Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 10, Issue, 02, pp.65571-65575, February, 2018

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

CLINICAL EFFECTS OF EGFR INHIBITORS ON EGFR EXON19 AND 21 MUTATIONSIN LUNG CANCER

[1]He-Ping Lin, [2]Xiao-Diao Zhang, [2]Xi-xian Lou and [3,*]Chang Cai

[1]Wenzhou Medical University, Wenzhou, China, 325035
[2]Department of Respiratory Medicine, the Third Affiliated Hospital of Wenzhou Medical University, Wenzhou, China, 325200
[3]Department of Respiratory and Critical Care Medicine, the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China, 325200

ARTICLE INFO

Article History:
Received 26th November, 2017
Received in revised form
23rd December, 2017
Accepted 08th January, 2018
Published online 28th February, 2018

Key words:
EGFR inhibitors,
EGFR 19 exon mutation
21 Exon,
Lung Cancer.

ABSTRACT

Objective: This study is to investigate the clinical efficacy of EGFR inhibitors on mutations in lung cancer patients with EGFR 19 and 21 exons.
Methods: A total of 178 lung cancer patients were selected from January 2012 to September 2016 in this study and their EGFR mutations were analyzed by Real-time PCR. Then the patients were divided into Exon 19 group (n = 89) and Exon 21 group (n = 89) according to EGFR mutation status, and being treated with EGFR inhibitor erlotinib. Finally, the clinical efficacy and safety of the two groups were analyzed.
Results: The average age of patients in Exon 19 group was lower than that of Exon21 group (P <0.05). The response Rate (RR) of the Exon19 group was 51.69%, while the RR of the Exon21 group was 48.31% (P> 0.05). The median overall survival (OS) were 56.00 months (95CI%: 54.054,57.946) and 49.00 months(95CI%: 47.682, 50.316)in the Exon 19 group and Exon21 group respectively. The median Progression-free Survival (PFS) were 50.00 (95CI%: 47.529,52.471) and 41.00 (95CI%: 38.738,43.262)in the Exon 19 group and Exon21 group respectively. Furthermore, the incidence of adverse reactions was similar between the two groups (P> 0.05).
Conclusion: Lung cancer patients with EGFR 19 exon mutation are younger than those with EGFR 21 exon mutations, which may get more benefits from EGFR inhibitor therapy.

Copyright © 2018, He-Ping Lin et al. *This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.*

Citation: He-Ping Lin, Xiao-Diao Zhang, Xi-xian Lou and Chang Cai, 2018. "Clinical Effects of EGFR Inhibitors on EGFR exon19 and 21 Mutationsin Lung Cancer", *International Journal of Current Research*, 10, (02), 65571-65575.

INTRODUCTION

Lung cancer is one of the highest mortality malignancies in the world, and its traditional therapies include surgery and radiotherapy (Chen wanqing *et al*., 2013). However, in the process of obtaining certain therapeutic effect, the treatment of this method is not only prone to serious adverse reactions, but also easy to induce drug resistance and affect follow-up treatment (Zhang tan*et al*., 2013). Therefore, the clinical research needs to continuously explore the new lung cancer treatment plan. Epidermal growth factor receptor (epidermal substituting factor receptor, EGFR) is a hot topic in recent years, and a lot of studies (Wang yaqi*et al*., 2015; Luo Djing*et al*., 2013; Tian chunqin, 2017) confirm that EGFR activity is closely related to the growth, proliferation, invasion and metastasis of malignant tumors.

Corresponding author: **Chang Cai,**
Department of Respiratory and Critical Care Medicine, the First Affiliated Hospitalof Wenzhou Medical University, Wenzhou, China, 325200.

However, the latest study (Takeda, 2014) shows that EGFR-TKIs can be used to treat EGFR mutation patients, and there may be a difference in efficacy, which may be related to the EGFR mutation site. EGFR mutation sites included 18-21 exons, with 19 and 21 exons mutations most common. So far, however, has not yet been about EGFR TKIs treatment different EGFR mutation in lung cancer patients with large sample study, and on different sites of EGFR mutations in lung cancer patients with EGFR TKIs - the control study treatment effect is also very few. In this study, 178 patients with lung cancer were included in the study, and EGFR-TKIs Erlotianil was treated to analyze the clinical difference between EGFR 19 mutations and 21 mutated lung cancer in EGFR inhibitors. To provide a reference for patients with EGFR mutation lung cancer. The specific report is as follows.

MATERIALS AND METHODS

Patients

From January 2010 to September 2012, there were 178 cases of lung cancer in our hospital, including 99 males (55.62%) and 79 female cases (44.38%).Age 45~75 years old, average age (58.98 ± 7.93); Smoking 64 cases (35.96%) and no smoking 114 (64.04%); The maximum diameter of tumor was 1.24~6.43cm and the mean maximum diameter 3.69. Histological type: 133 cases of adenocarcinoma (74.72%), 40 cases of squamous cell carcinoma (22.47%), and 5 cases of large cell lung cancer (2.81%);Differentiation degree: low differentiation 101 cases (56.74%), middle and high differentiation 77 cases (43.26%);TNM stage Ⅰ ~ Ⅱ 78 cases (43.82%), Ⅲ ~ Ⅳ 100 cases (56.18%);Lymph node metastasis was 66 cases (37.08%) and no lymph node metastasis was 112 (62.92%).

The EGFR mutation was analyzed by real-time fluorescence quantitative polymerase chain reaction (PCR).EGFR mutation was divided into EGFR 19 mutations (Exon 19) group and EGFR 19 mutation (Exon21) group.All patients were confirmed by pathology or biopsy by biopsy, informed consent of the study, and informed consent of the patients and their families. None of the patients had any anti-tumor treatment before the treatment; Its general condition score (PS) 0 ~ 4 points; It is expected to survive more than 3 months.

METHODS

Erlotini (production company: Shanghai roche pharmaceutical co., LTD.) was given to both groups. National prescription: J20090116;Standard:) oral treatment, 150mg each time, 1 time per day, the patient was given 60min before the morning meal. Treatment for 4 weeks was 1 session, and both groups were treated for at least 2 weeks. During the treatment, blood routine, liver and kidney function, electrocardiogram and CT chest examination were regularly examined.After the two groups were discharged from the hospital, the patients were given a regular follow-up period of 6~60 months. The routine biochemical indexes, adverse drug reactions and survival cycles of two groups were monitored during the follow-up period. The total of 178 patients were included in the study, and the success rate was 100%.

Observation indexes

General information is used to study the patient's general information by means of questionnaire method and interview. Including name, sex, age, contact information, household registration, living environment, smoking, maximum diameter of tumor, histologic type, differentiation degree, TNM staging, lymph node metastasis, etc.The clinical efficacy evaluation criterion (RECIST) is divided into total relief (CR), partial relief (PR), stability (SD) and progress (PD).CR was maintained for more than 4 weeks for tumor lesions.The reduction degree of PR was greater than 30% for the total length of focal length, and the maintenance time was over 4 weeks.SD was less than 30% or increase of the total size of the focal length. < 20%, the duration of the SD was over 4 weeks; The total increase of PD was greater than 20%, and its absolute value increased by 5mm or new lesions.The survival time OS begins with the patient receiving the treatment starting date, until the end of follow-up or death; The PFS begins with the patient receiving treatment and ends at the end of follow-up or the apparent progression of the disease. For safety reference, the national cancer institute general standard (NCICT3.0) was used to evaluate the treatment of adverse reactions.

Statistical processing

Using SPSS17.0 software to perform statistical analysis of the data, the mean value of the metering data was calculated using the mean value of the mean number (x-plus or minus s), which was expressed by t-test, and the utilization rate of count data (%) indicated that x2 test was used. Kaplan-meier curves were used in the survival cycle of the two groups, and $P<0.05$ was statistically significant.

RESULTS

Comparison of general information of the two groups of patients

Among the 178 patients selected in this study, 99 were male (55.62%) and 79 female (44.38%).Age 45~75 years old, average age (58.98 + 7.93);TNM stage Ⅰ ~ Ⅱ 78 cases (43.82%), Ⅲ ~ Ⅳ 100 cases (56.18%);Lymph node metastasis was 66 cases (37.08%) and no lymph node metastasis was 112 (62.92%).The patients were divided into Exon 19 (n =89) and Exon21 group (n =89) according to the different mutated subtypes of EGFR, and the general data of the two groups were compared.

The differences in age distribution between the two groups were significant, and the age of Exon 19 group was lower than that of Exon21 group ($P < 0.05$).In the two groups, there were similar levels of gender, smoking, tumor maximum diameter, histological type, differentiation degree, TNM stage and lymph node metastasis, and the differences were not statistically significant ($P > 0.05$).Result as shown in table 1.

Comparison of clinical efficacy between the two groups

The CR 13 patients in the Exon19 group were 13, PR 33, SD 22, and PD 21, RR was 51.69%. The CR 10 patients in Exon21 group were 10, PR 33, SD 24, PD 22, RR was 48.31 %. There was no significant difference in RR between the two groups, and there was no statistical significance (P BBB 0 0.05). Result as shown in table 2.

The effect of long-term treatment of two groups of patients

The median OS median of patients in the Exon19 group was 56.00 (95CI % : 54.054, 57.946), and the median PFS was 50.00 (95CI % : 47.529, 52.471).The median OS median of patients in Exon21 group was 49.00 (95CI % : 47.684, 50.316), and the median PFS was 41.00 (95CI % : 38.738, 43.262).The OS and PFS of the Exon19 group were higher than the Exon21 group (x2 = 11.600, 8.986, P= 0.000, 0.003).See figure 1.

Incidence of adverse reactions in the two groups

The incidence of adverse reactions was similar in both groups, with no significant difference (P BBB 0 0.05). See table 4.

Table 1. Comparison of general demographic data of two groups of patients

	Exon 19 Group（n=89）	Exon21 Group（n=89）	*P*
Gender			
Male	52（58.43）	47（52.81）	0.451
Female	37（41.57）	42（47.19）	
Age			
45~60	49（55.06）	35（39.33）	0.036
≥60	40（44.94）	54（60.67）	
Smoking			
Yes	33（37.08）	31（34.83）	0.755
No	56（62.92）	58（65.17）	
Maximum diameter of tumor（cm）			
<3	34（38.20）	40（44.94）	0.362
≥3	55（61.80）	49（55.06）	
Histological types			
Adenocarcinoma	62（69.66）	71（79.78）	0.300
Squamous cell carcinoma	24（26.97）	16（17.98）	
Large cell lung cancer	3（3.37）	2（2.25）	
Differentiation			
Low differentiation	49（55.06）	52（58.43）	0.650
Medium and high differentiation	40（44.94）	37（41.57）	
TNM Staging			
Ⅰ~Ⅱ	37（41.57）	41（46.07）	0.546
Ⅲ~Ⅳ	52（58.43）	48（53.93）	
Lymph node metastasis			
Yes	30（33.71）	36（40.45）	0.352
No	59（66.29）	53（59.55）	

Table 2. Results of recent treatment of patients

Group	n	CR	PR	SD	PD
Exon19 Ⅰ~Ⅱ	32	6（18.75）	17（53.13）	5（15.63）	4（12.50）
Exon19 Ⅲ~Ⅳ	57	7（12.28）	16（28.07）	17（29.82）	17（29.82）
Exon21 Ⅰ~Ⅱ	37	7（18.92）	18（48.65）	6（16.22）	6（16.22）
Exon21 Ⅲ~Ⅳ	52	3（5.77）	15（28.85）	18（34.62）	16（30.77）

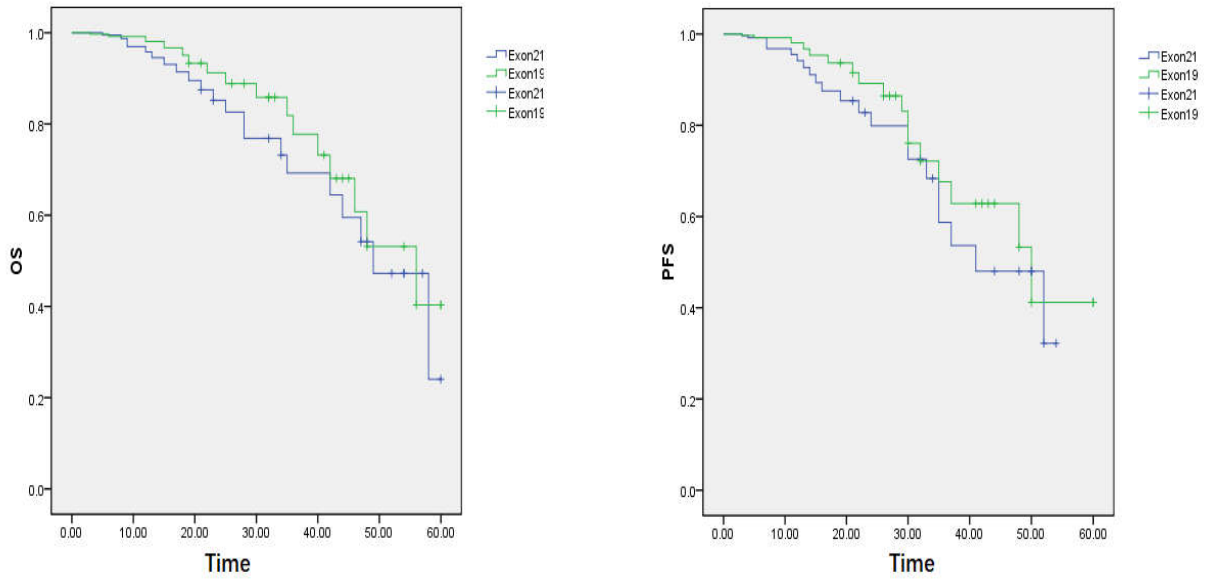

Table 4. Incidence of adverse reactions in the two groups

Group	Rash			Diarrhea			Mild liver Dysfunction	Mild white blood cell decline
	Ⅰ	Ⅱ	Ⅲ	Ⅰ	Ⅱ	Ⅲ		
Exon19	23	2	1	20	4	0	7	8
Exon21	22	3	2	21	4	1	7	6
P	0.863	0.650	0.560	0.859	1.000	0.316	1.000	0.578

DISCUSSION

EGFR belongs to the family of receptor tyrosine kinase transmembrane glycoprotein, involving the extracellular ligand binding area, tyrosine kinase in the cell area, the anchoring zone connected cells inside and outside across a cell membrane, etc., its ligands including the epidermal growth factor, transforming growth factors, such as double adjustable protein (Measure *et al*., 2016). When EGFR binds with ligand, EGFR can form dimer with itself or other members of the ERbB family, the tyrosine kinase region of phosphorylated cells, and initiate downstream signaling cascade. Or in cells, the cell membrane expression is reduced, and the feedback regulating signal is transmitted (Maemondo, 2014). At present, studies (Wang Yan *et al*., 2012; Xie Yilin *et al*., 2015) have confirmed that EGFR can participate in the proliferation, invasion and metastasis of tumor cells through Ras-Raf-MAPKs pathway, PI3K/Akt pathway, PLC- gamma-dag/ip3-pkc pathway and JAK/STAT pathway. This means that EGFR is one of the targets of lung cancer treatment, egfr-tki is the key to lung cancer treatment, while EGFR tyrosine kinase coding region gene mutation is a necessary precondition for egfr-tki to treat lung cancer (Krawczy*et al*., 2013).

The most common mutation type of EGFR (Togashi*et al*., 2012) was the most common mutation type of EGFR, which was the most common type of mutation in EGFR. Through this study, 89 patients with Exon19 and the analysis of 89 patients with Exon21 EGFR mutation type and the relationship between clinical pathological features, according to EGFR mutation types associated with age, Exon 19 patients younger than Exon21 group ($P < 0.05$); The types of mutations are not related to gender, smoking, the maximum diameter of tumor, histological type, differentiation degree, TNM staging, lymph node metastasis, etc., which is consistent with (Liu Renwang*et al*., 2014).However, jiang wenrong (Jiang Wenrong, 2013) pointed out that the EGFR mutation type had no correlation with gender and age ($P< 0.05$), which was controversial with the study in this paper. This may be related to the area, sample size and so on. Therefore, the correlation between EGFR mutation type and clinicopathology of lung cancer patients should be further discussed.

Erlotini, as an EGFR-TKI preparation, blocks the binding site of adenosine triphosphate in cell receptors and prevents downstream signal transmission and plays an anti-tumor role. Moreover, it has the advantages of high efficiency, high specificity, good tolerance of patients and low toxicity, which can significantly prolong the survival time of EGFR-TKI sensitive patients and improve their quality of life (Lee*et al*., 2013; Nakade *et al*., 2014). In this study, erlotini was used as EGFR-TKI preparation to analyze the clinical effect of EGFR-TKI on different types of EGFR mutation. There was no significant difference in RR between the two groups, and there was no statistically significant difference (P BBB 0 0.05), but the OS and PFS of the Exon19 group were higher than the Exon21 group (x2 = 11.600, 8.986, P= 0.000, 0.003). This may be related to the dynamics of TKI drugs in different subtypes of patients, or to the sensitivity of patients with different subtypes to TKI drugs. Zhu (2008) study, using Western blotting the treatment detection of EGFR, Erk and Akt phosphorylation of inhibition, the treatment noted in exon 19 lack of EGFR mutations in cells, Erk and Akt phosphorylation higher inhibition, is helpful to produce the stagnation of the cell cycle G1.

The survival time of the NSCLC19 exon of the NSCLC19 patients was longer than that in the patients with the mutation of exon of the NSCLC19, and the difference was statistically significant ($P < 0.05$). In the study of Sordella (18), because of the mutation of 19 exons, the phosphorylation of EGFR molecule is located in the alpha c-helix, and the exon mutation of 21 exons leads to the phosphorylation of EGFR molecule in the a-loop region. There are significant differences in the downstream signaling pathways activated by the two mutations, and some of the tyrosine residues in L858R mutations are highly phosphorylated, and the response rate of TKIs is low. Lee (2015) *et al*., including 8 clinical studies including NEJ002, EURTAC and LUXLUNG6, total 1,649 patients.It was pointed out that there was a longer PFS (11.8 months vs 10.0 months, P= 0.006) after the mutation of the exon mutation was more than 21 exon L858R mutation. But the domestic study, Liu Renwang (Liu Renwang *et al*., 2014) research in traditional first-line adjuvant chemotherapy treatment postoperatively, show 19 exons mutations in patients with a median survival period and exon 21 group no statistical difference (1051 vs 1076 days, $P = 0.566$). In this study, the study suggested that patients with NSCLC had more benefit in treatment of EGFR-TKI, but their benefits were slightly different in the treatment scheme.

In this study, the main adverse reactions of both groups were rash, diarrhea, mild liver dysfunction, and mild leukocyte reduction. And adverse reaction rate is close to two groups of patients ($P < 0.05$) it shows EGFR inhibitors for the treatment of EGFR exon 19 and 21 exon safety of mutations in lung cancer patients, the incidence of adverse reactions with li-li guo (Guo Lili, 2014) etc. The results of the study. Finally, due to time and geographical limitations, the study included only 178 sample size, and did not exclude the influence of the living environment and other factors. The statistical effect was not strong and the results were biased. Therefore, in the follow-up study, we will continue to expand the sample size, include more research indexes, eliminate the interference factors, and analyze the clinical efficacy difference of EGFR inhibitor in the treatment of patients with different EGFR gene mutations. To sum up, EGFR 19 exon mutated lung cancer patients were lower than EGFR 21 exon mutation lung cancer patients, and benefited more from EGFR inhibitor erotinib treatment, and the survival cycle was longer.

REFERENCES

Chen wanqing, zheng rongshou, zhang thought, *et al*. 2012. Analysis of the morbidity and mortality of malignant tumors in China in 2013 (J). Chinese tumor, 26(1):1-7.

Guo Lili, li Wise, Tang Junfang, *et al*. 2014. Erlotini's clinical efficacy analysis of advanced non-small cell lung cancer with EGFR mutation (*J*). *Journal of medical research,* , 46(3):138-140.

Jiang wenrong, CAI yong Jun, Miao ying xin *et al*. 2013. Correlation analysis of EGFR mutation and clinical characteristics of patients with lung cancer in Shanghai (J). Test medicine, 32(1):30-34.

Krawczy K, P., Kowalski, D.M., Krawczyk, K.W. *et al*. 2013. Predictive and prognostic factors in second- and third-line erlotinib treatment in NSCLC patients with known status of the EGFR gene (J). *Oncology reports,* 30(3):1463-1472.

Lee CK, Wu YL, Ding PN, *et al*. 2015. Impact of specific epidermal growth factor receptor (EGFR) mutations and clinical characteristics on outcomes after treatment with

EGFR tyrosine kinase inhibitors versus chemotherapy in EGFR-mutant lung cancer: a meta-analysis. *J Clin Oncol*, 33(17): 1958-1965. 11

LeeJK, ShinJY, KimS. *et al*. 2013. Primary resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in patients with non-small-cell lung cancer harboring TKI-sensitive EGFR mutations: An exploratory study (J). Annals of oncology: official journal of the European Society for Medical Oncology, 24(8):2080-2087.

Liu renwang, liu jinhao, li xin, *et al*. 2014. Clinical features comparison and prognostic analysis of EGFR 19 and 21 exon mutated lung cancer patients (J). *China lung cancer journal,* 17(11):804-811.

Luo djing, ma jin 'an, zhang jinming, *et al*. Molecular imaging of EGFR mutation in non-small cell lung cancer (J). China lung cancer journal, 2013, 20(6):415-420.

Maemondo, m. Y., Ishii, y. *et al*. 2014. A phase II study of erlotinib monotherapy in the pre - treated non - small cell lung cancer with EGFR gene mutation who have never/light smoking history: Re - evaluation of EGFR gene status (NEJ006 / TCOG0903) (J). Journal of lung cancer: Journal of the International Association for the study of lung cancer, 5 (2) : 195-200.

Measure by, Pan Xue XingYuFei, etc. 2016. Resistance to apoptosis ligand 1 single resistance and epidermal growth factor receptor tyrosine kinase inhibitor is sensitive to the epidermal growth factor receptor mutations in lung cancer cell apoptosis ligand 1 expression and the influence of T cell function (J). J cancer, (12) : 886-892.

NakadeJ, TakeuchiS, NakagawaT. *et al*. 2014. Triple inhibition of EGFR, met, and VEGF suppresses regrowth of HGF-triggered, erlotinib-resistant lung cancer harboring an EGFR mutation (J). *Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer*, 9(6):775-783.

Sordella R, Bell DW, Haber DA, *et al*. 2004. Gefitinib-sensitizing EGFR mutations in lung cancer activate anti-apoptotic pathways. Science, 305(5687): 1163-1167.

Takeda, M., Okamoto, I., Nakagawa, K. *et al*. 2014. The Survival outcome assessed according to tumor response and shrinkage pattern in patients with EGFR mutation - positive non - small cell lung cancer treated with gefitinib or erlotinib (J). *Journal of thoracic oncology: official publication of the International Association for the Study of lung cancer,* 9 (2) : 200-204.

Tian chunqin, zhao xinhan, geng huisheng, *et al*. 2017. A systematic evaluation of the efficacy of EGFR inhibitor in the treatment of clinical selective non-small cell lung cancer (J). *Journal of lung diseases in China (electronic version),* 10(4):450-456.

Togashi, Y., Masago, K., Hamatani, Y. *et al*. 2012. Successful erlotinib rechallenge for leptomeningeal metastases of lung adenocarcinoma after erlotinib-induced interstitial lung disease: A case report and review of the literature (J). Lung cancer: *Journal of the International Association for the Study of Lung Cancer,* 77(2):464-468.

Wang yan, Li Junling, wang zi-ping, etc. 2012. The epidermal growth factor receptor gene mutations of unknown late the treatment in patients with non-small cell lung cancer treatment failure analysis for it, after treatment the curative effect of (J). J cancer, (10) : 780-784.

Wang yaqi, wang xing, yan shi, *et al*. 2015. Progress of neoadjuvant therapy for nonsmall cell lung cancer (J). Journal of Chinese lung cancer, 20(5):352-360.

Xie Yilin, Liang jizhen, su ning and so on. 2015. The curative effect of geiminib and erlotini in first-line treatment of patients with advanced NSCLC in EGFR gene sensitive mutation (J). *Journal of southern medical university*, ,35(3):446-449.

Zhang tan, wang yi, fang yi, *et al*. 2013. Research status of non-small cell lung cancer targeting therapy (J). China journal of clinical pharmacology, 33(11):1054-1057.

Zhu JQ, Zhong WZ, Zhang GC, *et al*. 2008. Better survival with EGFR exon 19 than exon 21 mutations in gefitinib-treated non-small cell lung cancer patients is due to differential inhibition of downstream signals. Cancer Lett, 265(2): 307-317.

****