The impact of baseline brain metastases on clinical benefits and progression patterns after first-line crizotinib in anaplastic lymphoma kinase-rearranged non-small cell lung cancer

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Abstract

Baseline brain metastasis (BBM) commonly occurs in anaplastic lymphoma kinase (ALK)-rearranged non-small cell lung cancer. Crizotinib prolongs the survival of patients with ALK rearrangement but lacks significant effect on brain metastasis. It remains unclear whether BBM and local therapy affect therapeutic outcomes and progression patterns during crizotinib treatment.

Patients with ALK-positive (immunotherapy) non-small cell lung cancer were screened from West China Hospital between May 2013 and January 2019. A total of 155 patients were enrolled in this research, with entirely recorded statistics to analyze retrospectively.

Baseline brain metastasis occurred in 64 patients (55.7%). Thirty-seven patients received local therapy, while 24 patients did not. We observed higher overall response rate in patients receiving local therapy (70.2% vs. 41.7%, P = .026), but no statistical difference was found in median progression free survival (mPFS) (12.0 months vs 13.0 months, P = .633). A significantly shorter mPFS was found in patients not receiving local treatment compared with the 16.5 months mPFS of patients without BBM (P = .029). Intracranial progressions were recorded in 35 patients with BBM (71%) and 16 patients who don't have (30%). As for extracranial progression, there is a higher occurrence rate (75.5%) in patients who had baseline extracranial metastases versus 49.0% in BBM patients. A significantly higher occurrence rate of multiple progression was noted in patients with BBM (14/49 vs. 6/53).

Baseline intracranial metastasis changes the location and number of progressions after the first-line crizotinib and results in poor prognosis. There is no evidence that local treatment for brain metastasis had a protective effect on intracranial progression.

Abbreviations: ALK = anaplastic lymphoma kinase, BBM = baseline brain metastasis, CR = complete remission, DCR = disease control rate, mPFS = median progression-free survival, NSCLC = non-small cell lung cancer, ORR = overall response rate, PR = partial response, TKI = tyrosine kinase inhibitor.

Keywords: anaplastic lymphoma kinase rearrangement, baseline brain metastasis, crizotinib, non-small cell lung cancer, progression pattern

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1. Introduction

Lung cancer has been the most common cancer due to the highest incidence and death rate in China.[1] For non-small cell lung cancer (NSCLC), especially non-smokers, driver gene alterations are discovered in most cases. Anaplastic lymphoma kinase (ALK) rearrangement is the second common gene aberration, which accounts for nearly 5% in NSCLC.[2] As ALK inhibitors have been developed, prognoses of "ALK-positive" patients have changed fundamentally. Crizotinib is the first-generation tyrosine kinase inhibitor (TKI) targeting ALK protein and achieved 10.7 months progression-free survival (PFS), 74% overall response rate (ORR) in first-line treatment,[3] which promoted the recommendation of crizotinib as the first-line therapy. In NSCLC, brain metastasis is particularly common, approximately 10% of newly diagnosed patients with NSCLC have brain metastasis, and 25–40% happened brain metastases over the disease course.[4] Compared with wild type NSCLC, ALK-positive NSCLC is prone to have more advanced stages and metastases, while the brain is the most common site.[5] However, the low CSF-to-plasma ratio and transduction of P-glycoprotein (ABCB1/ABCG2) limited crizotinib's effect on intracranial lesions.[6–8] For the above reasons, the brain is also the most common progression site in crizotinib-resistant patients, which accounts for nearly 40% after the first or second-line crizotinib treatment.[9,10] In patients with baseline brain metastases, a higher incidence rate of

brain progression was reported.[11] Local therapy is 1 of the most effective means for the control of brain metastasis and plays an important role in the treatment of NSCLC.[12] The combination of local therapy and crizotinib is believed to increase crizotinib concentration in the brain[13] and allow patients with local progression to continue to benefit from crizotinib.[14,15] For patients with baseline brain metastasis, some researchers reported local therapy could slow the occurrence of brain progression. Still, far less is known about the effect of baseline brain metastasis, and local therapy on therapeutic outcome and progression patterns in crizotinib treated ALK-rearranged NSCLC. We designed this study to determine whether brain metastasis in baseline and probably appended local therapy are related to therapeutic benefits of crizotinib and progression pattern in ALK-positive NSCLC.

2. Methods

2.1. Patient cohort

This retrospective study was approved by the Ethic Committee of West China Hospital (Sichuan University, Chengdu, China). Patients aged 18 years or older with NSCLC who had received crizotinib as first-line treatment during the period from May 2013 to January 2019 at west china hospital were identified. ALK expression detection was measured by ALK immunohistochemistry (Ventana ALK D5F3). Patients' medical records, including age at diagnosis, gender, comorbidities, baseline brain metastasis, other metastatic locations, treatment modalities, time to progression, sites, and the number of progressions were reviewed and recorded. The initial staging was finished by CT, MRI and bone scans. All patients took oral crizotinib 250 mg per day, other treatments were used following physicians' advice and patients' will. Imaging follow-up was arranged every 3 months or whenever necessary according to physicians' discretion. Response Evaluation Criteria in Solid Tumors version 1.1 was used for evaluating treatment responses. Response was defined as complete remission (CR), partial response (PR), stable disease (SD), or progressive disease. The ORR was referred to the proportion of patients with CR and PR to treatment, while disease control rate (DCR) was defined as the proportion of patients with CR, PR and stable disease. Duration from the beginning of crizotinib to first-time disease progression was defined as progression-free survival (PFS).

2.2. Statistical methods

We used SPSS statistics 23.0 for data analysis. Independent-samples t test and chi-square tests were performed. Kaplan–Meier method was adopted for drawing and description of survival data. P-values of < 0.05 were considered to indicate a statistically significant difference.

3. Results

3.1. Baseline features of patients

A total of 155 patients, including 76 males and 79 females, were included in this study. The patients were divided into 2 groups according to whether patients have baseline brain metastasis (BBM). Baseline characteristics were summarized in Table 1. The first group, group A, included 64 patients with baseline brain metastasis, 30 (46.9%) patients were males and 34 (53.1%)

Table 1

Baseline characteristics of patients with ALK-rearranged NSCLC.

Characteristics	Group A BBM (n=64) (n, %)	Group B NO BBM (n=91) (n, %)	P
Age at diagnosis (median/range)	49 (24–69)	51 (30–78)	.053
Sex			
Man	30 (46.9)	46 (50.5)	.652
Woman	34 (53.1)	45 (49.5)	
Smoker	15 (23.4)	21 (23.1)	.958
Stage			
III	0 (0)	7 (7.7)	.060
IV	64 (100.0)	84 (92.3)	
Histology			
Adenocarcinoma	58 (90.6)	80 (87.9)	.340
Squamous cell carcinoma	0 (0)	3 (3.3)	
Others	6 (9.3)	8 (8.8)	

ALK = anaplastic lymphoma kinase, BBM = baseline brain metastasis, NSCLC = non-small cell lung cancer.

females, the median age at the time of crizotinib treatment is 49 (range spanned 24–69 years), all patients were stage IV. There were 58 (90.6%) adenocarcinoma cases, 0 of squamous cell carcinoma and 6 (9.3%) of other histology types in group A. The second group, group B, included 91 patients without baseline brain metastasis, 46 (50.5%) patients were males and 45 (49.5%) females, the median age at the time of crizotinib treatment is 51 (range spanned 30–78 years), seven patients were stage III, 84 were stage IV. There were 80 (87.9%) cases of adenocarcinoma, 3 (3.3%) of squamous cell carcinoma and 8 (8.8%) of other histology types in group B. There was no significant difference in baseline characteristics between 2 groups.

3.2. General curative effect of crizotinib in patients

All patients in this study were treated with 250 mg oral crizotinib. The curative effect of crizotinib in our patients was summarized in Table 2. In group A, curative effects of 61 patients were recorded. The ORR was 59.0%, and the DCR was 98.4%. In group B, curative effects of 85 patients were recorded. The ORR was 43.5%, and the DCR was 96.5%. Considering local treatment is generally used in patients with BBM and subdivision can help us clarify whether local therapies have impact on our patients, patients who had brain metastases were further divided into 2 groups according to the application of local therapies (radiotherapy or surgical treatment). We observed a 70.2% ORR in patients with locally treated BBM, significantly higher than 41.7% of patients with untreated BBM (P=.026).

In the distribution of efficacy evaluations, no significant difference was found between patients with BBM (group A) and those without BBM (group B) (P=0.151). There was also no statistical difference between patients with locally treated BBM and patients with untreated BBM (P=.056). However, the difference was significant between locally treated patients and group B (P=.017) (Table 2).

3.3. Therapeutic outcomes of crizotinib and progression patterns

Progression occurred in 49 patients who had BBM and 53 patients who not. The median PFS (mPFS) of group A was 12 months (95%CI 9.857–14.143), that of group B was 16.5 months (95%CI 10.975–22.025). The difference between group

Table 2

Therapeutic evaluation of crizotinib.

Efficacy evaluation	BBM (n, %)			No BBM (n, %) (85)
	Local therapy (37)	No local therapy (24)	Total (61)	
CR	0 (0)	0 (0)	0 (0)	0 (0)
PR	26 (70.2)	10 (41.7)	36 (59.0)	37 (43.5)
SD	11 (29.7)	13 (54.2)	24 (39.3)	46 (54.1)
PD	0 (0)	1 (4.2)	1 (1.6)	3 (3.5)
ORR	70.2%	41.7%	59.0%	43.5%
DCR	100%	95.8%	98.4%	96.5%
P		.056		.151
P (patients with treated BBM and patients without BBM)				.017
P (patients with untreated BBM and patients without BBM)				.983

BBM = baseline brain metastasis, CR = complete remission, PR = partial response, SD = stable disease, PD = progressive disease, ORR = overall response rate, DCR = disease control rate.

A and B was statistically significant ($P = .021$) (Fig. 1A). The results showed that patients without BBM had significantly longer mPFS than those who had. We compared the median mPFS of locally treated patients with that of the others. For patients in Group A, mPFS of patients treated with local therapy is 13 months (95%CI 10.510–15.490) while 12 months (95%CI 7.104–16.896) in those not treated, without a statistical difference ($P = .633$) (Fig. 1B). When compared to 16.5 months in subgroups of patients with BBM, shorter survival and significant differences were discovered in those not receiving local treatment (16.5 m $vs.$ 12.0 m, $P = .029$) (Fig. 1C). No significant statistical difference was found in mPFS between group B and patients who received local therapy ($P = .111$) (Fig. 1D).

When crizotinib resistance occurred, progression was recorded in 49 patients with BBM and 53 patients without BBM. Significantly statistical difference of progression site and number in patients with BBM and without BBM was revealed ($P < .001$). Intracranial progressions occurred in 35 (71%) patients with BBM and 16 (30%) patients who don't have. As for extracranial progressions, there is a higher occurrence rate (75.5%) in patients who had only baseline extracranial metastases versus 49.0% of patients with BBM. Additionally, patients with baseline intracranial metastases are prone to progress in multiple organs (14/49 vs 6/53), especially in extracranial organs (4/14 vs 3/37). As for the local therapy, the difference between subgroups of
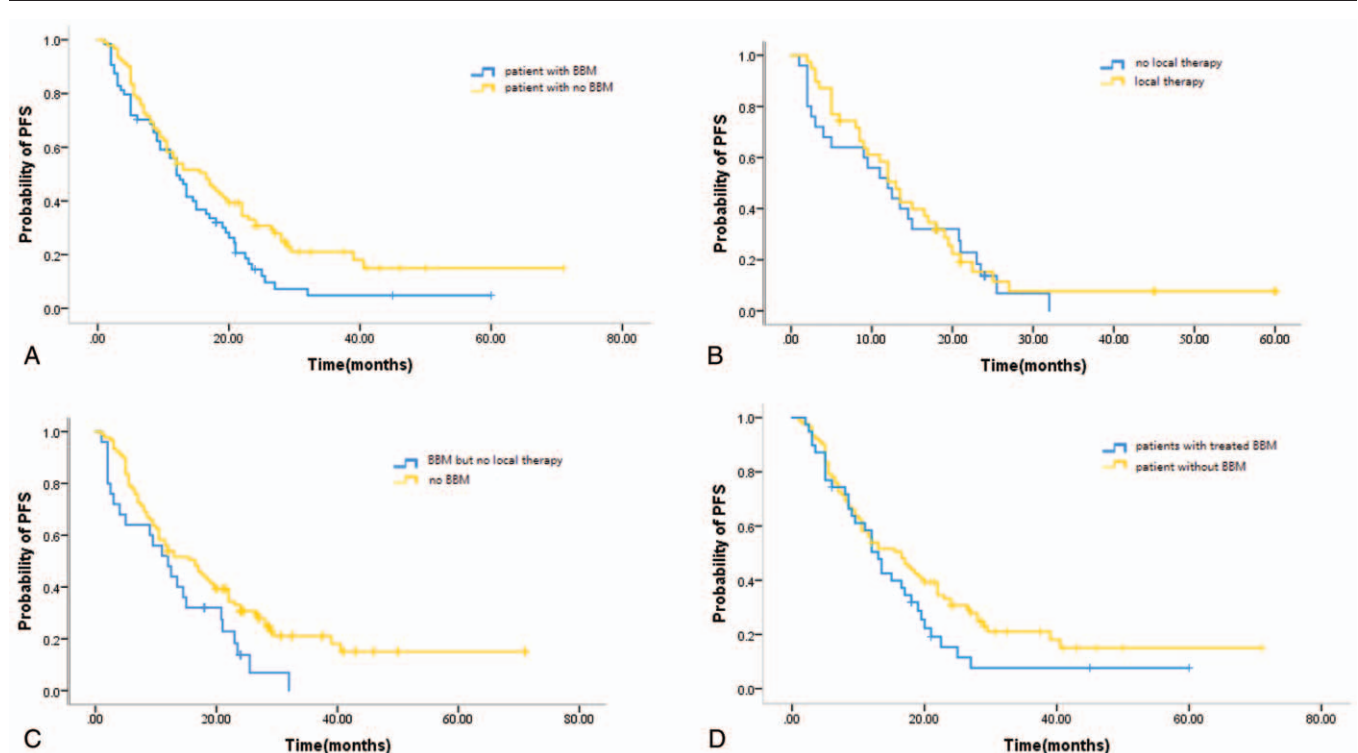
Figure 1. Progression-free survival of patients. Figure 1 A Comparison between group A and group B. (A, n=64; B, n=91; p=0.021); Figure 1B Comparison between baseline brain metastasis patients performed and not performed local therapy. (performed, n=39; not performed, n=25; p=0.633); Figure 1C Comparison between baseline brain metastasis patients who haven't performed local therapy and patients who don't have brain metastasis. (without baseline brain metastasis, n=91; not performed, n=25; p=0.029); Figure 1D Comparison between baseline brain metastasis patients who performed local therapy and patients who don't have brain metastasis (without baseline brain metastasis, n=91; performed, n=39; p=0.111).

Table 3

Progression site and number of patients.

Progressions	Group A BBM (n=64)			Group B No BBM (n=91)
	Local therapies	No local therapies	Total	
Progression occurrence	29	20	49	53
Intercranial site (%)	15 (52)	10 (50)	25 (51)	13 (24)
Inter- and extracranial site (%)	5 (17)	5 (25)	10 (20)	3 (6)
Extracranial oligo-metastasis (%)	6 (21)	4 (20)	10 (20)	34 (64)
Extracranial multi-metastasis (%)	3 (10)	1 (5)	4 (8)	3 (6)
P		.856		<.001

BBM = baseline brain metastasis.

patients with BBM is not statistically significant ($P=.856$) (Table 3 and Fig. 2)

4. Discussion

In ALK-positive NSCLC patients, the brain is both a common metastasis site and a common site of progression. Brain invasion has a significant impact on survival. According to existing studies, nearly 40% of enrolled ALK-rearranged patients have progressive brain metastases at the time of death,[16] indicating that management of central nervous system progression is especially crucial for ALK-positive patients. Compared with second-generation ALK TKIs (such as alectinib, ceritinib, etc), crizotinib, the first-generation TKI, has a low efficacy to brain lesions.[17] Passive diffusion restriction and P-glycoprotein's active efflux may account for this difference.[8]

There is no statistically significant difference in survival between crizotinib-alectinib sequential therapy and full-time alectinib in the first-line treatment.[18] Considering the complex resistance mechanisms of second-generation ALK TKIs and
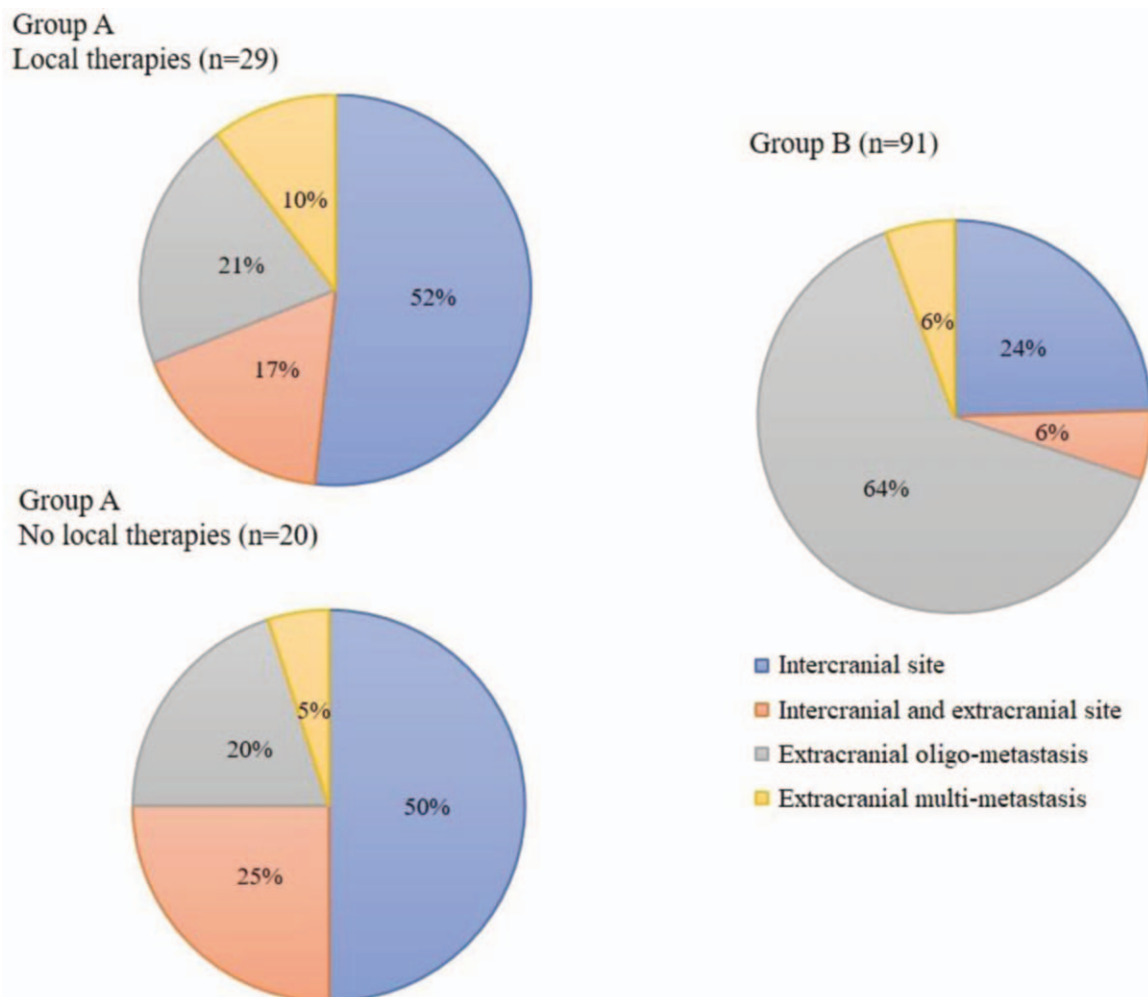

Figure 2. Progression patterns.

crizotinib's price advantage, crizotinib is still the most commonly used ALK TKI in China, which emphasizes the importance of research about crizotinib in patients with brain metastasis. In our study, the synchronous application of crizotinib and local therapy did not delay the occurrence of progression. However, it achieved higher response rates to crizotinib. Meanwhile, BBM indeed changes the site and the number of progressions.

In our research, BBM affects patients' ability to benefit from crizotinib (first-generation ALK TKI), which especially increased the ratio of brain progression. Between patients with BBM and patients without BBM, the difference of crizotinib response is not statistically significant ($P = .151$). Considering that local treatment is a significant confounding factor, we compared not-treated ones in group A with group B. Again, no significant difference was observed ($P = .983$). This result further confirmed the existence of BBM didn't have an impact on drug response. For patients without BBM, either crizotinib or alectinib promise a longer mPFS of first-line treatment than that for patients with BBM, and it's more marked in crizotinib. According to the statistic from clinical trials,[15,19] a spread of fifty percent was shown in mPFS between patients with BBM and who not (7.4 months vs 14.7 months). Based on our data, 4.5 months' disparity proves BBM point to poor survival, and the difference is existent regardless of the application of local therapy ($P = .021$). Although the difference of mPFS between locally treated patients and patients without BBM is not statistically significant ($P = .111$), the curve shows a promising tendency that patients' survival without BBM is better than patients with treated BBM. Results of some earlier studies support the local therapy before administration of targeted drug could promise a longer PFS.[13] One small sample study (n = 25) finished by Chinese researchers shows brain radiation before crizotinib achieved a longer mPFS among patients with BBM.[20] Reasons for this improvement may include radiation before targeted therapy affects blood-brain-barrier, breaks P-glycoprotein, and increases the infiltration of crizotinib in the brain.[21] In our research, local therapy didn't change patients' survival obviously ($P = .633$), like clinical trial profile1005, profile1007, profile1014 also didn't answer whether radiation impacts PFS. It should be noted that while most patients received radiation and targeted therapy during the same period, and we failed to determine their order unambiguously.

Local therapy was reported to improve the control rate of intracranial lesions and even delay brain progression.[22] In profile1005 and profile 1007, patients who accepted brain radiation therapy before second-line crizotinib achieved better disease control and longer intracranial time to progression. Our study shows that local therapy increases ORR in patients with BBM (70.2% vs. 41.7%, $P = .026$), which proves local therapy has a positive impact on the control of brain lesions, even the control of the whole body is also improved. It should be noted that the difference in tumor response between treated group A patients and group B had statistical meaning ($P = .017$) as well as the difference of ORR ($P = .006$). Although local treatment can achieve local control in patients with BBM, in principle, there is no evidence that local therapy has an impact on the efficacy of target therapy. There are 2 possible reasons for the higher PR. The first is about reducing tumor load. Since surgery or radiation destroys lesions in the brain, lower tumor load helps targeted drugs play a greater role in treating limited residual focuses. Another reason is that local therapy may release tumor-specific antigens and then activate the immune system.[7]

Study for progression patterns can help doctors predict progression sites and make an early intervention. For chemotherapy, a retrospective study has suggested that disease progression after first-line chemotherapy mostly occurs at sites where baseline metastasis existed.[23] In patients with BBM and experienced disease progression, nearly 70% happened brain metastasis, far above patients without BBM. The difference between patients with and without BBM is obvious ($P < .001$), strongly suggesting that BBM is an important factor in predicting tumor progression sites. A much smaller brain metastasis proportion may be related to the integrity of blood-brain-barrier. In addition to the impact on brain recurrence, BBM also changes the number and presence of extracranial metastases. Two subgroups of group A (treated or not treated) don't have a statistically significant difference ($P = .856$), which can't prove local treatment impacts the occurrence of intra or extracranial progression. Altogether, our results showed that patients without brain metastases at baseline prefer to happen extracranial metastasis when crizotinib resistant; intracranial progression is more common in patients who have baseline brain metastasis. Local therapies have no impact on this situation.

Our study also had some limitations. First, this research is a retrospective study, so the quality of medical information was inherently limited, and the full extent of our study was constrained. Second, our patients were not stratified according to the type of local therapy for further analysis. Third, we didn't perform a targeted analysis basing on the number and position of brain metastasis. Finally, we only calculated the survival time until patients got the first progression, while there were no records for total PFS in first-line therapy and OS.

Taken together, baseline brain metastasis before first-line crizotinib treatment could indicate a high possibility of intracranial progression and shorter progression-free survival when resistance occurs. Local treatment for brain metastasis cannot reverse this trend but may help patients acquire a better degree in evaluating efficacy. Monitoring brain progression is equally important for patients with BBM, regardless of whether local treatment was given or not. More detailed follow-up should be considered for different metastases at baseline.

Author contributions

Yuqi Chen and Chengzhi Cai prepared the manuscript and the literature search; Chengzhi Cai and Yanying Li collected and assembled clinical data; Yuqi Chen and Chengzhi Cai conducted statistical analysis; All authors read and approved the final manuscript.

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References

[1] Cao M, Chen W. Epidemiology of lung cancer in China. Thorac Cancer 2019;10:3–7.

[2] Pikor LA, Ramnarine VR, Lam S, et al. Genetic alterations defining NSCLC subtypes and their therapeutic implications. Lung Cancer 2013;82:179–89.

[3] Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 2014;371:2167–77.

[4] Abdallah SM, Wong A. Brain metastases in non-small-cell lung cancer: are tyrosine kinase inhibitors and checkpoint inhibitors now viable options? Curr Oncol 2018;25(Suppl 1):S103–14.

[5] Rangachari D, Yamaguchi N, VanderLaan PA, et al. Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. Lung Cancer 2015;88:108–11.

[6] Costa DB, Kobayashi S, Pandya SS, et al. CSF concentration of the anaplastic lymphoma kinase inhibitor crizotinib. J Clin Oncol 2011;29:e443–5.

[7] El Chediak A, Shamseddine A, Bodgi L, et al. Optimizing tumor immune response through combination of radiation and immunotherapy. Med Oncol 2017;34:165.

[8] Wrona A, Dziadziuszko R, Jassem J. Management of brain metastases in non-small cell lung cancer in the era of tyrosine kinase inhibitors. Cancer Treat Rev 2018.

[9] Leduc C, Besse B. Clinical benefit of continuing ALK inhibition with crizotinib beyond initial disease progression in patients with advanced ALK-positive NSCLC. Ann Oncol 2014;25:2092.

[10] Duruisseaux M, Besse B, Cadranel J, et al. Overall survival with crizotinib and next-generation ALK inhibitors in ALK-positive non-small-cell lung cancer (IFCT-1302 CLINALK): a French nationwide cohort retrospective study. Oncotarget 2017;8:21903–17.

[11] Lei YY, Yang JJ, Zhong WZ, et al. Clinical efficacy of crizotinib in Chinese patients with ALK-positive non-small cell lung cancer with brain metastases. J Thorac Dis 2015;7:1181–8.

[12] Tsakonas G, De Petris L, Ekman S. Management of brain metastasized non-small cell lung cancer (NSCLC) - From local treatment to new systemic therapies. Cancer Treat Rev 2017.

[13] Metro G, Lunardi G, Floridi P, et al. CSF Concentration of Crizotinib in Two ALK-Positive Non-Small-Cell Lung Cancer Patients with CNS Metastases Deriving Clinical Benefit from Treatment. J Thorac Oncol 2015;10:e26–7.

[14] Hong X, Chen Q, Ding L, et al. Clinical benefit of continuing crizotinib therapy after initial disease progression in Chinese patients with advanced ALK-rearranged non-small-cell lung cancer. Oncotarget 2017;8:41631–40.

[15] Yoshida T, Oya Y, Tanaka K, et al. Clinical impact of crizotinib on central nervous system progression in ALK-positive non-small lung cancer. Lung Cancer 2016;97:43–7.

[16] Johung KL, Yeh N, Desai NB, et al. Extended survival and prognostic factors for patients with alk-rearranged non-small-cell lung cancer and brain metastasis. J Clin Oncol 2016;34:123–9.

[17] Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. N Engl J Med 2017;377:829–38.

[18] Ito K, Hataji O, Kobayashi H, et al. Sequential therapy with crizotinib and alectinib in ALK-rearranged non-small cell lung cancer-a multicenter retrospective study. J Thorac Oncol 2017;12:390–6.

[19] Camidge DR, Dziadziuszko R, Peters S, et al. Updated Efficacy and Safety Data and Impact of the EML4-ALK Fusion Variant on the Efficacy of Alectinib in Untreated ALK-Positive Advanced Non-Small Cell Lung Cancer in the Global Phase III ALEX Study [published correction appears in J Thorac Oncol. 2019 Nov;14(11):2023]. J Thorac Oncol 2019;14:1233–43.

[20] Ni J, Li G, Yang X, et al. Optimal timing and clinical value of radiotherapy in advanced ALK-rearranged non-small cell lung cancer with or without baseline brain metastases: implications from pattern of failure analyses. Radiat Oncol 2019;14:44.

[21] Bianco C, Tortora G, Bianco R, et al. Enhancement of antitumor activity of ionizing radiation by combined treatment with the selective epidermal growth factor receptor-tyrosine kinase inhibitor ZD1839 (Iressa). Clin Cancer Res 2002;8:3250–8.

[22] Costa DB, Shaw AT, Ou SH, et al. Clinical experience with crizotinib in patients with advanced ALK-rearranged non-small-cell lung cancer and brain metastases. J Clin Oncol 2015;33:1881–8.

[23] Rusthoven KE, Hammerman SF, Kavanagh BD, et al. Is there a role for consolidative stereotactic body radiation therapy following first-line systemic therapy for metastatic lung cancer? A patterns-of-failure analysis. Acta Oncol 2009;48:578–83.