracranial ORR was 73.7% (95% CI: 62.3–85.1) and the intracranial DCR was 93.0% (95% CI: 86.3–99.6), which are better than those of the ASCEND-7 study (ORR: 73.7% vs 51.5% and DCR: 93.0% vs 85.7%). The ASCEND-7 [13] is the only study aiming to evaluate the efficacy and safety of ceritinib (750 mg QD under fasted condition) in the treatment of advanced ALK-rearrangement NSCLC metastatic to the brain and/or leptomeninges. In addition, our real-world data showed that the estimated 6-month and 12-month event-free probabilities of intracranial lesions were 94.1% (95% CI: 87.8-100.1) and 68.1% (95% CI: 54.1–85.7), respectively. Through subgroup analysis, we found that the estimated 12-month event-free probability of intracranial lesions was relatively higher in patients with prior brain radiotherapy (93.8% vs 47.1%, $P = 0.0006$). By the end of the last follow-up, 15 patients had an intracranial PFS, reaching the endpoint, of which the median intracranial PFS was 8.75 months. Although the median intracranial PFS of all patients was not reached, the prediction results suggested the median intracranial PFS was non-evaluable (95% CI: 12.9-NE). All of the above data have never been reported yet.

Furthermore, in terms of the whole body efficacy evaluation, the ORR and DCR obtained in this study were 87.7% (95% CI: 79.2–96.2) and 98.2% (95% CI: 94.8–100.0), respectively. The preliminary efficacy data in this study are superior to those in the ASCEND-2 study (ORR: 87.7% vs 38.6% and DCR: 98.2% vs 77.1%) [7]. Compared with the Japanese patient subgroup analysis made in the ASCEND-5 study [12], this study obtains a superior DCR (98.2% vs 90.9%). According to the ASCEND-7 study, the estimated 6-month event-free probability of whole body lesions reached 100% (the highest) in the subgroup of prior brain radiotherapy and no prior TKI, and 64.4% (the lowest) in the subgroup of prior brain radiotherapy and prior TKI. The estimated 12-month event-free probability of whole body lesions reached 77.9% (the highest) in the subgroup of no prior brain radiotherapy and no prior TKI, and 67.4% (the lowest) in the subgroup of prior brain radiotherapy and prior TKI. While, the 6-month and 12-month event-free probabilities of whole body lesions estimated in this study were 94.1% (95% CI: 87.9-100.1) and 74.7% (95% CI: 61.8–90.3), respectively. In our subgroup analysis, the estimated 6-month event-free probability of whole body lesions reached 100.0% (the highest) in the subgroup of prior brain radiotherapy and no prior TKI, and 66.7% (the lowest) in the subgroup of no prior brain radiotherapy and no prior TKI. The estimated 12-month event-free probability of whole body lesions reached 93.9% (the highest) in the subgroup of prior brain radiotherapy and prior TKI and 64.2% (the lowest) in the subgroup of no prior brain radiotherapy and prior TKI. It is shown that the ORR, DCR and estimated event-free probability of our real-world data are superior to those of previous studies in terms of whole body efficacy. By the end of the last follow-up in this study, 12 patient had a whole body PFS, reaching the endpoint, of which the median whole body PFS was 7.6 month. Although the median whole body PFS of all patients was not reached, the prediction results suggested that the median whole body PFS was not evaluable (95% CI: 15.2-NE) but definitely longer than the 7.9 months in the ACEND7 study. However, due to the small sample size and short follow-up duration of this study, efficacy data need to be collected continuously in the subsequent follow-ups. In addition, we showed a 74-year-old female patient with ALK rearrangement and intracranial metastasis. This patient reduced the dose of ceritinib to 150 mg QD due to intolerable side effects. After taking 7.5 months, she still obtained continuous remission of intracranial lesions, and the intracranial PFS up to 12.9 months. We thought despite the low concentration of cerebrospinal fluid in ceritinib, IC50 is also the lowest. Therefore, it still showed good intracranial control even when it was reduced to 150 mg QD.

In terms of AEs, we have previously studied the safety of ceritinib (450 mg QD under fed condition) in the treatment of ALK-rearrangement NSCLC patients in China, where a total of 109 patients were enrolled. The incidence rates of all AEs and Grade 3–4 AEs were 89.9% and 22.9%, respectively. The most

common AEs (mainly in Grade 1–2) were diarrhea (60.6%) and elevated transaminases, namely high ALT (38.5%) and high AST (37.6%). Aiming at patients with BM, this study found that 77.2% of them developed AEs, and the most common AEs included diarrhea (19.3%), nausea (10.5%), vomiting (10.5%) and anorexia (8.8%). Besides, ALT increased in 3 patients and AST increased in 1 patient. The incidence rates in this study were generally lower than those in the previous study.

Conclusion

According to our real-world data, ceritinib administered at a dose of 450 mg QD under fed condition to ALK-rearrangement NSCLC patients with BM in China demonstrates superior ORR and DCR, as well as PFS and event-free probability that are expected to be improved. Especially in patients with prior brain radiotherapy, both the estimated 12-month event-free probability of intracranial lesions and the whole body ORR are improved.

Abbreviations

QD: Quaque die/once a day
ALK: Anaplastic lymphoma kinase
NSCLC: Non-small cell lung cancer
ORR: Objective response rate
DCR: Disease control rate
RANO: Response Assessment in Neuro-Oncology
PFS: Progression-free survival
AEs: Adverse events
BM: Brain metastases
NE: Not evaluable
EFP: Event-free probability
TKI: Tyrosine kinase inhibitor
GI: Gastrointestinal
RT-PCR: Reverse transcription-polymerase chain reaction
IHC: Immunohistochemistry
FISH: Fluorescence in situ hybridization
NGS: Next-generation sequencing
RECIST: Response Evaluation Criteria in Solid Tumors
CR: Complete response
PR: Partial response
SD: Stable disease
PD: Progression disease
ALT: Alanine aminotransferase
AST: Aspartate aminotransferase
CA: Carbohydrate antigen
CI: Confidence interval
BRAF V-raf murine sacoma viral oncogene homolog B1

Declarations

Ethics approval and consent to participate: The ethics of this study was approved by the institutional review board of the West China Hospital, Sichuan University (Approval number: 2020-690). The informed consent from patients was waived.

Consent for publication: Not applicable.

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Authors' contributions: Wang K., Huang M.J., Qiu Z.X. provided ideas. Qiu Z.X., Liu C.R., Wang K. analyzed and interpreted the patient data. Xian X.H., Yu M. completed patients' follow-up. Qiu Z.X. was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Figures

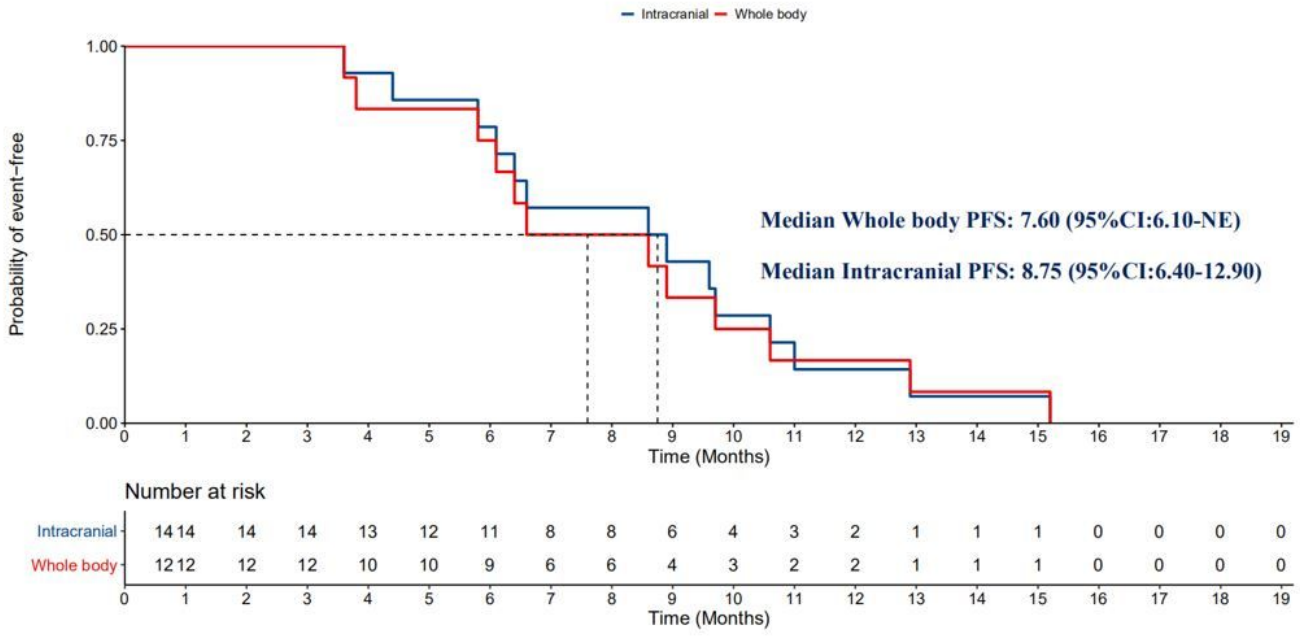

Figure 1

Survival Curve Based on the Median PFS of Patients Reaching the Endpoint Among the patients who reached the endpoint, the median intracranial PFS was 8.75 months (95% CI: 6.4-12.9) and the median whole body PFS was 7.6 months (95% CI: 6.1-NE).

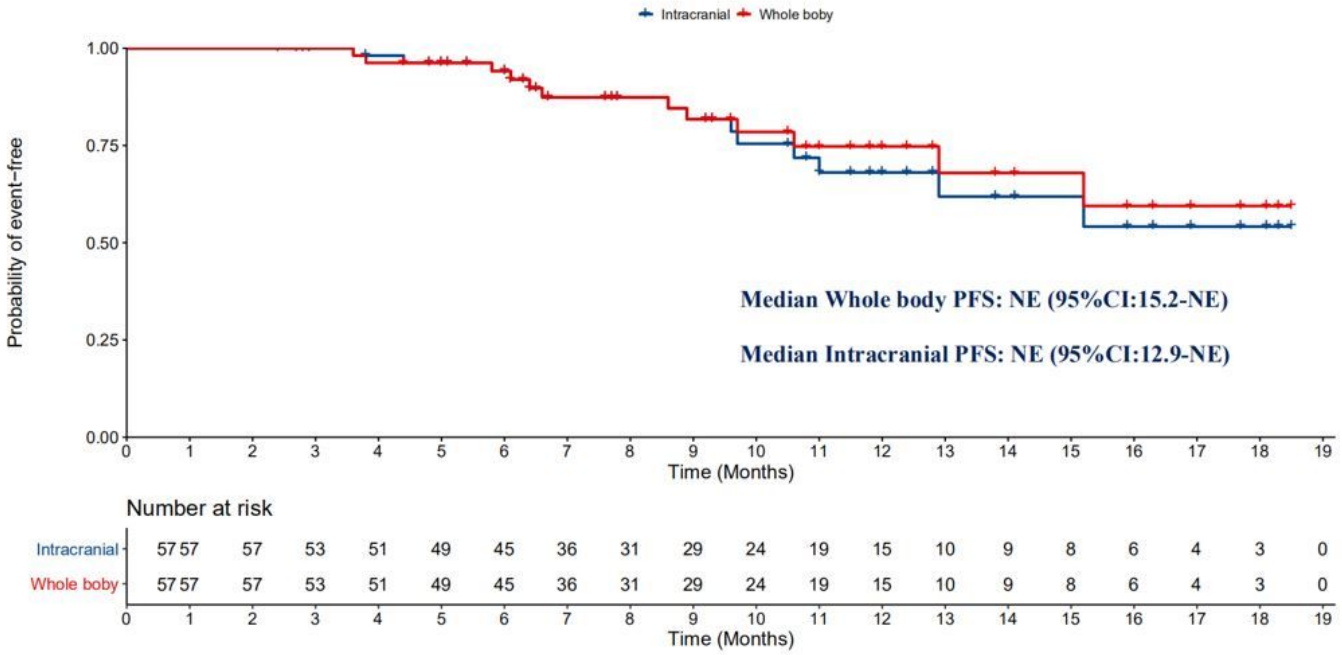

Figure 2

Survival Curve Based on the Median PFS of All Patients The prediction results suggested the median intracranial PFS was non-evaluable (95% CI: 12.9-NE) and the median whole body PFS was non-evaluable (95% CI: 15.2-NE).

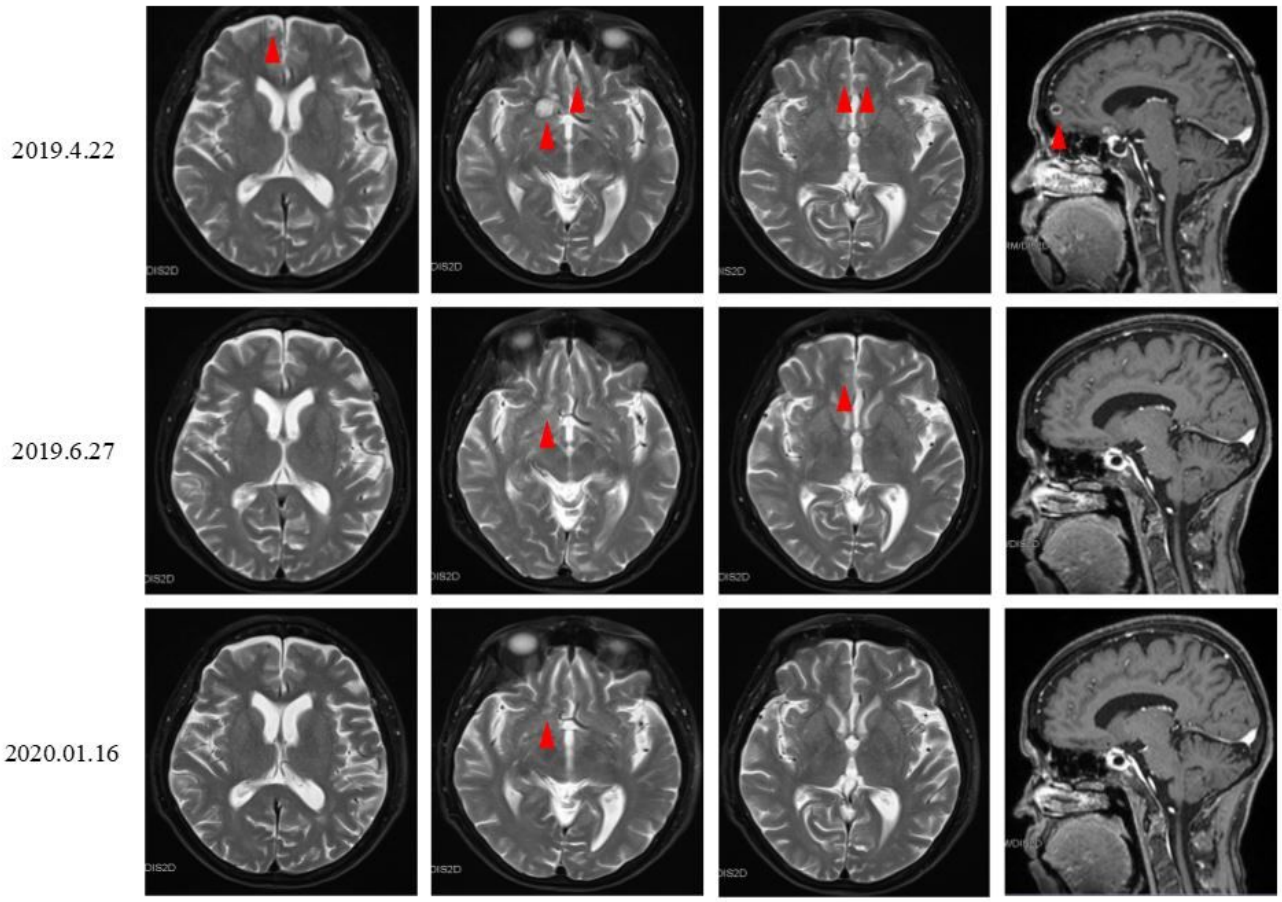

Figure 3

Changes in Patient's Brain MRI Images A 74-year-old female patient with ALK rearrangement and intracranial metastasis. This patient reduced the dose of ceritinib to 150mg QD (from April 23st 2019) due to intolerable side effects. After taking 7.5 months, she still obtained continuous remission of intracranial lesions, and the intracranial PFS up to 12.9 months.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- renamed11b74.pdf
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