EFFICACY AND SAFETY OF ANLOTINIB COMBINED WITH ICOTINIB IN THE TREATMENT OF ADVANCED NON-SMALL-CELL LUNG CANCER

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ABSTRACT

Introduction*: We aimed to explore the efficacy and safety of Anlotinib combined with icotinib in the treatment of advanced non-small-cell lung cancer (NSCLC).*

Materials and methods*: 23 patients with local advanced/advanced NSCLC with epidermal growth factor receptor (EGFR)-positive were included in this study. All patients received oral icotinib and anlotinib.*

Results: The disease control rate of the whole population was 78%. The progression-free survival (PFS) rate at the 20th month was 70.58%. Moreover, the average medication cycle of the whole population was (13.2 ± 7.8), and the median medication cycle was 10(1-38). The most common adverse reactions were hypertension (47.83%) and hand-foot syndrome (43.48%). There were three cases of grade 3 adverse reactions, including hand-foot syndrome, hypertension, and diarrhea.

Conclusion*: For patients with local advanced/advanced NSCLC with EGFR-positive, Anlotinib combined with icotinib can not only delay the drug resistance to achieve better clinical efficacy, but also has good safety and tolerability.*

Keywords: *advanced non-small cell lung cancer, safety, Anlotinib, icotinib, efficacy.*

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Introduction

Lung cancer is a kind of malignant tumor, and the cancer cells mainly originate from the mucous membrane epithelium of the bronchus. Nearly 85% of primary lung cancers worldwide are non-small cell lung cancer (NSCLC), and most of the patients are advanced or metastatic NSCLC at the time of diagnosis. Five–year survival for all stages is approximately 17%. Mutations in the epidermal growth factor receptor (EGFR) gene that change the structure of the EGFR protein are oncogenic drivers in some NSCLC tumors[(1)]. The incidence of EGFR positive NSCLC is about 10% - 15% in the western population and 50% in the Asian population[(2)].

90% of EGFR mutation sites are the deletion of exon 19 (ex19del) or the leucine-arginine substitution mutation of exon 21 (leu858Arg)[(3)].

The presence of EGFR mutations in patients with NSCLC is associated with the sensitivity to small-molecule tyrosine kinase inhibitors (TKIs). For some patients with NSCLC, both first and second generation TKIs are the standard first-line treatment plan. However, the sensitivity of patients to TKIs may vary depending on the type of mutation. Patients with NSCLC of EGFR mutation at ex19del benefit more from EGFR-TKIs[(4)]. Despite the long-lasting response, TKIs are faced with the problem of drug resistance. The median progression-free survival (mPFS) of the first-generation TKIs

(gefitinib, erlotinib, icotinib) in newly-treated advanced patients is about 12 months[5-7], that of the second-generation TKIs (afatinib and dacomitinib) is 11.0 months and 14.7 months, respectively[8,9], and that of the third-generation TKIs (osimertinib) is about 19 months[10]. When the disease progresses, approximately 30%-60% of patients using first-generation or second-generation TKIs acquire the EGFR-T790M mutation, which is sensitive to the third-generation drug, osimertinib. When all targeted drugs are resistant, chemotherapy, palliative treatment or clinical trials are recommended. The effect of immune checkpoint inhibitors is poor in NSCLC patients with driving gene mutations such as EGFR[11]. Consequently, the strategy of prolonging remission and promoting tumor control based on EGFR-TKIs is very important at this stage.

Anlotinib is a small molecule multi-target anti-angiogenic drug. Its targets include VEGFR 1/2/3, FGFR 1/2/3 and PDGFR α/β. Compared with bevacizumab, erlotinib can inhibit angiogenesis more comprehensively, avoid drug resistance caused by signal pathway complementation, and achieve the effect of efficient inhibition of angiogenesis. Moreover, Anlotinib is currently the only oral anti-angiogenic drug approved for marketing in the treatment of advanced non-small-cell lung cancer. Therefore, we aimed to explore the efficacy and safety of Anlotinib combined with icotinib in the treatment of advanced NSCLC.

Patients and methods

Patients

This study was approved by the Ethics committee of our hospital. All patients provided the informed consent. From September 2018 to September 2020, 23 patients with local advanced / advanced NSCLC with epidermal growth factor receptor (EGFR)-positive who were admitted to the Affiliated Hospital of Guangdong Medical University were included in this study.

Inclusion criteria:

• patients with stage III B - IV NSCLC;

• patients had at least 10% of the cells were stained with EGFR-positive (21L858R or 19del), and without K-RAS gene mutation;

• untreated patients or patients 6 months after the end of adjuvant therapy;

• patients with an estimated survival time of less than three months;

• patients were confirmed as advanced NSCLC by pathological and cytological diagnosis;

• patients older than 18 years.

Exclusion criteria:

• patients with drug contraindications, allergies and intolerance;

• patients with heart, liver, kidney or other important organ failure;

• patients with high-risk hypertension or diabetes mellitus who can not control blood glucose;

• patients with other malignant tumors;

• patients with mental disease or severe disturbance of consciousness;

• patients with the risk of massive hemoptysis;

• patients who had recently received anti-tumor treatment.

Treatment

For patients with EGFR-positive advanced NSCLC, whether it is exon 19 deletion or exon 21 mutation, icotinib (Zhejiang BEDA Pharmaceutical Co., Ltd., Approval no.: H20110061) combined with Anlotinib (Zhengda Tianqing Pharmaceutical Group Co., Ltd, Approval no.: H20180004) was used for treatment. Patients received oral icotinib (150 mg, TID, on an empty stomach or with food) and Anlotinib (12 mg, QD, on an empty stomach in the morning) until the occurrence of intolerable adverse reactions or disease progression. A total of 21 days is a treatment cycle. All patients have received at least one treatment of Anlotinib combined with icotinib.

Evaluation indexes

Complete remission (CR): all known lesions are disappeared, no new lesions are appeared, and the status quo is maintained for at least 4 weeks;

Partial remission (PR): Among all the measurable lesions in the patient, the sum of the single diameters of the largest lesions is reduced to 30%, no new lesions are generated, and the status quo is maintained for at least 4 weeks;

Stable disease (SD): The lesions have not reached the standard of partial or complete remission and disease progression, no new lesions appear, and the status quo is maintained for at least 6-8 weeks;

Disease progression (DP): The lesions have increased by 20%, and new lesions have appeared;

Clinical disease control rate = (number of patients with complete remission + number of patients with partial remission + number of patients with stable disease) / total number of patients. At the same time, investigate the progress of clinical progression-free survival (PFS) and overall survival

(OS), and analyze the clinical efficacy. PFS: the period from the beginning of treatment to the observation of disease progression or death for any reason. OS: the time from the first medication to death for any reason. Efficacy and safety were evaluated in all patients taking at least one dose of the study drug. The patients were followed up after treatment to analyze the occurrence of major toxic and side effects and observe whether the patients have skin rash, diarrhea, and bleeding.

Statistical analysis

Statistical analysis was made by software SPSS24.0 (International Business Machines, corp., Armonk, NY, USA). Continuous data are expressed as mean ± standard deviation (SD) or median, with quartile ranges depending on the situation. Categorical data are expressed as a percentage. The comparison between groups was carried out by ANOVA. ORR and DCR were calculated with corresponding two-sided 95% confidence intervals (CI). Kaplan-Meier method was used to analyze PFS and OS. The deadline for data collection is September 2020.

Results

General clinical characteristics

Among the 23 patients included in the study, 8 were male and 15 were female, aged 41-82 years, and the average age was (64 ± 14.1) years. 78% of patients were pathologically classified as adenocarcinoma, most of which were stage VI, accounting for 87%. There are 2 patients with stage IIIA and 1 patient with stage IIIC. Among the enrolled patients, 9 patients had brain metastases at the time of diagnosis, and 8 patients had PS score ≥ 2 points at the start of treatment. For EGFR mutation, 13 patients had exon 21 mutation (21L858R) and 10 patients had exon 19 deletion (19del) (Table 1).

Survival analysis of patients with NSCLC

After erlotinib combined with icotinib treatment, the specific follow-up status of all patients was shown in Figure 1. Among them, 13 patients were still in the process of treatment, 5 progressed or died, and 5 stopped taking drugs due to various reasons. Moreover, 18 patients had partial remission and 5 patients had stable disease. The objective response rate (ORR) was 78%, and the disease control rate (DCR) was 100% (Table 2).

The clinical efficacy was significant. The

Items	Number	Percentage
Age (Years)	64 (41-82)	
Gender		
Male	8	35%
Female	15	65%
Histopathology		
Adenocarcinoma	18	78%
Non adenocarcinoma	5	22%
Stage		
Stage III	3	13%
Stage IV	20	87%
Brain metastases		
Yes	9	39%
No	14	61%
Somking history		
Yes	4	17%
No	19	83%
ECOG PS		
1	15	65%
2	6	26%
3	2	9%
Mutation site		
19del	10	43%
21L858R	13	57%

Table 1: General clinical characteristics.
ECOG PS: Eastern Cooperative Oncology Group performance status

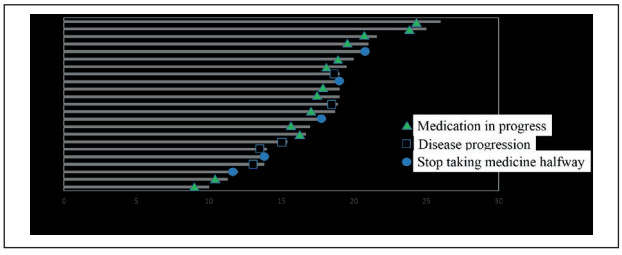

Figure 1: Follow-up status of the whole population.

Efficacy	ITT (n=23)	Mutation site		Brain metastases		PS scores	
		19Del (n=10)	21L858R (n=13)	Yes (n=9)	No (n=14)	PS=1 (n=15)	PS≥2 (n=8)
PR	18	10	8	7	11	12	6
SD	5	0	5	2	3	3	2
ORR	78.00%	100%	61%	78%	78%	80%	75%
DCR	100%	100%	100%	100%	100%	100%	100%
12-month PFS rate	100%	100%	100%	100%	100%	100%	100%
20-month PFS rate	70.58%	78.85%	60%	62.5%	75%	78.6%	50%

Table 2: Efficacy analysis of the overall population and subgroups.

12-month PFS rate is 100%, and the 20-month PFS rate is 70.8% (Figure 2A). For the analysis of EGFR driver gene mutation sites, 10 patients had 19del, their ORR was 100%, and the 20-month PFS rate was 78.85%. The other 13 patients had 21L858R, their ORR was 61%, and the 20-month PFS rate was 60% (Figure 2B). For the 7 patients with brain metastases, their ORR was 78%, and the 20-month PFS rate was 62%. For the 16 patients with non-brain metastases, their ORR was 78%, and the 20-month PFS rate was 75% (Figure 2C). This study included 8 patients with PS ≥ 2 points, and their ORR reached 75%, the 20-month PFS rate was 50%, and the

median PFS was 22 months (Figure 2D).

Efficacy analysis of patients with NSCLC

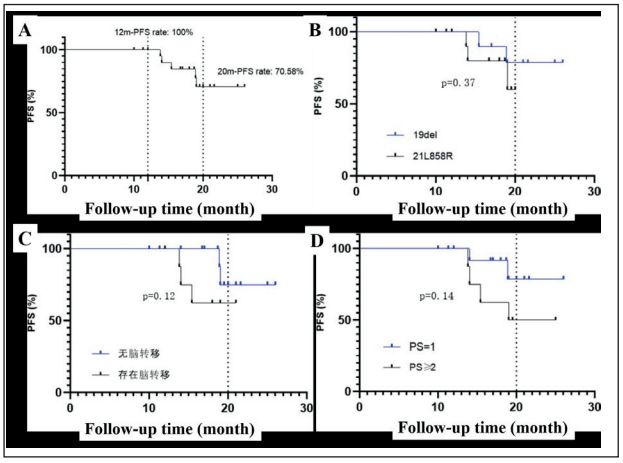

Figure 2: Efficacy analysis of the whole population and subgroups. (**A**) Survival curve of the whole population; (**B**) Comparison of survival curves of patients with different mutation sites; (**C**) Comparison of survival curves in patients with or without brain metastases; (**D**) Comparison of survival curves between patients with different PS scores.

Among the 23 enrolled patients, 18 had an initial dose of 12 mg of Anlotinib, and 3 reduced it to 10 mg within 3-5 treatment cycles. The initial dose of Anlotinib for the other 5 patients was 10 mg. The average number of cycles for the 23 patients was 13.2, the longest was 38, and the median was 10(1-38). Among the 8 patients with PS ≥ 2, the average cycle number of taking Anlotinib was 13.6, the longest cycle was 21, and the median cycle was 15(2-21).

Safety analysis of patients with NSCLC

The most common adverse reactions were hypertension (47.83%) and hand-foot syndrome (43.48%). The main adverse reactions with an incidence of more than 10% are loss of appetite, nausea, diarrhea, skin rash, etc. (Table 3). There were three cases of grade 3 adverse reactions, including hand-foot syndrome, hypertension, and diarrhea.

Discussion

Adverse reactions	Total number	Total incidence	Grade I - II		Grade I - II	
			Number	Percentage	Number	Percentage
Rash	4	17.39%	4	17.39%	0	0.00%
Hand foot syndrome	10	43.48%	9	39.13%	1	4.35%
Oral mucositis	2	8.70%	2	8.70%	0	0.00%
hypertension	11	47.83%	10	43.48%	1	4.35%
Diarrhea	5	21.74%	4	17.39%	1	4.35%
Loss of appetite	8	34.78%	8	34.78%	0	0.00%
Nausea	7	30.43%	7	30.43%	0	0.00%

Table 3: Adverse reactions of the overall population.

For patients with EGFR-positive advanced NSCLC, whether it is 19del or 21L858R, targeted therapy is the standard treatment, but it faces the problem of drug resistance after taking the drug for about 10 months. At present, how to delay drug resistance is the focus of clinical attention. One treatment strategy is to use the third generation targeted drug (ositinib) directly for initial treatment, which is derived from the dual benefits of PFS and OS obtained from FLAURA study(10). The other treatment strategy is the first generation of targeted drugs combined with chemotherapy, based on the difference of OS obtained in NEJ009 study(12). However, it is not recommended in the guideline considering the side effects.

Both preclinical and clinical evidence have proved that dual blockade of EGFR and VEGF pathways is a strategy to delay drug resistance. A preclinical study showed that EGFR mutations may be accompanied by the activation of vascular pathways, and that VEGF and EGFR pathways are related to each other. In many clinical trials, inhibition of EGFR and VEGF pathways (A + T mode) can significantly delay drug resistance and improve mPFS(13-16). However, nearly 20% - 30% of EGFR positive patients have primary drug resistance and poor efficacy when they received anti-angiogenic drugs combined with TKIs(15). Through NGS sequencing, we can not only identify the sensitive mutations of tumor, but also find the co-existing gene mutations that affect the therapeutic effect. EGFR-positive NSCLC has significant intratumoral heterogeneity, accompanied by a variety of coexisting genetic mutations, which may affect the effectiveness of TKIs(17-19). Furthermore, considering that EGFR and VEGF have Cross talk and synergistic effect, many clinical studies have confirmed that the combination of first generation targeted drugs and anti-angiogenic drugs can delay drug resistance.

In the current retrospective study, the ORR of Anlotinib combined with ikotinib regimen reached 78% and the 20-month PFS rate was 70.58%, which is a significant treatment effect and significantly better than the historical data of single drug. The main adverse reactions of the combination medication are hypertension, hand-foot syndrome, and decreased appetite, and most of them are grade 1-2 adverse reactions, which are safe and well-tolerated. In addition, the average medication cycle of Anlotinib is 13.2, and the compliance is good. The possible reason is that the dual oral medication is more easily accepted by patients who are initially treated. We also explored the beneficiaries of this program. In the subgroup analysis of the CTONG1509 and

RELAY studies, comparing with TKI monotherapy, the patients with 21L858R have obtained the benefits of PFS of 8.3 months and 8.2 months, respectively, while the patients with 19del have only obtained the benefits of PFS of 5.4 months and 7.1 months, indicating that the A +T program seems to be more beneficial to the patients with 21L858R[15,16]. However, in this study, for the patients with 19del, the ORR is 100%, and the 20-month PFS rate is 78.85%, which suggests that the clinical benefit is more obvious. However, the sample size still needs to be expanded for further analysis.

For patients with brain metastases with poor prognosis, a clinical study has shown that compared with single EGFR-TKIs, EGFR-TKIs combined with bevacizumab has significantly improved the survival benefit of patients with multiple brain metastases. And in the subgroup analysis of Anlotinib ALTER0303, compared with placebo, Anlotinib can significantly prolong the mPFS of NSCLC patients with asymptomatic brain metastases[21]. In this study, the ORR of patients with brain metastases was 78%, and the 20-month PFS rate was 62.5%, which also achieved significant clinical benefits. As we all know, the brain is a common metastasis site after the first generation of targeted drugs is resistant. Combining anti-angiogenic drugs may reduce the risk of brain metastasis or brain progression.

There are also some limitations in this study. First, the sample size of the study is small, and there are many censorship events, which result in that the data are not yet mature. Second, Patients lack the data of polygenic test, and we cannot further mine predictive or prognostic factors from the genetic level. Although the PFS data are still immature, the 20-month PFS rate is as high as 70.58%, which has significantly delayed drug resistance and is worthy of clinical promotion.

Conclusion

In clinical practice, for patients with EGFR-positive advanced/advanced NSCLC, the use of Anlotinib combined with icotinib can not only delay drug resistance to achieve better clinical efficacy, but also has a good safety.

References

1) Franek J, Cappelleri JC, Larkin-Kaiser KA, Wilner KD, Sandin R. Systematic review and network meta-analysis of first-line therapy for advanced EGFR-positive non-small-cell lung cancer. Future Oncol. 2019; 15(24): 2857-2871.

2) Shi Y, Au JS, Thongprasert S, Srinivasan S, Tsai CM, Khoa MT, Heerema K, Itoh Y, Cornelio G, Yang PC. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). J Thorac Oncol. 2014; 9(2): 154-62.

3) Midha A, Dearden S, McCormack R. EGFR mutation incidence in non-small-cell lung cancer of adenocarcinoma histology: a systematic review and global map by ethnicity (mutMapII). Am J Cancer Res. 2015; 5(9): 2892-911.

4) Ettinger DS, Wood DE, Akerley W, Bazhenova LA, Borghaei H, Camidge DR, Cheney RT, Chirieac LR, D'Amico TA, Demmy TL, Dilling TJ, Dobelbower MC, Govindan R, Grannis FW Jr, Horn L, Jahan TM, Komaki R, Krug LM, Lackner RP, Lanuti M, Lilenbaum R, Lin J, Loo BW Jr, Martins R, Otterson GA, Patel JD, Pisters KM, Reckamp K, Riely GJ, Rohren E, Schild SE, Shapiro TA, Swanson SJ, Tauer K, Yang SC, Gregory K, Hughes M. National comprehensive cancer network. Non-Small Cell Lung Cancer, Version 6.2015. J Natl Compr Canc Netw. 2015; 13(5): 515-24.

5) Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, Nishiwaki Y, Ohe Y, Yang JJ, Chewaskulyong B, Jiang H, Duffield EL, Watkins CL, Armour AA, Fukuoka M. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009; 361(10): 947-57.

6) Wu YL, Zhou C, Liam CK, Wu G, Liu X, Zhong Z, Lu S, Cheng Y, Han B, Chen L, Huang C, Qin S, Zhu Y, Pan H, Liang H, Li E, Jiang G, How SH, Fernando MCL, Zhang Y, Xia F, Zuo Y. First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study. Ann Oncol. 2015; 26(9): 1883-1889.

7) Shi YK, Wang L, Han BH, Li W, Yu P, Liu YP, Ding CM, Song X, Ma ZY, Ren XL, Feng JF, Zhang HL, Chen GY, Han XH, Wu N, Yao C, Song Y, Zhang SC, Song W, Liu XQ, Zhao SJ, Lin YC, Ye XQ, Li K, Shu YQ, Ding LM, Tan FL, Sun Y. First-line icotinib versus cisplatin/pemetrexed plus pemetrexed maintenance therapy for patients with advanced EGFR mutation-positive lung adenocarcinoma (CONVINCE): a phase 3, open-label, randomized study. Ann Oncol. 2017; 28(10): 2443-2450.

8) Park K, Tan EH, O'Byrne K, Zhang L, Boyer M, Mok T, Hirsh V, Yang JC, Lee KH, Lu S, Shi Y, Kim SW, Laskin J, Kim DW, Arvis CD, Kölbeck K, Laurie SA, Tsai CM, Shahidi M, Kim M, Massey D, Zazulina V, Paz-Ares L. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. Lancet Oncol. 2016; 17(5): 577-89.

9) Wu YL, Cheng Y, Zhou X, Lee KH, Nakagawa K, Niho S, Tsuji F, Linke R, Rosell R, Corral J, Migliorino MR,

Pluzanski A, Sbar EI, Wang T, White JL, Nadanaciva S, Sandin R, Mok TS. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. Lancet Oncol. 2017; 18(11): 1454-1466.

10) Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, Dechaphunkul A, Imamura F, Nogami N, Kurata T, Okamoto I, Zhou C, Cho BC, Cheng Y, Cho EK, Voon PJ, Planchard D, Su WC, Gray JE, Lee SM, Hodge R, Marotti M, Rukazenkov Y, Ramalingam SS, FLAURA Investigators. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 2018; 378(2): 113-125.

11) Cavanna L, Citterio C, Orlandi E. Immune checkpoint inhibitors in EGFR-mutation-positive TKI-treated patients with advanced non-small-cell lung cancer network meta-analysis. Oncotarget. 2019; 10(2): 209-215.

12) Johnson BE, Kabbinavar F, Fehrenbacher L, Hainsworth J, Kasubhai S, Kressel B, Lin CY, Marsland T, Patel T, Polikoff J, Rubin M, White L, Yang JC, Bowden C, Miller V. ATLAS: randomized, double-blind, placebo-controlled, phase IIIB trial comparing bevacizumab therapy with or without erlotinib, after completion of chemotherapy, with bevacizumab for first-line treatment of advanced non-small-cell lung cancer. J Clin Oncol. 2013; 31(31): 3926-34.

13) Kato T, Seto T, Nishio M, Goto K, Yamamoto N, Okamoto I, Tao L, Yu W, Khaznadar T, Tajima K, Shibata M, Seki A, Yamamoto N. Erlotinib Plus Bevacizumab Phase ll Study in Patients with Advanced Non-Small-Cell Lung Cancer (JO25567): Updated Safety Results. Drug Saf. 2018; 41(2): 229-237.

14) Saito H, Fukuhara T, Furuya N, Watanabe K, Sugawara S, Iwasawa S, Tsunezuka Y, Yamaguchi O, Okada M, Yoshimori K, Nakachi I, Gemma A, Azuma K, Kurimoto F, Tsubata Y, Fujita Y, Nagashima H, Asai G, Watanabe S, Miyazaki M, Hagiwara K, Nukiwa T, Morita S, Kobayashi K, Maemondo M. Erlotinib plus bevacizumab versus erlotinib alone in patients with EGFR-positive advanced non-squamous non-small-cell lung cancer (NEJ026): interim analysis of an open-label, randomised, multicentre, phase 3 trial. Lancet Oncol. 2019; 20(5): 625-635.

15) Cheng Y, He Y, Li W, Zhang HL, Zhou Q, Wang B, Liu C, Walding A, Saggese M, Huang X, Fan M, Wang J, Ramalingam SS. Osimertinib Versus Comparator EGFR TKI as First-Line Treatment for EGFR-Mutated Advanced NSCLC: FLAURA China, A Randomized Study. Target Oncol. 2021; 16(2): 165-176.

16) Nakagawa K, Garon EB, Seto T, Nishio M, Ponce Aix S, Paz-Ares L, Chiu CH, Park K, Novello S, Nadal E, Imamura F, Yoh K, Shih JY, Au KH, Moro-Sibilot D, Enatsu S, Zimmermann A, Frimodt-Moller B, Visseren-Gruel C, Reck M, RELAY Study Investigators. Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019; 20(12): 1655-1669.

17) Wang Z, Cheng Y, An T, Gao H, Wang K, Zhou Q, Hu Y, Song Y, Ding C, Peng F, Liang L, Hu Y, Huang C, Zhou C, Shi Y, Zhang L, Ye X, Zhang M, Chuai S, Zhu G, Hu J, Wu YL, Wang J. Detection of EGFR mutations in plasma circulating tumour DNA as a selection criterion for first-line gefitinib treatment in patients with advanced lung adenocarcinoma (BENEFIT): a phase 2, single-arm, multicentre clinical trial. Lancet Respir Med. 2018 Sep;6(9):681-690. DOI: 10.1016/S2213-2600(18)30264-9. Epub 2018 Jul 17. Erratum in: Lancet Respir Med. 2018; 6(9): e50.

18) Hong S, Gao F, Fu S, Wang Y, Fang W, Huang Y, Zhang L. Concomitant Genetic Alterations with Response to Treatment and Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Patients With EGFR-Mutant Advanced Non-Small Cell Lung Cancer. JAMA Oncol. 2018; 4(5): 739-742.

19) Model F, Remon J, Mateo J, Westphalen CB, Barlesi F, Lolkema MP, Normanno N, Scarpa A, Robson M, Meric-Bernstam F, Wagle N, Stenzinger A, Bonastre J, Bayle A, Michiels S, Bièche I, Rouleau E, Jezdic S, Douillard JY, Reis-Filho JS, Dienstmann R, André F. Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group. Ann Oncol. 2020; 31(11): 1491-1505.

20) Han B, Li K, Wang Q, Zhang L, Shi J, Wang Z, Cheng Y, He J, Shi Y, Zhao Y, Yu H, Zhao Y, Chen W, Luo Y, Wu L, Wang X, Pirker R, Nan K, Jin F, Dong J, Li B, Sun Y. Effect of Anlotinib as a Third-Line or Further Treatment on Overall Survival of Patients with Advanced Non-Small Cell Lung Cancer: The ALTER 0303 Phase 3 Randomized Clinical Trial. JAMA Oncol. 2018 Nov 1;4(11):1569-1575. DOI: 10.1001/jamaoncol.2018.3039. Erratum in: JAMA Oncol. 2018; 4(11): 1625.

21) Jiang S, Liang H, Liu Z, Zhao S, Liu J, Xie Z, Wang W, Zhang Y, Han B, He J, Liang W. The Impact of Anlotinib on Brain Metastases of Non-Small Cell Lung Cancer: Post Hoc Analysis of a Phase III Randomized Control Trial (ALTER0303). Oncologist. 2020; 25(5): e870-e874.

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