Efficacy Differences of First-line EGFR-TKIs Alone vs. in Combination with Chemotherapy in Advanced Lung Adenocarcinoma Patients with Sensitive EGFR Mutation and Concomitant Non-EGFR Genetic Alteration(s)

Guowei Zhang (dugu4986@126.com)
The Affiliated Cancer Hospital of Zhengzhou University
Ruirui Cheng
First Affiliated Hospital of Zhengzhou University
Yuanyuan Niu
The Affiliated Cancer Hospital of Zhengzhou University
Huijuan Wang
The Affiliated Cancer Hospital of Zhengzhou University
Xiangtao Yan
The Affiliated Cancer Hospital of Zhengzhou University
Mina Zhang
The Affiliated Cancer Hospital of Zhengzhou University
Xiaojuan Zhang
The Affiliated Cancer Hospital of Zhengzhou University
Jinpo Yang
The Affiliated Cancer Hospital of Zhengzhou University
Chunhua Wei
The Affiliated Cancer Hospital of Zhengzhou University
Zhiyong Ma
The Affiliated Cancer Hospital of Zhengzhou University

Research Article

Keywords: Non-small cell lung cancer, EGFR mutation, concomitant genetic alteration , targeted therapy, chemotherapy

Posted Date: March 10th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-254564/v1

Abstract

Objective: To explore whether EGFR-TKI combined with chemotherapy would benefit patients with advanced lung adenocarcinoma with both sensitive EGFR mutation and concomitant non-EGFR genetic alterations.

Materials and Methods: Cases of advanced lung adenocarcinoma with EGFR mutation combined with concomitant non-EGFR genetic alterations were retrospectively collected. And the patients were required to receive first-line EGFR-TKI and chemotherapy combination or EGFR-TKI monotherapy. Demographic, clinical and pathological data were collected, and the electronic imaging data were retrieved to evaluate the efficacy and time of disease progression. Survival data were obtained through face-to-face or telephone follow-up. The differences between the two groups in objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS) were investigated.

Results: 107 patients were included, including 63 in the combination therapy group and 44 in the monotherapy group. The ORR were 78% and 50% (P =0.003), and DCR were 97% and 77% (P =0.002), respectively. At a median follow-up of 13.7 months, a PFS event occurred in 38.1% and 81.8% of patients in the two groups, with median PFS of 18.8 and 5.3 months, respectively (P <0.0001). Median OS was unreached in the combination group, and 27.8 months in the monotherapy group (P =0.31). According to the Cox multivariate regression analysis, combination therapy was an independent prognostic factor of PFS.

Conclusion: In patients with EGFR-mutant advanced lung adenocarcinoma with concomitant non-EGFR genetic alterations, combination of TKI and chemotherapy was significantly superior to EGFR-TKI monotherapy, which should be the preferred treatment option.

Key Points

- Clinical use of NGS makes discovery of concomitant genetic alterations associated with EGFR This kind of patients should be treated as a separate subtype.
- Chemo-targeted combination is superior than TKI alone in this type of patients, which is a possible reason of why this combination treatment benefits the EGFR-mutant patients

1. Background

Lung cancer is the leading cause of cancer-related death worldwide [1], and non-small-cell lung cancer (NSCLC) accounts for approximately 85% of all cases [2]. NSCLC with sensitive epidermal growth factor receptor (*EGFR*) mutations may be susceptible to treatment with EGFR tyrosine kinase inhibitors (EGFR-TKI), a breakthrough in lung cancer treatment this century that has opened a new chapter in the targeted therapy of solid tumors. At present, NSCLC with *EGFR* mutations has become the most important subtype of NSCLC. The *EGFR* mutation rate is as high as 51.4% in Asian patients with lung adenocarcinoma [3], making it particularly important to optimize the treatment protocol for NSCLC with *EGFR* mutations.

Ongoing in-depth research has raised new questions about treatment of NSCLC with *EGFR* mutations, the most important of which is the effect of combination therapy with EGFR-TKI and other drugs, especially chemotherapy drugs.

The clinical trial NEJ009 has shown promising results of chemotherapy combined with a first-generation EGFR-TKI: Among patients with sensitive *EGFR* mutations receiving pemetrexed/carboplatin combined with gefitinib, progression-free survival (PFS) is 20.9 months, and overall survival (OS) is 50.9 months [4], suggesting that combination therapy may be a potential new treatment protocol. However, the mechanism and the target population of combination therapy are unknown. One hypothesis is that for NSCLC patients with both *EGFR* mutation and concomitant non-EGFR genetic alteration(s), combination therapy inhibits the EGFR pathway and also counteracted the bypass activation associated with the concomitant alteration(s), thereby achieving better efficacy. To date, no evidence-based study is available to support this hypothesis. This study was designed to test this hypothesis.

2. Materials And Methods

2.1 Patients

We searched the electronic medical records of the Affiliated Cancer Hospital and the First Affiliated Hospital of Zhengzhou University to include patients treated between January 2018 and May 2020 who met the following criteria: histologically confirmed lung adenocarcinoma; clinical or pathological stage IV (tumor–node–metastasis [TNM] stage, edition 8); performance status (PS) score 0-2; and next-generation sequencing with biopsy specimens at initial diagnosis. Due to the retrospective nature of this analysis, we were unable to ensure any consistent testing platform or panel. The panels all included at least epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), proto-oncogene tyrosine-protein kinase 1 (*ROS1*), Kirsten rat sarcoma virus gene (*KRAS*), the c-Met tyrosine kinase gene (*MET*), rapidly accelerated fibrosarcoma (*RAF*), human epidermal growth factor receptor 2 (*HER2*), rearranged during transfection (*RET*), and tumor protein 53 (*TP53*); sensitive *EGFR* mutations (exons 18-21); and at least one non-*EGFR* mutation. The patients had to have first-line treatment with a first- to third-generation EGFR-TKI alone or in combination with chemotherapy, at least one evaluable lesion (per Response Evaluation Criteria in Solid Tumors [RECIST] 1.1), and complete imaging data.

Based on first-line treatment mode, the patients were divided into the monotherapy (targeted therapy) group and the combination therapy (targeted therapy combined with chemotherapy) group. Information such as demographics, PS score, stage (IVA, IVB), central nervous system (CNS) metastases, *EGFR* mutation sites, type of concomitant non-EGFR alteration(s), and first-line treatment protocol was collected.

2.2 Efficacy evaluation and follow-up

Imaging evaluation were performed every 6 weeks after the initial dosing, including enhanced chest and upper abdominal CT and enhanced CT of any tumor site present at baseline, as well as enhanced brain magnetic resonance imaging (MRI) in patients with CNS metastases. Electronic imaging data were retrieved, and the efficacy was evaluated based on RECIST 1.1 to determine best response and the time of disease progression. The patients were followed up by face-to-face visit or telephone to collect their survival status. Endpoints included progression-free survival (PFS), overall survival (OS), objective remission rate (ORR), and disease control rate (DCR). PFS was defined as the time from initial dosing to disease progression (per RECIST 1.1) or death. OS was defined as the time from initial dosing to death.

2.3 Statistical analysis

The chi-squared test or Fisher's exact test was performed to compare ORR and DCR between the two groups. The Kaplan-Meier method was used for survival analysis and to plot PFS and OS curves. The log-rank test was used to analyze the differences in PFS and OS between the two groups. Cox multivariate regression analysis was performed to determine if treatment protocol was an independent prognostic factor. Factors included in the Cox regression analysis were sex, age, PS score, stage, CNS metastases, *EGFR* mutation sites, non-*EGFR* mutation(s), and TKI. We used GraphPad Prism 8.0 to perform survival analysis. And all other statistical analyses were performed by SPSS v25.0.

3. Results

A total of 107 eligible patients were included in this study, including 63 in the combination therapy group and 44 in the monotherapy group. Sixty-seven patients were women and 40 were men. The mean age was 58.3 ± 12.1 years. PS score was 0-1 in all the patients except two patients in the monotherapy group (PS = 2). *EGFR* mutations were all exon 19 deletion or exon 21 L858R point mutation, except for one rare mutation in each group (S768I and G719C).

As for concomitant alterations, 83 of 107 patients had a single mutation, including *TP53* mutation (n = 53), *MET* amplification (n = 13), *KRAS* mutation (n = 3), and other mutations (n = 14; including *BRAF* mutation, *HER2* amplification, *CDK4* amplification, *PTEN* mutation, *DDR2* mutation, *TSC1* mutation, and *PIK3CA* mutation). Twenty-four patients had two or more concomitant alterations, of whom 19 patients had *TP53 mutation* combined with other alteration(s) (including *ATM* mutation, *SMAD4* mutation, *MET* amplification, *MYC* amplification, *APC* mutation, *PIK3CA* mutation, *CTNNB1* mutation, *NTRK1* rearrangement, *RB1* mutation, *AXL* mutations, *ALK* mutations, and *CDK4* mutations). See Table 1 for the balanced baseline characteristics between the two groups.

Table 1
Baseline demographics and clinical characteristics

	Total (N = 107)	Monotherapy (n = 44)	Combination Therapy (n = 63)	P value
Sex (F/M)	67/40	30/14	37/26	0.320
Mean age (years)	58.3 ± 12.1	59.2 ± 12.8	57.7 ± 11.7	0.681
ECOG PS				0.175
0	24	8	16	
1	81	34	47	
2	2	2	0	
Stage				0.049
IVA	22	5	17	
IVB	85	39	46	
***EGFR* mutation sites**				0.950
19 exon deletion	50	20	30	
21 exon L858R	55	23	32	
Other	2	1	1	
Non-*EGFR* mutations				0.044
TP53 mutation	53	16	37	
MET amplification	13	10	3	
KRAS mutation	3	1	2	
Other single mutations	14	6	8	
≥ 2 mutations	24	11	13	
TKIs				0.150
First-generation	102	40	62	
Second-generation	2	2	0	
Third-generation	3	2	1	

First-generation TKIs were used in 62 of 63 patients in the combination therapy group and 40 of 44 patients in the monotherapy group (only a few patients received second- or third-generation TKIs, see Table 1).Chemotherapy in the combination therapy group: 38 patients received pemetrexed combined

platinum, 17 patients received pemetrexed and platinum combined bevacizumab, six patients received pemetrexed alone, and two patients received a non-pemetrexed platinum-based two-drug regimen. The median number of treatment cycles was 6 (1-32).

In the combination therapy group, 49 patients achieved partial remission (PR), 12 had stable disease (SD), and two had progressive disease (PD). In the monotherapy group, 22 patients achieved PR, 12 had SD, and 10 had PD. The ORR was 78% in the combination therapy group and 50% in the monotherapy group (p = 0.003), and the DCR was 97% and 77% respectively (p = 0.002).

The patients were followed up through August 24, 2020, with a median follow-up time of 13.7 months. As of last follow-up, 60 patients occurred PFS events（56.1%）, and the median PFS was 9.2 months (Figure 1a). PFS events was observed in 24 patients（38.1%） in the combination therapy group and 36 patients （81.8%） in the monotherapy group. Median PFS was 18.8 months and 5.3 months, respectively (hazard ratio [HR] = 0.23; 95% CI 0.13-0.41; p < 0.0001) (Figure 1b). Multivariate analysis showed that treatment protocol (combination therapy vs monotherapy) was an independent prognostic factor for PFS (HR = 0.13; 95% CI 0.06-0.28; p < 0.001). Sex and stage were also independent prognostic factors for PFS (Table 2).

Table 2
Multivariate Cox regression analysis of prognostic factors on PFS of all enrolled patients

Variable	N	*P*-value	*HR*	95% CI
Sex				
Female	67	0.002	0.358	0.185-0.693
Male	40			
Age (years)				
≥65	30	0.201	0.585	0.275-1.330
≤ 65	77			
ECOG PS				
0	24	0.133	0.558	0.260-1.193
1-2	83			
Clinical Stage				
IVA	22	0.003	0.404	0.221-0.737
IVB	85			
CNS metastasis				
Yes	39	0.330	0.717	0.367-1.400
No	68			
EGFR mutation				
19 exon deletion	50	0.297	1.393	0.747-2.596
Other	57			
Concomitant non-EGFR mutation				
TP53	53	0.611	0.841	0.431-1.640
Other	54			
Number of concomitant non-EGFR mutations				
1	83	0.152	0.478	0.174-1.313
≥2	24			
Treatment protocol				
Combination therapy	63	<0.001	0.132	0.062-0.281
TKI monotherapy	44			

Type of EGFR-TKI				
First-generation	102	0.182	0.275	0.041-1.831
Other	5			

As of last follow-up, 22 patients（20.6%）, including eight patients（12.7%） in the combination therapy group and 14（31.8%） in the monotherapy group died, with a median OS of 28.6 months (Figure 2a). The median OS had not been reached in the combination therapy group, whereas the estimated median OS was 27.8 months in the monotherapy group (HR = 0.45; 95% CI 0.19-1.05; p = 0.31) (Figure 2b).

4. Discussion

As soon as EGFR-TKIs became available, a series of clinical trials, such as INTACT 1 [5], INTACT 2 [6], TALENT [7], and TRIBUTE [8], were conducted to investigate the effect of chemotherapy alone or in combination with TKIs in non-selected patients with advanced NSCLC. However, the results from these studies were all negative. The reasons may include potential antagonism between platinum drugs and EGFR-TKIs [9] or that cell cycle–specific chemotherapy drugs are difficult to play a role because EGFR-TKIs arrest the tumor cell cycle at G1 phase [10].

Based on these hypotheses and the results from basic research, the combination strategy was largely eschewed for some time. However, in 2013, FASTACT-2, a large phase III randomized controlled trial [11], used a combination therapy protocol known as intercalated therapy to avoid concomitant use of chemotherapy and TKI, thereby preventing cell cycle arrest from impairing the efficacy of chemotherapy. Specifically, a group of Asian patients with advanced NSCLC received 28-day cycles of chemotherapy with gemcitabine (days 1, 8) and carboplatin (day 1), as well as erlotinib on days 15-28. After up to six cycles of chemotherapy, oral erlotinib was given every day until disease progression. The results showed that PFS and OS were significantly longer in the chemotherapy-combined-with-erlotinib group than in the erlotinib-alone group. A similar study, ISCAN [12], reached similar conclusions, although the time point for intercalated chemotherapy was slightly different.

In 2016, JMIT, a phase II randomized controlled trial, was designed based on a different hypothesis, that platinum drugs and EGFR-TKIs are antagonistic [13]. Pemetrexed was given in combination with oral gefitinib (daily, from day 1 of chemotherapy) without using a intercalated strategy. In addition, this was the first trial to enroll patients with advanced NSCLC and sensitive *EGFR* mutations. The results showed that PFS, the primary endpoint, was significantly longer in the combination group than in the gefitinib-alone group.

In 2018, the initial results of study NEJ009 [14] challenged the presumed mechanism of the clinical benefits observed in FASTACT-2 and JMIT. The trial investigated the efficacy of gefitinib alone or in combination with chemotherapy in patients with advanced non-squamous NSCLC and sensitive *EGFR* mutations. The chemotherapy regimen was pemetrexed combined with carboplatin, a platinum-based two-drug regimen, and gefitinib was given from day 1 of chemotherapy without a preset interval. The trial

achieved the best outcomes with chemo-targeted combination therapy, as this regime extended PFS from 11.9 months to 20.9 months ($p < 0.001$) and OS from 38.8 months to 50.9 months ($p = 0.021$) [4], suggesting that intercalated chemotherapy with TKI (based on the theory of TKI-induced cell cycle arrest) or the use of non-platinum-containing chemotherapy in combination with TKI (based on the theory of antagonism between platinum drugs and TKI) was unwarranted. The failure of early clinical trials is likely related to a lack of precise patient selection.

During this period, researchers are also developing a more in-depth understanding of lung cancer with *EGFR* mutations. High-throughput technology shows that 45% to 55% of patients with *EGFR* mutations also harbor a concomitant non-EGFR genetic alteration(s), and these patients are far less responsive to EGFR-TKIs than those with pure *EGFR* mutations [15,16]. This may be related to the resistance that rapidly develop in association with the activation of alternate pathways, and chemotherapy combined with TKI may prevent rapid activation of alternate pathways because the regime works on both EGFR and non-EGFR pathways. Our study indirectly confirms this hypothesis: In the TKI monotherapy group, the ORR was 50%, the median PFS was 5.3 months, which were significant lower or shorter than the historical data of first-line EGFR-TKI therapies. In the combination therapy group, the ORR was 78%, the median PFS was 18.8 months, the HR of disease progression was reduced by 77%, and the HR of death was reduced by 55%. These data indicate that the combination therapy overcomes the shortcomings of TKI monotherapy in patients with both EGFR and concomitant non-EGFR genetic alteration(s), which may be one of the benefit logics of chemo-targeted combination strategy. Answering questions such as whether patients with a pure *EGFR* mutation will benefit from the combination therapy (and if so, what is the mechanism) and the clinical benefits relative to those observed in patients with both EGFR and non-*EGFR* alterations will facilitate the precise selection of a treatment protocol.

This study has obvious limitations due to the nature of retrospective analyses and the small sample size. For example, this study showed that approximately 25% of patients harbored two or more non-*EGFR* mutations in this real-world clinical setting, but according to Cox multivariate regression analysis, the number of non-*EGFR* mutations was not an independent prognostic factor for PFS. The number of non-*EGFR* mutations seen in this study may be incorrect, or it may be unbalanced due to the different testing platforms and panels used across studies, which along with the small sample size makes it impossible to draw any definitive conclusion about the relationship between the number of non-*EGFR* mutations and the efficacy of combination therapy.

5. Conclusion

The efficacy of combination therapy in patients with both EGFR and concomitant non-EGFR genetic alteration(s) may be an important contributor to the superior efficacy of combination therapy over EGFR-TKI monotherapy in patients with *EGFR* mutations in general. However, given the nature of this retrospective analysis and the small sample size, prospective studies are needed to validate the results. In the future, we will investigate the efficacy of combination therapy versus EGFR-TKI monotherapy in

patients with a pure *EGFR* mutation in order to guide clinical decision-making for patients with *EGFR* mutations with or without concomitant non-EGFR genetic alteration(s).

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of the Affiliated Cancer Hospital and the First Affiliated Hospital of Zhengzhou University. And informed consent was obtained from all participants. No additional administrative permission is required to access the raw data from electronic medical records of the Affiliated Cancer Hospital and the First Affiliated Hospital of Zhengzhou University. We confirm that all methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request. It’s not publicly available because the data also forms part of an ongoing study.

Competing interests

All authors declared no actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within that could inappropriately influence (bias) this article.

Funding

No funding.

Authors' contributions

Guowei Zhang wrote the main manuscript text. Ruirui Cheng and Yuanyuan Niu conducted data collation and analysis. Xiaojuan Zhang, Jinpo Yang and Chunhua Wei performed patient follow-up. Huijuan Wang and Xiangtao Yan prepared figures 1-2. Mina Zhang and Zhiyong Ma prepared tables 1-2. All authors reviewed the manuscript.

Acknowledgements

The authors thank all patients and their families for their contributions to this study.

References

1. RL Siegel, KD Miller, A. Jemal, Cancer statistics, 2019, CA Cancer J Clin 69(1) (2019) 7–34.
2. RS Herbst, JV Heymach, SM Lippman, Lung cancer, N Engl J Med 359(13) (2008) 1367–80.
3. Y. Shi, JS Au, S. Thongprasert, S. Srinivasan, CM Tsai, MT Khoa, K. Heeroma, Y. Itoh, G. Cornelio, PC Yang, 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 9(2) (2014) 154 – 62.
4. Y. Hosomi, S. Morita, S. Sugawara, T. Kato, T. Fukuhara, A. Gemma, K. Takahashi, Y. Fujita, T. Harada, K. Minato, K. Takamura, K. Hagiwara, K. Kobayashi, T. Nukiwa, A. Inoue, Gefitinib Alone Versus Gefitinib Plus Chemotherapy for Non-Small-Cell Lung Cancer With Mutated Epidermal Growth Factor Receptor: NEJ009 Study, J Clin Oncol 38(2) (2020) 115–123.
5. G. Giaccone, RS Herbst, C. Manegold, G. Scagliotti, R. Rosell, V. Miller, RB Natale, JH Schiller, J. Von Pawel, A. Pluzanska, U. Gatzemeier, J. Grous, JS Ochs, SD Averbuch, MK Wolf, P. Rennie, A. Fandi, DH Johnson, Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial–INTACT 1, J Clin Oncol 22(5) (2004) 777 – 84.
6. RS Herbst, G. Giaccone, JH Schiller, RB Natale, V. Miller, C. Manegold, G. Scagliotti, R. Rosell, I. Oliff, JA Reeves, MK Wolf, AD Krebs, SD Averbuch, JS Ochs, J. Grous, A. Fandi, DH Johnson, Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial–INTACT 2, J Clin Oncol 22(5) (2004) 785 – 94.
7. U. Gatzemeier, A. Pluzanska, A. Szczesna, E. Kaukel, J. Roubec, F. De Rosa, J. Milanowski, H. Karnicka-Mlodkowski, M. Pesek, P. Serwatowski, R. Ramlau, T. Janaskova, J. Vansteenkiste, J. Strausz, GM Manikhas, J. Von Pawel, Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non-small-cell lung cancer: the Tarceva Lung Cancer Investigation Trial, J Clin Oncol 25(12) (2007) 1545–52.
8. RS Herbst, D. Prager, R. Hermann, L. Fehrenbacher, BE Johnson, A. Sandler, MG Kris, HT Tran, P. Klein, X. Li, D. Ramies, DH Johnson, VA Miller, TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer, J Clin Oncol 23(25) (2005) 5892–9.
9. CM Tsai, JT Chen, DJ Stewart, CH Chiu, CL Lai, SY Hsiao, YM Chen, KT Chang, Antagonism between gefitinib and cisplatin in non-small cell lung cancer cells: why randomized trials failed?, J Thorac Oncol 6(3) (2011) 559–68.
10. H. Cheng, SJ An, XC Zhang, S. Dong, YF Zhang, ZH Chen, HJ Chen, AL Guo, QX Lin, YL Wu, In vitro sequence-dependent synergism between paclitaxel and gefitinib in human lung cancer cell lines, Cancer Chemother Pharmacol 67(3) (2011) 637–46.

11. YL Wu, JS Lee, S. Thongprasert, CJ Yu, L. Zhang, G. Ladrera, V. Srimuninnimit, V. Sriuranpong, J. Sandoval-Tan, Y. Zhu, M. Liao, C. Zhou, H. Pan, V. Lee, YM Chen, Y. Sun, B. Margono, F. Fuerte, GC Chang, K. Seetalarom, J. Wang, A. Cheng, E. Syahruddin, X. Qian, J. Ho, J. Kurnianda, HE Liu, K. Jin, M. Truman, I. Bara, T. Mok, Intercalated combination of chemotherapy and erlotinib for patients with advanced stage non-small-cell lung cancer (FASTACT-2): a randomised, double-blind trial, Lancet Oncol 14(8) (2013) 777 – 86.
12. H. Jian, W. Li, Z. Ma, J. Huang, J. Feng, Y. Song, B. Gao, H. Zhu, M. Tao, C. Bai, S. Ma, H. Pan, S. Qin, D. Hua, Y. Yu, S. Lu, Intercalating and maintenance gefitinib plus chemotherapy versus chemotherapy alone in selected advanced non-small cell lung cancer with unknown EGFR status, Sci Rep 7(1) (2017) 8483.
13. Y. Cheng, H. Murakami, PC Yang, J. He, K. Nakagawa, JH Kang, JH Kim, X. Wang, S. Enatsu, T. Puri, M. Orlando, JC Yang, Randomized Phase II Trial of Gefitinib With and Without Pemetrexed as First-Line Therapy in Patients With Advanced Nonsquamous Non-Small-Cell Lung Cancer With Activating Epidermal Growth Factor Receptor Mutations, J Clin Oncol 34(27) (2016) 3258–66.
14. A. Nakamura, A. Inoue, S. Morita, Y. Hosomi, T. Kato, T. Fukuhara, A. Gemma, K. Takahashi, Y. Fujita, T. Harada, K. Minato, K. Takamura, K. Kobayashi, T. Nukiwa, Phase III study comparing gefitinib monotherapy (G) to combination therapy with gefitinib, carboplatin, and pemetrexed (GCP) for untreated patients (pts) with advanced non-small cell lung cancer (NSCLC) with EGFR mutations (NEJ009), Journal of Clinical Oncology 36(15_suppl) (2018) 9005–9005.
15. J. Wang, J. Zhao, H. Bai, X. Wang, Y. Wang, J. Duan, H. Chen, S. Meng, Y. Tian, DCL Huang, YL Wu, 465P-A phase IIIb open-label study of afatinib in EGFR TKI-naïve patients (pts) with EGFR mutation-positive (EGFRm+) NSCLC: Exploratory biomarker analysis, Annals of Oncology 30 (2019) ix153-ix154.
16. S. Hong, F. Gao, S. Fu, Y. Wang, W. Fang, Y. Huang, L. Zhang, 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 4(5) (2018) 739–742.

Figures

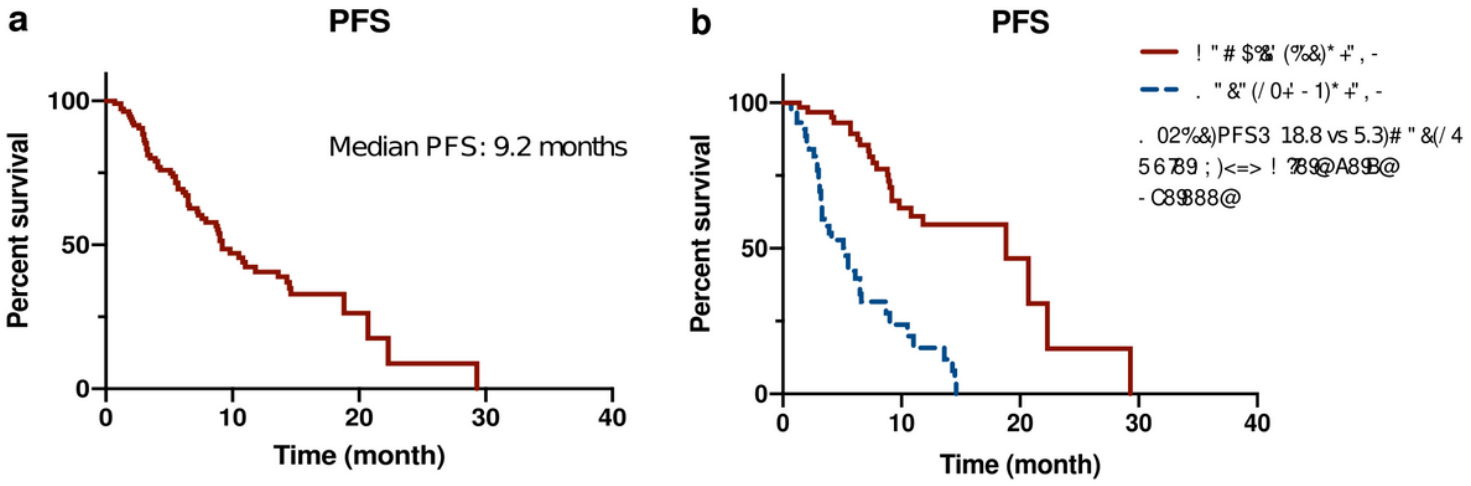

Figure 1

Progression-free survival (PFS) of all enrolled patients (a), and patients of combination group or monotherapy group (b)

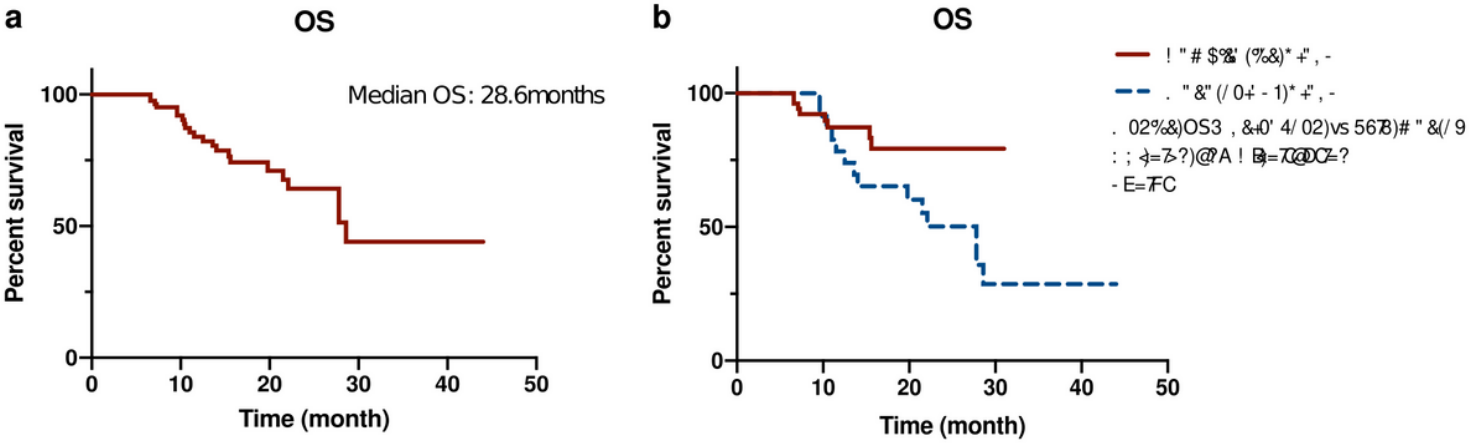

Figure 2

Overall survival (OS) of all enrolled patients (a), patients of combination group or monotherapy group (b)