Original Article

TP53 mutations predict for poor survival in *ALK* rearrangement lung adenocarcinoma patients treated with crizotinib

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Background: Advanced non-small cell lung cancer (NSCLC) patients who harbor anaplastic lymphoma kinase (*ALK*) rearrangement are sensitive to an ALK inhibitor (crizotinib), but not all *ALK*-positive patients benefit equally from crizotinib treatment. We analyze the impact of *TP53* mutations on response to crizotinib in patients with *ALK* rearrangement NSCLC.

Methods: Sixty-six *ALK* rearrangement NSCLC patients receiving crizotinib were analyzed. 21 cases were detected successfully by the next generation sequencing validation FFPE before crizotinib. *TP53* mutations were evaluated in 8 patients in relation to disease control rate (DCR), objective response rate (ORR), progression-free survival (PFS) and overall survival (OS).

Results: *TP53* mutations were observed in 2 (25.00%), 1 (12.50%), 1 (12.50%) and 4 (50.00%) patients in exons 5, 6, 7 and 8, respectively. The majority of patients were male (75.00%, 6/8), less than 65 years old (62.50%, 5/8) and never smokers (75.00%, 6/8). ORR and DCR for crizotinib in the entire case series were 61.90% and 71.43%, respectively. Statistically significant difference was observed in terms of PFS and OS between *TP53* gene wild group and mutation group patients (P=0.038, P=0.021, respectively).

Conclusions: *TP53* mutations reduce responsiveness to crizotinib and worsen prognosis in *ALK* rearrangement NSCLC patients.

Keywords: Non-small cell lung cancer (NSCLC); anaplastic lymphoma kinase (*ALK*); *TP53*; crizotinib

Submitted Jan 17, 2018. Accepted for publication Apr 09, 2018.
doi: 10.21037/jtd.2018.04.98
View this article at: http://dx.doi.org/10.21037/jtd.2018.04.98

Introduction

Lung cancer is one of the most common cancers and the leading cause of cancer death in the world (1). In the past decades, advances in molecular analysis and the development of targeted therapies have changed the identification of oncogenic drivers, the treatment and the survival for lung cancer. Anaplastic lymphoma kinase (*ALK*) rearrangement is one of the driver genes which detected in 3–7% of patients with non-small cell lung cancer (NSCLC) (2). For these patients, ALK tyrosine kinase inhibitors (TKIs) have been developed. Crizotinib is a first generation ALK-TKI that shows efficacy in the treatment of *ALK* rearrangement NSCLC (3). According to clinical studies of crizotinib (PROFILE 1005, PROFILE 1007, PROFILE1014), the major populations were lung adenocarcinoma (ADC) and an objective response rate (ORR) to crizotinib is approximately 60% and its median progression-free survival (PFS) is nearly 10 months (4). However, it is known that many cases ultimately acquired resistance to crizotinib (5). In addition, about 30% *ALK*-positive patients to the treatment of crizotinib demonstrate primary resistance which early progressive disease (PD) after the first month of treatment (6,7).

The mechanisms of acquired resistance included secondary mutations or copy number gain (CNG) in the ALK kinase domain and up regulation of bypass signaling pathways (8). However, to our knowledge, the mechanisms of primary resistance to ALK inhibitor for these patients remain elusive. And only some primary resistance mechanisms have been hypothesized, such as mutations of the EGFR pathway and BIM polymorphisms (9-11).

According to reports, the tumor suppressor of *TP53* gene mutations occur in approximately 25–50% NSCLC patients (12,13). Ma *et al.* (14) has demonstrated regardless of *EGFR* and *KRAS* mutation status, non-disruptive *TP53* mutations are independent markers of shorter overall survival (OS) in patients with advanced NSCLC. There is preclinical evidence in the human NSCLC cell lines NCI-H1299 and A549 showed a relationship between *TP53* gene mutations and responsiveness to TKIs (15). Canale *et al.* (16) had reported that *TP53* mutations reduce responsiveness to EGFR-TKIs and poor prognosis in *EGFR*-mutated NSCLC patients.

However, the relationship of *TP53* gene status and the efficacy of crizotinib in *ALK* positive NSCLC patients was unclear. In this study we proposed to evaluate the role of *TP53* mutation in *ALK* rearrangement advanced NSCLC patients that received crizotinib treatment. We analyzed the status of *TP53* gene and its association with the effect of crizotinib in Chinese patients with *ALK*-positive NSCLC.

Methods

Patients

Eligible patients were required to have pathologically confirmed NSCLC and sufficient tissue for analysis. Clinical and pathologic data prospectively collected for analyses included age at diagnosis, gender, smoking status, and stage according to the new International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society multidisciplinary classification. This study was approved by the ethics committee of Fujian Provincial Cancer Hospital, Fujian Medical University Cancer Hospital, Fuzhou Fujian, China, and a written informed consent was obtained from each participant before the initiation of any study-related procedure.

Targeted next-generation sequencing

A total of 66 ALK positive patients treated with crizotinib. However, 28 specimens were not enough and 38 specimens were evaluated by NGS. For 38 patients, including parts of patients with *ALK* positive pts treatment before crizotinib, targeted region capture combined NGS was successfully performed in 21 patients. Genomic DNA sequencing libraries were prepared using the protocols recommended by the Illumina TruSeq DNA Library Preparation Kit. For samples close to the minimum input requirement, additional pre-capture PCR cycles were performed to generate sufficient PCR product for hybridization. The libraries were hybridized to custom-designed probes (Integrated DNA Technology) including all exons of 170 genes and selected intron of *ALK*, *RET* and *ROS1* for the detection of Genomic rearrangements. DNA sequencing was performed on a HiSeq3000 sequencing system (Illumina, San Diego, CA) with 2×75 bp paired-end reads. The reads were aligned to the human genome build GRCh37 using BWA (a Burrows-Wheeler aligner). Somatic single nucleotide variant (sSNV) and indel calls were generated using MuTect and GATK, respectively. Somatic copy number alterations were identified with CONTRA. Genomic rearrangements were identified by the software developed in house analyzing chimeric read pairs.

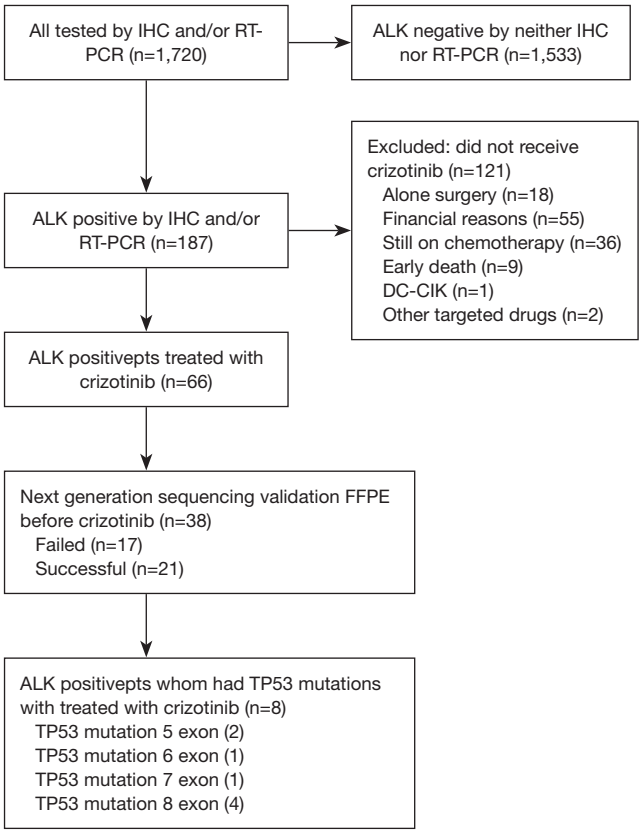

Figure 1 Flow chart of the study design.

Response evaluation

Patients received crizotinib treatment (250 mg, twice daily) and had clinical data available including general characteristics, treatment efficacy and adverse reactions to treatment. Imaging data were independently reviewed by authors to evaluate their treatment responses according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 PFS was calculated from the date of initiating targeted drugs treatment to radiologic or clinical observation of disease progression.

Statistical analyses

The response rate among subgroups and survival was described with Kaplan-Meier methodology and the log-rank test was used to compare survival among subgroups. Statistical analysis was performed using SPSS version 19.0 software (IBM, Armonk, NY, USA). All P values were 2-sided, and a P value of <0.05 was considered statistically significant.

Results

Patient characteristics

From July 2013 to May 2016, a total of 1,720 patients were enrolled in this study. Among them, 187 (10.87%) were identified as *ALK*-positive and 66 of them received oral crizotinib. Because of the tissue sample insufficient and specimen quality testing, 21 of them was successfully performed by targeted region capture combined NGS. The flow chart of the study design is shown in *Figure 1*. Clinic-pathological characteristics of patients were reported in *Table 1*. The majority of patients were male (52.38%, 11/21), less than 65 years old (61.90%, 13/21) and never smokers (80.95%, 17/21). All patients had a diagnosis of ADC (100%, 21/21). All patients received crizotinib (100%, 21/21). NGS detection found many accompanied genes, including mTOR pathway (*PIK3CA* p.E545K, *FBXW7* p.R505L, *STK11* p.D194E, *PTEN* p.R130G, *MTOR* p.E1799K, *MTOR* p.P2273L), RAS pathway (*NRAS* p.G12D), *TP53* exon 5 (p.R158L, p.H179R), exon 6 (p.R213Q), exon 7 (p.G245S), exon 8 (p.Y271*, p.V272M, p.R273H, p.C277F) (*Figure 2*), *SMARCA4* (p.R451L, p.E882K, p.R469W), *AR* (p.E355K), *APC* (p.P2559L, p.T1910S), *CCND1* (p.M82V), *CTNNB1* (p.S45P), *BRAF* (p.D594G), *RB1* (p.G449E) and *NF1* (p.A2437S).

TP53 mutation

Out of the 21 patients with successfully targeted region capture combined NGS, 8 (38.10%) patients showed a *TP53* mutation: 25.00% (2/8) were on exon 5, 12.50% (1/8) on exon 6, 12.50% (1/8) on exon 7, and 50.00% (4/8) on exon 8 (*Table 1*). The majority of patients were male (75.00%, 6/8), less than 65 years old (62.50%, 5/8) and never smokers (75.00%, 6/8). There were no significant differences noted with regard to age, sex, smoking history, ECOG PS, histology, number of previous treatments, between patients with and without the *TP53* gene (*Table 2*).

TP53 mutation and response to crizotinib

ORR and disease control rate (DCR) for crizotinib in the entire case series were 61.90% and 71.43%, respectively. *TP53* gene wild group was found to be significantly associated with a higher ORR and DCR to crizotinib with respect to *TP53* gene mutation group. An ORR of 76.92% and a DCR of 84.62% were observed in patients with *TP53*

Table 1 Follow-up survival of 21 patients with NSCLC with *TP53* gene status received crizotinib by targeted next-generation sequencing

Case No.	Sex/age (years)	Smoking status	Targeted NGS	PFS (months)	OS (months)
1	M/59	No	*EML4-ALK*, TP53 p.V272M, *SMARCA4* p.R451L	1.0	15.3
2	M/56	No	*EML4-ALK*, TP53 p.R273H, *CCND1* p.M82V	1.5	12.6
3	M/71	Yes	*EML4-ALK*, TP53 p.H179R, *PIK3CA* p.E545K	1.0	17.2
4	M/76	No	*EML4-ALK*, TP53 p.C277F, *NRAS* p.G12D, *PTEN* p.R130G	1.0	8.4
5	F/58	No	*EML4-ALK*, TP53 p. Y271*	5.1	25.6
6	F/69	No	*EML4-ALK*, TP53 p.R158L	9.3	36.2
7	M/39	Yes	*EML4-ALK*, TP53 p.G245S, *SMARCA4* p.E882K, *MTOR* p.E1799K	13.9	21.4+
8	M/36	No	*EML4-ALK*, TP53 p.R213Q, *SMARCA4* p.R469W, *MTOR* p.P2273L	7.3	34.6
9	M/68	Yes	*FBXO36-ALK*, *NF1* p.A2437S	21.2	46.7+
10	F/56	No	*EML4-ALK*, *AR* p.E355K	10.4	38.5
11	F/41	No	*EML4-AL*K, *APC* p.P2559L, *APC* p.T1910S	15.1	47.8
12	F/76	No	*EML4-ALK*	7.6	29.3
13	F/53	No	*EML4-ALK*	11.4	34.2
14	M/71	Yes	*EML4-ALK*, *CTNNB1* p.S45P	8.3	22.9
15	M/44	No	*EML4-ALK*	13.7	23.5+
16	F/39	No	*EML4-ALK*	9.5	32.3
17	F/75	No	*EML4-ALK*	6.4	16.8
18	M/56	No	*EML4-ALK, RB1* p.G449E	10.6	17.8+
19	M/55	No	*EML4-ALK*, *FBXW7* p.R505L	12.6	36.4
20	F/45	No	*EML4-ALK*, *STK11* p.D194E	6.9	30.9
21	F/63	No	*EML4-ALK*, *BRAF* p.D594G	5.7	39.2

*, representation oversight (NA). NSCLC, non-small lung cancer cell; M, male; F, female; NGS, next-generation sequencing; PFS, progression-free survival; OS, overall survival.

gene wild group, and an ORR of 37.50% and a DCR of 50.00% were observed in patients with *TP53* gene mutation group (*Table 3*).

TP53 mutation and survival

Statistically significant difference was observed in terms of PFS and OS between *TP53* gene wild group and mutation group patients (P=0.038, P=0.021, respectively). The PFS in *TP53* gene mutation group patients was shorter than that in *TP53* gene wild group (3.3 *vs.* 10.4 months). The OS of *TP53* gene mutation group was poorer than *TP53* gene wild group (21.4 *vs.* 34.2 months). PFS and OS of *TP53* gene on exon 5 were 9.3, 36.2 months and 1.0, 17.2 months), respectively; PFS and OS of *TP53* gene on exon 6 were 7.3 and 34.6 months; PFS and OS of *TP53* gene on exon 7 were 13.9 months, more than 21.4 months; PFS and OS of *TP53* gene on exon 8 were 5.1 and 25.6 months, 1.0 and 15.3 months, 1.5 and 12.6 months, and 1.0 and 8.4 months, respectively (*Table 1*, *Figure 3*).

Discussion

To our knowledge, our study is the first to explore the relationship between *TP53* gene mutation status and the effect of crizotinib in Chinese patients with *ALK*-positive advanced

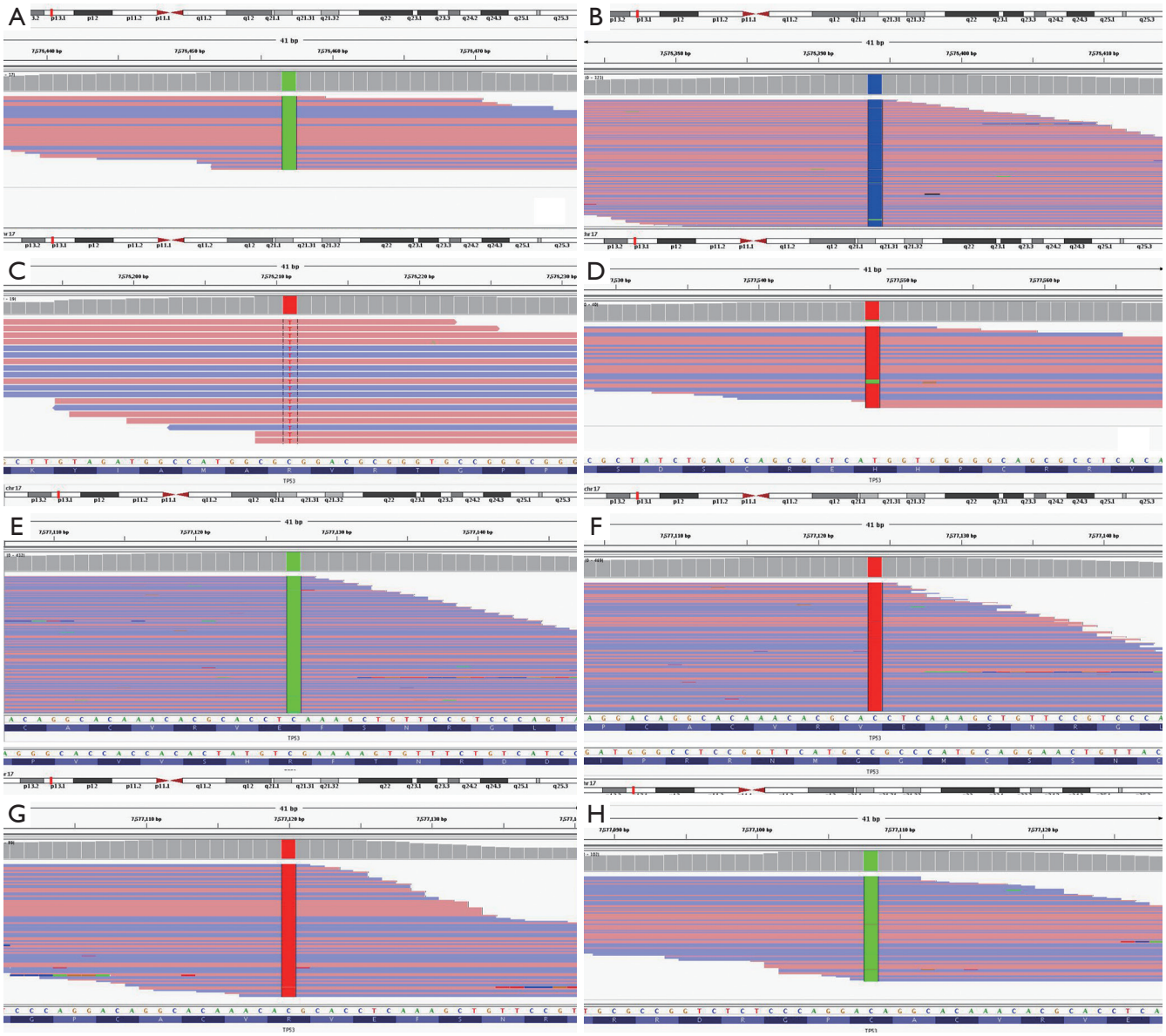

Figure 2 Targeted next-generation sequencing of *TP53* gene IGV (A) exon 5 R158L, (B) exon 5 H179R, (C) exon 6 R213Q, (D) exon 7 G245S, (E) exon 8 E271*, (F) exon 8 V272M, (G) exon 8 R273H, (H) exon 8 C277F). *, representation oversight (NA).

NSCLC. NSCLC patients with *ALK* rearrangement are highly sensitive to crizotinib. Nowadays, a series of trial data (phase I–III) involving in ALK positive advanced NSCLC patients demonstrated the efficacy of crizotinib was good and adverse reactions could be tolerated (4,17,18). The data from East Asian patients also showed the ORR to crizotinib was 88% and its median PFS was 11.1 months (19). Unfortunately, some *ALK*-positive patients have been with shorter PFS after treatment with crizotinib which might be presence primary resistance to crizotinib. Up to now, the mechanisms of acquired resistance to ALK inhibitors can be divided into 2 types: ALK dominant or ALK non-dominant. ALK dominant includes secondary mutations and CNG in the *ALK* gene; ALK non-dominant includes the activation of bypass tracks, such as *EGFR*, *MET*, *KIT*, *KRAS* and *IGF-1R* (8). However, it is unclear that the causes of short PFS in ALK positive patients after crizotinib treatment. Some studies have explored the mechanisms of crizotinib primary resistance. Zhang *et al.* (9) reported patients with the BIM deletion polymorphism had a significantly shorter PFS (182

vs. 377 days, P=0.008) and lower ORR (44.4% *vs.* 81.7%, P=0.041) compared with those without in 69 *ALK/ROS1* positive patients with crizotinib treatment. Doebele *et al.* (10) reported that a patient received re-biopsy after 61 days on crizotinib which showed stable disease. This biopsy demonstrated a lack of an *ALK* gene rearrangement by FISH, but the presence of an *EGFR* exon 21 mutation by direct sequencing. There is still a lack in the mechanisms reports of primary resistance to crizotinib with *ALK*-positive NSCLC.

Table 2 The clinical characteristics of *ALK* positive NSCLC with *TP53* gene status

Variable	*TP53* status		P
	Positive (n=8)	Negative (n=13)	
Age, median [range], years	58 [36–76]	57 [39–76]	1.000
<65	5	9	
≥65	3	4	
Sex			0.239
Male	6	5	
Female	2	8	
Smoking history			0.802
Non-smoker	7	13	
Smoker	1	0	
ECOG PS			0.688
0–1	8	11	
≥2	0	2	
Histology			0.802
Adenocarcinoma	7	13	
Non-adenocarcinoma	1	0	
No. of previous treatments			1.000
0–1	3	5	
≥2	5	8	

ALK, anaplastic lymphoma kinase; NSCLC, non-small lung cancer cell; ECOG PS, Eastern Cooperative Oncology Group performance status.

It is reported that *TP53* gene mutations occur in approximately 50% of lung cancer patients and are more common in squamous cell lung carcinoma than in lung ADC (12). In the lung ADC cancer, TP53 mutation rates ranges from 25% to 40% (20,21). In addition, some reports showed the prevalence of ALK-rearranged with p53 mutation was about 9.1% (1/11) to 28.6% (2/7) (22,23). In our study, we observed a mutation percentage of 38.1% in 21 *ALK* positive ADC patients. Therefore, coexisting with TP53 mutations in ALK positive ADC patients is still further to explore in a larger research, especially for comparing ALK rearrangement patients with ALK negative patients. The p53 protein regulates cellular response to a variety of cellular stress signals by inducing cell cycle arrest (24). The normal function disruption of p53 disrupts this cellular response, leading to possible malignant cell transformation. Gene mutations lead to a loss of p53 functions, however non-disruptive mutations could remain some of the p53 protein functional properties (25). Therefore, we analyzed the relationship of efficacy and survival between *ALK* positive and *TP53* gene status with crizotinib therapy.

It is the first time to put forward that patients with *TP53* gene mutation can no response to crizotinib. In our study, *TP53* gene mutation group was found to be significantly associated with a lower ORR (76.92% *vs.* 37.50%) and DCR (50.00% *vs.* 84.62%) to crizotinib with respect to *TP53* gene wild group. In addition, significant shorter PFS (3.3 *vs.* 10.4 months, P=0.038) and OS (21.4 *vs.* 34.2 months, P=0.021) were observed in patients with *TP53* gene mutation group patients than *TP53* gene mutation group. In particular, 4 of 8 *TP53* mutated patients showed PD within two months of crizotinib therapy. Therefore, we think *ALK* positive patients with *TP53* gene mutation would influence the efficacy of crizotinib treatment. Likewise, in *EGFR* mutation populations, Canale *et al.* (16) also demonstrated *TP53* mutations were associated with a significantly lower DCR

Table 3 Efficacy of crizotinib in patients with 21 cases of *ALK* positive NSCLC positive patients with *TP53* gene status

TP53 gene status	CR	PR	SD	PD	ORR/%	DCR/%	PFS (months)
TP53 wild	0	10	1	2	76.92	84.62	10.4
TP53 mutation	0	3	1	4	37.50	50.00	3.3

ALK, anaplastic lymphoma kinase; NSCLC, non-small lung cancer cell; CR, complete response; PR, partial response; SD, stable disease; PD, progression disease; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival.

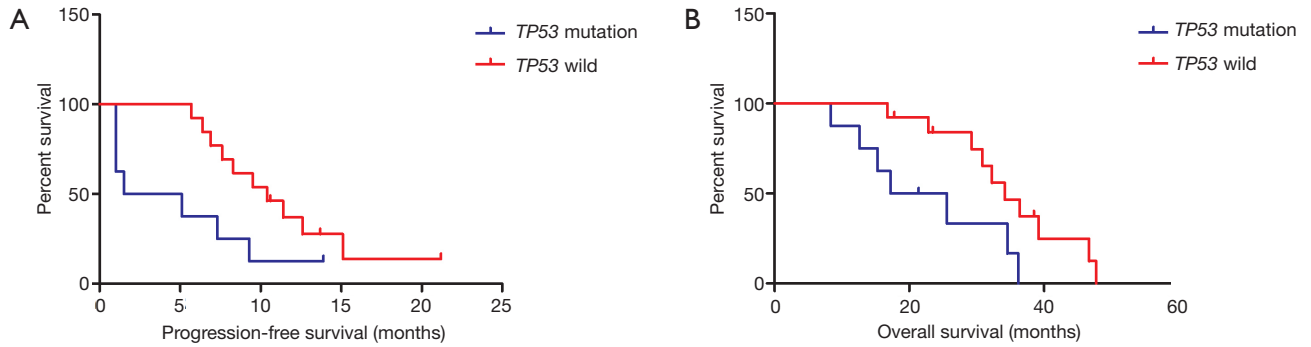

Figure 3 Progression-free survival (A) and overall survival (B) of crizotinib in anaplastic lymphoma kinase (*ALK*) positive adenocarcinoma.

respect to wild patients. However, no statistically significant difference was observed in terms of PFS and OS between two groups. Their most significant result was that *TP53* exon 8 mutation was associated with the worst prognosis. Our study also found *ALK* positive patients with *TP53* exon 8 mutation were poorer survival than other mutation types. The *TP53* mutant type has been found to be an important factor for gefitinib-induced apoptosis in NSCLC cell lines and reduces gefitinib-induced apoptosis (26). We think that *TP53* could have a role as prognostic factor to ALK inhibitors, rather than predictive factor. In the future, we should carry out well-designed prospective multicenter studies to demonstrate the correlation between *TP53* gene status and ALK inhibitors including other generations in patients with *ALK*-positive disease.

We also recognize that there are several limitations to our study. First, due to a small sample, the conclusions should be bias a certain extent. Second, this was a retrospective study, and therefore selection bias was inevitable. Hence, future research will continue to increase the population in the hope of reducing the bias to some extent.

In conclusion, we described the relationship between *TP53* gene and the efficacy of crizotinib in *ALK* rearrangement patients. And the *TP53* mutant patients were associated with poor ORR and shorter PFS. However, more work and further studies should be performed to explore the significance of *TP53* gene in patients with *ALK*-positive NSCLC who were treated with ALK inhibitors.

Acknowledgements

Funding: This study was supported in part by grants from the National Clinical Key Specialty Construction Program (2013); Leading Project Foundation of Science Department of Fujian Province (2016Y0019); Leading Project Foundation of Science Department of Fujian Province (2015Y0011).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the ethics committee of Fujian Provincial Cancer Hospital, Fujian Medical University Cancer Hospital, Fuzhou Fujian, China, and a written informed consent was obtained from each participant before the initiation of any study-related procedure.

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Cite this article as: Wang WX, Xu CW, Chen YP, Liu W, Zhong LH, Chen FF, Zhuang W, Huang YJ, Huang ZZ, Chen RR, Guan YF, Yi X, Lv TF, Zhu WF, Lu JP, Wang XJ, Shi Y, Lin XD, Chen G, Song Y. *TP53* mutations predict for poor survival in *ALK* rearrangement lung adenocarcinoma patients treated with crizotinib. J Thorac Dis 2018;10(5):2991-2998. doi: 10.21037/jtd.2018.04.98

