

Efficacy of First-Third generation EGFR inhibitor combined with chemotherapy as first-line treatment for advanced lung adenocarcinoma in a real-world setting

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Abstract

Background

To explore the optimal treatment strategy for patients who harbor sensitive EGFR mutations, a head-to-head study was performed to compare chemotherapy and gefitinib-erlotinip, osimertinib treatment in combination or with either agent alone as first-line therapy, in terms of efficacy and safety.

Methods

A total of 200 untreated patients with advanced lung adenocarcinoma who harbored sensitive EGFR mutations were randomly assigned to receive gefitinib-erlotinip combined with pemetrexed and carboplatin group, gefitinib-erlotinip osimertinib combined with pemetrexed and carboplatin group, pemetrexed plus carboplatin alone group, or gefitinib-erlotinip alone group, osimertinib alone group.

Results

The progression-free survival (PFS) of patients in the gefitinib-erlotinip combination group Mean Survival Time PFS 22.00 month,95%CI[16.29,27.70] and osimertinib gefitinib-erlotinip combination group Mean Survival Time PFS 40.00 month,95%CI[28.12,51.87]was longer than that of patients in the chemotherapy alone group PFS10,81 months, 95% CI,[8.99–12.64],gefitinib-erlotinip alone group PFS14.00 month.95%CI[11.98-20.01], osimertinib alone group PFS 26.66 month 95%CI[24.77-29.22].The gefitinib-erlotinip osimertinib combinational resulted in longer overall survival (OS) than chemotherapy alone (HR = 0.46, $p = 0.016$) or gefitinib-erlotinip alone (HR = 0.36, $p = 0.01$). osimertinib alone (HR = 0.26, $p = 0.01$).

Conclusions

Our finding suggested that treatment with pemetrexed plus carboplatin combined with gefitinib-erlotinip and pemetrexed plus carboplatin combined with gefitinib-erlotinip osimertinib group could provide better survival benefits for patients with lung adenocarcinoma harboring sensitive EGFR mutations.

Background

Lung cancer is the leading cause of cancer deaths worldwide [1], about 85% of cases are diagnosed as non-small-cell lung cancer (NSCLC) [2].The median age of NSCLC patients is 70 years and the disease is usually diagnosed in advanced stages, when curative surgery is no longer feasible [3].In metastasized disease, first-line chemotherapy is often not successful and the 5-year survival rate is only 4.2% [3]. NSCLC is histologically classified into the major subtypes adenocarcinoma (~ 40%) [4, 5],Recurring mutations have been reported in genes coding for epidermal growth factor receptors (EGFR) in 10–40% of adenocarcinomas [6, 7, 8], *EGFR* mutations can lead to constitutive activation of anti-apoptotic and proliferation signaling pathways, which promote cancer progression [9],EGFR tyrosine kinase inhibitors (TKI) are the preferred first-line treatment for advanced NSCLC with *EGFR* mutations [10, 11], Treating NSCLC is challenging because of the advanced age of patients. As EGFR-TKI avoid the systemic side effects of traditional chemotherapy, they might be more suitable for treating elderly patients [12]. Osimertinib, a third-generation EGFR-TKI that selectively binds the C797 residue inhibiting the T790M mutation, has shown high activity in term of Progression-Free Survival (PFS) and overall response rate in *EGFR*-T790M positive patients [13, 14] and efficacy superior to gefitinib/erlotinib in the first-line treatment by approximately a 9 months advantage in PFS [15]. However, acquired resistance occurs also to osimertinib either in T790M-positive NSCLC patients or in patients treated in first-line [16, 17].EGFR-dependent or independent mechanisms of resistance have been described even if they remain not completely understood [16].*EGFR* G796/C797, L792 and L718/G719 mutations, *MET* and *HER2* amplification, *BRAF*, *KRAS*, and *PIK3CA* mutations, oncogenic fusion mutations in *FGFR3*, *RET*, and *NTRK* were recently identified in a large cohorts of osimertinib-resistant lung cancer patients either treated in second-line [18, 19] and in first-line [20]. Knowledge of these mechanisms is relevant in order to develop new therapeutic strategies to overcome TKI-resistance; however, how prevent or delay the acquisition of resistance remains an important issue. Some data indicated that in PC9 cell line and xenograft models, the combination of gefitinib with pemetrexed or the intermittent combination of pemetrexed and gefitinib prevented some the appearance of gefitinib resistance mediated by T790M mutation and epithelial-mesenchymal transition [20]. However, the combination was ineffective when gefitinib was administered before pemetrexed. Theoretically, Chemotherapy, given its different and more generic mechanism of action, can postpone the resistance to EGFR-TKIs by limiting the tumor heterogeneity, thus improving the efficacy of treatment either in first-and second-line. Osimertinib combined or intercalated with chemotherapy deserves to be considered either for patients in progression after first/second-generation TKIs or in first-line setting. Our study was undertaken to explore a long-term survival outcomes in the combination of osimertinib with pemetrexed add platinum and the combination of gefitinib/erlotinib with pemetrexed add carboplatin in elderly lung adenocarcinoma patients.

Study Design And Patients

Our study was a five-arm randomized open-label phase II study, A pemetrexed-carboplatin plus gefitinib-erlotinib group, A pemetrexed-carboplatin plus gefitinib-erlotinib plus osimertinib group, pemetrexed plus carboplatin group, gefitinib-erlotinib group, osimertinib group as first-line therapy for lung adenocarcinoma patients. The study was approved by the Institutional Review Board of the Shan-Xi Bethune Hospital and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided informed consent before any study-related procedure. Patients were eligible for our study if they were 45-84 years old, had a histologic or cytologic diagnosis of locally advanced or metastatic adenocarcinoma (Stage IIIB or IV).The staging was performed according to the 7th edition of the TNM classification. Patients required at least one measurable lesion meeting Response Evaluation Criteria in Solid Tumors (RECIST) guidelines and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1.Patients were excluded with surgical-complex therapy, radio-complex therapy, if they had received systemic anticancer therapy for advanced disease; had unstable systemic disease, including active infection, uncontrolled hypertension, unstable angina. The study was conducted according to the Declaration of Helsinki and

approved by the Shan-Xi Bethune Hospital, Taiyuan City, Shanxi Province Ethics Committee. All participants included in the study signed written informed consent before treatment.

Randomization

Patients were allocated in a 1:1:1:1:1; ratio using minimization software. Randomization was stratified by different treatments. Throughout the study, clinicians and study participants were not masked to the identity of the study treatment.

Treatment protocol

Before TKI therapy, Tumor gene mutation profile, including EGFR T790M, ALK-M, KRAS-M, METM, RETM, ROS, and so on gene, was performed. If the test was positive, first-generation TKI therapy drugs, Gefitinib, Erlotinib, were used. Eligible patients were randomized to one of the following treatment arms: Patients with advanced lung adenocarcinoma were randomly assigned to five groups. The combination group A: received pemetrexed (500 mg/m² on Day 1) plus carboplatin (10 mg /m², on Day 1) combined with gefitinib (250 mg/day on Days 5–21 day or erlotinip (150 mg/day on Days 5–21 day) and repeated every four weeks for up to six cycles and then continued to receive pemetrexed plus carboplatin combined with gefitinib or Erlotinip every four weeks. The combination group B: received pemetrexed and carboplatin plus gefitinib-erlotinib plus osimertinib, pemetrexed and carboplatin plus gefitinib-erlotinib usage as before, when gefitinib-erlotinib plus pemetrexed and carboplatin occurs after resistance, add osimertinib, (80 mg/day on Days 5–21 day repeated every four weeks for up to six cycles. The chemotherapy group received the same chemotherapy regimen as the combination group every four weeks for up to six cycles and then continued to receive pemetrexed plus carboplatin alone every four weeks. The gefitinib or erlotinip group received gefitinib or erlotinip alone. osimertinib group received osimertinib alone, All therapies were continued until progression, unacceptable toxicity or death. Tumor response was assessed by use of CT with RECIST every 4 weeks until treatment cessation or disease progression.

Outcomes measure

The primary end point was PFS. Secondary end points included OS, overall response rate (ORR) and the adverse-event profile. PFS was defined as the time from the date of randomization to the first date of disease progression or death from any cause. For patients not known to have died as of the data cut-off date and who did not have objective progressive disease, PFS was censored at the date of the last objective progression-free disease assessment. OS was measured from the date of randomization to the date of death. For each patient who was not known to have died as of the data inclusion cut-off date for a particular analysis, OS was censored for that analysis at the date of last prior contact. Toxicity was graded according to National Cancer Institute Common Terminology Criteria for adverse events, version 4.0. Analyses were performed on an intention-to-treat (ITT) basis.

Statistical analysis

The leading parameter for sample size calculation was PFS. The sample size was set at 200 patients in total using a log-rank-test power analysis, on the basis of several assumptions. Clinical parameters and adverse events among five arms were analyzed using the χ^2 test. Survival results were summarized as median values and two-sided 95% confidence intervals (CIs) and were analyzed using Kaplan–Meier's technique, whereas the log-rank test was used for comparisons among subgroups. Multivariable adjusted hazard ratios (HRs) for all-cause mortality by patient and treatment pattern were estimated using Cox regression. HRs were calculated along with their corresponding 95% CIs as measurements of association. The graphs and statistical tests have been made using the GraphPad Prism software (versions 8.0.1, 9.0.0) and statistical tests were conducted using the SPSS software, version 22 (SPSS, Inc., Chicago, IL), was used for all statistical analyses.

Results

Between January 1, 2017 and June 30, 2021, 200 patients were randomly assigned to chemotherapy plus gefitinib-erlotinib group ($N = 40$), chemotherapy plus gefitinib-erlotinib osimertinib group ($N = 40$), chemotherapy group ($N = 40$) or gefitinib-erlotinib alone group ($N = 40$), osimertinib alone group ($N = 40$). The demographics were balanced between the treatment arms (Table 1). At the time of analysis of our study, due to disease progression, protocol violation (Figure 1); 30 gefitinib-erlotinib combination chemotherapy, 28 osimertinib gefitinib-erlotinib combination chemotherapy and 30 alone chemotherapy, 33 gefitinib-erlotinib, 29 Osimertinib discontinued the first-line combination respectively, have OS events.

The flowchart of our study is shown in Figure 1

Table 1 Patient baseline characteristics ($N = 200$)

Characteristic	No. (%)
Age (yr)	
45-69	126(63.00)
≥ 70	74(37.00)
Gender	
Male	89(44.73)
Female	110(55.26)
Gene mutation(Tested)	
EGFR +	120(60.00)
EGFR -	36(18.00)
Wild-type	4 (2.00)
T790M mutations +	37(18.50)
ALK mutations+	5 (2.50)
KRAS mutations+	11(5.50)
RET mutations+	7(3.50)
MET mutations+	7(3.50)
EGFR gene mutation site-n	
Exon18	9 (4.50)
Exon19	47(23.50)
Exon19 + Exon21	10(5.00)
Exon 20 +	6(3.00)
Exon21L858R	70(35.00)
Chemical-TKI therapy	
Yes	80(40.00)
No	120(60.00)
First-generation Chemical-TKI therapy	40(20.00)
First-Third generation Chemical-TKI therapy	40(20.00)
TKI therapy alone	
Yes	80(40.00)
No	120(60.00)
First generation TKI therapy alone	40(20.00)
Third generation TKI therapy alone	40(20.00)
Chemical-therapy alone	40(20.00)

Table 2. Results of Cox univariate and multivariate regression analysis

Characteristic	Univariable analyses		Multivariable analyses	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Age (yr)				
45-69	Reference		Reference	
≥70	0.49(0.30-0.81)	0.005	0.49 (0.28-0.89)	0.02
Gender				
Male	Reference		Reference	
Female	0.77(0.53-0.96)	0.04	0.92(0.56-1.53)	0.76
gene mutation				
No	Reference		Reference	
Yes	0.72(0.07-0.25)	0.01	0.15(0.07-0.29)	0.01
First add third generation TKItherapy with Chemicaltherapy				
No	Reference		Reference	
Yes	0.56(0.35-0.93)	0.02	1.50(0.42-5.31)	0.52
First add third generation TKItherapy alone				
No	Reference		Reference	
Yes	1.11(0.64-1.91)	0.72	0.71 (0.18-2.71)	0.62
chemical therapy alone				
No	Reference		Reference	
Yes	8.05(4.07-15.93)	0.001	5.97(1.45-24.44)	0.01

CI. Confidence interval. Cox regression models with adjustment for single factors showed a significant influence of age (yr) ($p = 0.005$), gender ($p = 0.04$) and *EGFR* status ($p = 0.01$), first add third generation TKItherapy with chemicaltherapy ($p = 0.02$) on OS. Accordingly, Age (yr) 55-69 had an 51% reduced risk of death compared to ≥ 70 (yr) (hazard ratio [HR] 0.49, 95% CI 0.30-0.81). Females had an almost 30% reduced risk of death compared to males (hazard ratio [HR] 0.71, 95% CI 0.53-0.96). Patients with an *EGFR* mutation had an almost 28% reduced risk of death compared to negative patients ([HR] 0.72, 95% CI 0.07-

0.25). First add third generation TKI therapy with chemotherapy had an almost 54% reduced risk of death compared to first add third generation TKI therapy alone. The mutant patients had a longer overall survival (OS) than the wild-type patients [53]. Our patient with 60% positive EGFR gene mutations demonstrated a longer progress-free OS survival than those with negative and wild-type gene. Nevertheless, EGFR mutations were more frequent in patients over 75 than in younger patients: 17% versus 8.1% ($P < 0.001$) [54].

Safety

Table 3

The most common grade 3–4 adverse events were Neutropenia: 7 patients (12.0%) in First generation Chemical-TKI therapy group, 5 patients (12.5%) in the chemotherapy group and 10 patients (25.00%) in First-Third generation Chemical-TKI therapy group, Fatigue: 5 patients (7.5%) in First generation Chemical-TKI therapy group, 6 patients (15.00%) in First-Third generation Chemical-TKI therapy group, 3 patients (7.5%) in First generation targety group, 2 patients (5.0%) in the chemotherapy group, Liver dysfunction: 4 patients (10.0%) in First generation Chemical-TKI therapy group and 3 patient (8%) in First generation target group and 5 patient (12.50%) in First-Third generation Chemical-TKI therapy. Skin rash: 4 patients (10.0%) in First generation Chemical-TKI therapy group, 6 patients (15.00%) in First-Third generation Chemical-TKI therapy group. Comparisons of grade 3–4 adverse events among five arms were performed, using χ^2 test. None of the p -value is small than 0.05. There were no grade 5 adverse events..

	First generation Chemical-TKI therapy group (N=40)		First generation TKI therapy group (N=40)		p	First-Third generation Chemical-TKI therapy group (N=40)		Third generation TKI therapy group (N=40)		p	Chemical therapy group (N=40)	
	All (%)	Grade 3–4 (%)	All (%)	Grade 3–4 (%)		Grade 3–4	All (%)	Grade 3–4 (%)	All (%)		Grade 3–4 (%)	All (%)
Skin rash	25(63.12)	4(10.0)	25(61.48)	2(5.00)	0.25	26(65.00)	6(15.00)	21(53.02)	0(0.00)	1.0	8 (20.0)	0(0.00)
Anorexia	21(53.12)	0(0.00)	17(42.21)	0(0.00)	1.0	24(60.00)	0(0.00)	13(31.81)	0(0.00)	1.0	16(40.0)	0(0.00)
Cough	18(46.12)	0(0.00)	16(40.23)	0(0.00)	1.0	19(45.00)	0(0.00)	13(33.31)	0(0.00)	1.0	13(33.31)	0(0.00)
Nausea	18(43.12)	0(0.00)	12(30.23)	0(0.00)	1.0	19(47.50)	0(0.00)	10(24.21)	0(0.00)	1.0	16(40.0)	0(0.00)
Fatigue	12(30.00)	5(12.5)	11(27.58)	3(7.50)	1.0	15(37.50)	6(15.00)	4(10.61)	0(0.00)	0.22	11(27.5)	2(5.0)
Diarrhea	19(47.12)	0(0.00)	17(43.34)	0(0.00)	1.0	24(60.00)	0(0.00)	13(31.81)	0(0.00)	1.0	8(20.0)	0(0.00)
Neutropenia	13(32.12)	7(12.00)	11(27.12)	4(10.00)	0.15	15(37.50)	10(25.00)	7(18.22)	0(0.00)	1.0	14(35.0)	5(12.5)
Anemia	17(43.00)	0(0.00)	14(35.12)	0(0.00)	1.0	18(45.00)	0(0.00)	7(27.31)	0(0.00)	1.0	16(40.0)	0(0.00)
Thrombocytopenia	17(40.07)	0(0.00)	13(32.12)	0(0.00)	1.0	18(45.00)	0(0.00)	11(27.31)	0(0.00)	1.0	10 (25.0)	0(0.00)
Increased LFT	22(54.54)	4(10.0)	17(41.72)	3(8.0)	0.35	24(60.00)	5(12.50)	5(13.61)	0(0.00)	1.0	10 (27.5)	0(0.00)

Discussion

Our study examined the efficacy of gefitinib-erlotinib combined with carboplatin and pemetrexed for first-line treatment of advanced NSCLC with sensitive EGFR mutations. The study met its primary end point (PFS) at the last day of follow-up (June 30, 2021). The PFS results for the five treatment arms are clearly divided by the performed test. The PFS of the combination group was significantly longer than those in the gefitinib-erlotinib alone group and chemotherapy alone group. The results of our study indicate that gefitinib-erlotinib combined with carboplatin and pemetrexed as first-line therapy provides better survival benefits than gefitinib-erlotinib alone. Similar results were also achieved in a previous study in which gefitinib plus pemetrexed provided greater PFS than gefitinib alone (15.8 months vs. 10.9 months, HR = 0.69) as first-line therapy for EGFR-mutated NSCLC [22]. The results in another prospective single arm clinical trial achieved a median PFS of 18.0 months for EGFR-mutated patients using pemetrexed plus gefitinib [23]. The median OS for our combination group was 32.0 months, which is similar to that reported in the FASTACT-2 study, intercalating chemotherapy with erlotinib [24]. Han reported the combination group PFS 17.5 months, OS 32.6 month was longer than those in the gefitinib-group IPFS 11.9 months, OS 25.8 month [25]. In another studies are same [26–30], [31]. In this setting, the most important question is whether the combination strategy is better than EGFR TKI alone. Somatic mutations of EGFR have been associated with sensitivity to EGFR-TKIs in patients with advanced NSCLC. However, most of those EGFR mutated NSCLC patients develop acquired EGFR TKI resistance after 10–14 months of first-line TKI treatment. It was reported that simultaneous treatment with gefitinib and pemetrexed prevented the appearance of gefitinib resistance mediated by the T790M mutation or epithelial-to-mesenchymal transition (EMT) in PC9 and HCC827 cells, respectively [32]. Sequential use of chemotherapy followed by gefitinib enhances the antitumor effect in NSCLC cell lines poorly responsive to reversible EGFR TKIs [33]. According to a previous study, the combination of EGFR TKIs and cisplatin is also an effective treatment against EGFR TKI-resistant cancer [34]. In addition, FASTACT2 used to

evaluate erlotinib plus gemcitabine and platinum therapy in NSCLC patients showed that the combination of platinum-based chemotherapy and TKI exhibited favorable tolerability and promising efficacy.[24] In this study, the median PFS,OS of patients reached 22months,32 months,in the combination group, but only 14 months,26 months in the TKI monotherapy group, thus confirming the superiority of the combination therapy mentioned before. In this study,we also discuss the efficacy of osimertinib as a second-line treatment in patients with EGFR T790M-positive advanced NSCLC who experience disease progression with prior first-generation EGFR-TKI treatment.Finally,40 patients met the enrollment criteria and were analyzed,The EGFR T790M secondary mutation is the most common resistance alteration in EGFR-mutant NSCLC patients treated with the first-or-second-generation TKIs[35 36 37 38].Our findings showed that in advanced adenocarcinoma patients with EGFR T790M mutation after obtaining first-generation EGFR-TKI resistance,Add osimertinib alone and osimertinib combination chemotherapy arms as the second-line treatment to control recurrent foci may be more effective in its action than in first-generation EGFR-TKI treatment alone and combination chemotherapy arms.It is noteworthy that osimertinib combined chemotherapy and osimertinib alone may exert survival benefits in advanced adenocarcinoma.In a clinical trial of AURA3,when patients who harbored T790M after drug resistance to first-line EGFR-TKI received osimertinib treatment,the median PFS was 10.1 months and the median OS was 26.8 months[39 40].In a investigation151patients T790M mutation NSCLC with an acquired resistance to first-line EGFR-TKIs then received osimertinib as subsequent treatment.defined first-line EGFR-TKI (PFS1) as the time from the first dose of first-line EGFR-TKI to progression or death, while the estimated median PFS of osimertinib (PFS2) was determined as the time from the first dose of osimertinib to progression or death.The ORR and DCR of osimertinib was 56.3% and 88.0%,respectively.The median PFS2 was 10.1months,OS of osimertinib was 30.2 months,median PFS1 + PFS2 was 27.5 months and the median OS from first-line EGFR-TKI to death was 61.3 months.[41]The current standard-of-care for such patients is the use of the osimertinib which irreversibly inhibits the activity of both the EGFR-activating (L858R, exon 19 deletion)[42 43]. In 2019, 9,28. At the European Medical Oncology Annual Meeting (ESMO) reported,Osimertinib alone had a significant reduction 60% (ORR) in adenocarcinoma,PFS 18.9 month,OS 38.6 month.A phase III trial evaluating osimertinib combined with platinum-pemetrexed vs osimertinib monotherapy could be the right step forward to significantly prolong the survival of *EGFR*-mutated NSCLC patients[44].Osimertinib had been frequently used as the backbone of combination treatment[45 46 47].After eradicating tumors with heterogeneity,adding chemotherapy to osimertinib might increase the response rate and improve PFS and OS with a low incidence of grade ≥ 3 AEs [48],At the same time,most of brain metastasis(BM) occurs in after first-generation EGFR-TKI treatment resistance.A large rando mized trial comparing osimertinib to gefitinib or erlotinib reported that PFS was significantly longer in the osimertinib arms,and time to CNS metastases was significantly delayed because osimertinib crosses the blood-brain barrier.[49]The efficacy of osimertinib in BM patients may be the increased concentration of osimertinib in CSF as compared with those of previous drugs (such as first and second-generation EGFR-TKI or chemotherapy)[13, 14].This extended its survival period,This intercalated combination strategy only caused a minimal increase in toxicities compared to gefitinib-erlotinib with chemotherapy.The common grade 3–4 treatment-related adverse events in combination arm were liver dysfunction,neutropenia,fatigue and skin rash.Combinational strategy resulted a modest increase in liver dysfunction than gefitinib-erlotinib arm,which is consistent with the results in JMIT study.

Conclusion

Our finding suggested that treatment with pemetrexed plus carboplatin combined with gefitinib-erlotinip and pemetrexed plus carboplatin combined with gefitinib-erlotinip osimertinib group could provide better survival benefits for patients with lung adenocarcinoma harboring sensitive EGFR mutations.Our study demonstrated that pemetrexed plus carboplatin combined with gefitinib-erlotinib osimertinib provided longer PFS,OS compared with either agent alone in patients with sensitive EGFR-mutan lung adenocarcinoma.The toxicity profiles show good tolerance by patients. First-Third generation Chemical-TKItherapy group was a good treatment option.This combinational strategy may yield new choices for the treatment of sensitive EGFR-mutant NSCLC.This trial was a monocenter study,and the results should be interpreted considering this limitation.These results need to be confirmed through a multicenter study.

Abbreviations

NSCLC:

Non-small-cell lung cancer

EGFR

epidermal growth factor receptors

TKIs

tyrosine kinase inhibitors

AE:

Adverse event

CI:

Confidence interval

DCR:

Disease control rate

ORR:

Objective response rate

CR

complete response

PR;

partial response ,

SD

stable disease

PD

progression disease

HR:

Hazard ratio

OS:

Overall survival

PFS:

Progression-free survival

QoL:

Quality of life

CSF

Brain effusion

CNS

Central Nervous System

Declarations

Ethics approval and consent to participate

All patients signed informed consent before treatment, including their consent to treatment and clinical information for further prognostic factors analysis. This study was approved by the Research Ethics Committee of Shan-Xi Bethune Hospital, The study was conducted according to the Declaration of Helsinki.

Consent for publication

All the authors had read the articles and consent for publication.

Availability of data and materials

All the data and materials, from Shanxi Bethune Hospital, Materials are available upon request. All data needed to evaluate the conclusions in the paper are present in the paper.

Competing interests

All authors declare no Competing interests in this work.

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Contributions

MWC, participated in the conception of the study, drafted the manuscript. ATH, performed the experiment. MWC, ATH, contributed significantly to analysis and manuscript preparation; ATH, participated in the sequence alignment. the design of the study and performed a statistical analysis. YP, conceived of the study,

participated in the design of the study,helped perform the analysis with constructive discussions.All of the authors read and approved the final manuscript.

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Figures

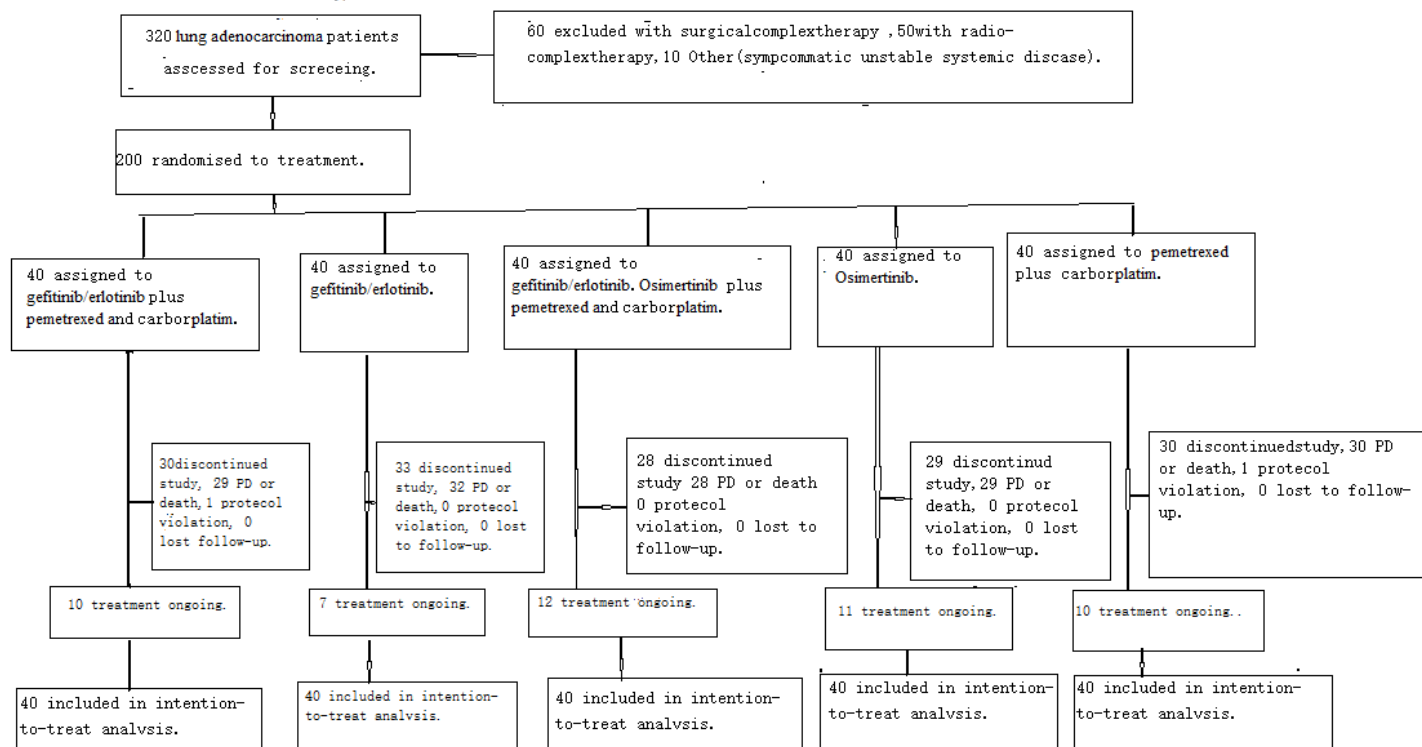


Figure 1

The flowchart of our study

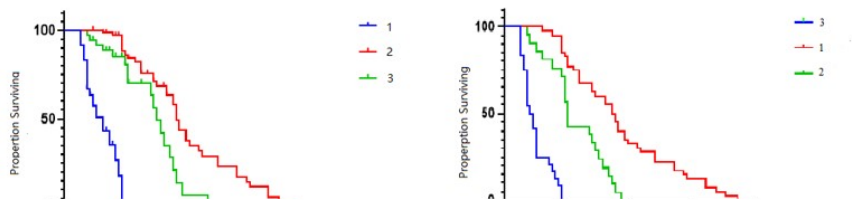


Figure 2

A. First generation Chemical-TKI therapy group PFS vs First generation TKI therapy group PFS vs chemotherapy (pemetrexed plus carboplatin) group PFS $P < 0.05$. Mean Survival Time 22.00 month, 95% CI [16.29, 27.70] vs 14.00 month, 95% CI [11.98, 20.01] vs 10.81 months, 95% CI [8.99–12.64]. Figure 2 B.1. First generation Chemical-TKI therapy group OS vs First generation TKI therapy alone OS vs chemotherapy (pemetrexed plus carboplatin) group OS $P < 0.05$. Mean Survival Time 32.00 month, 95% CI [25.29, 38.71] vs 28.00 month, 95% CI [14.58, 41.41] vs 11.51 months, 95% CI [8.96–13.64]. C.1. First-Third generation Chemical-TKI therapy group PFS vs Third generation TKI therapy PFS vs chemotherapy (pemetrexed plus carboplatin) group PFS. $P < 0.001$. Mean Survival Time 40.00, 95% CI [28.12, 51.87] vs 26.66, 95% CI [24.77, 29.22] vs 10.81 months, 95% CI [8.99–12.64]. Figure 2 D. First-Third generation Chemical-TKI therapy group OS vs Third generation TKI therapy group OS vs chemotherapy (pemetrexed plus carboplatin) group. $P < 0.05$. Mean Survival Time 48.00, 95% CI [42.81, 53.18] vs 36.00, 95% CI [34.71, 38.28] vs 11.51 months, 95% CI [8.96–13.64].

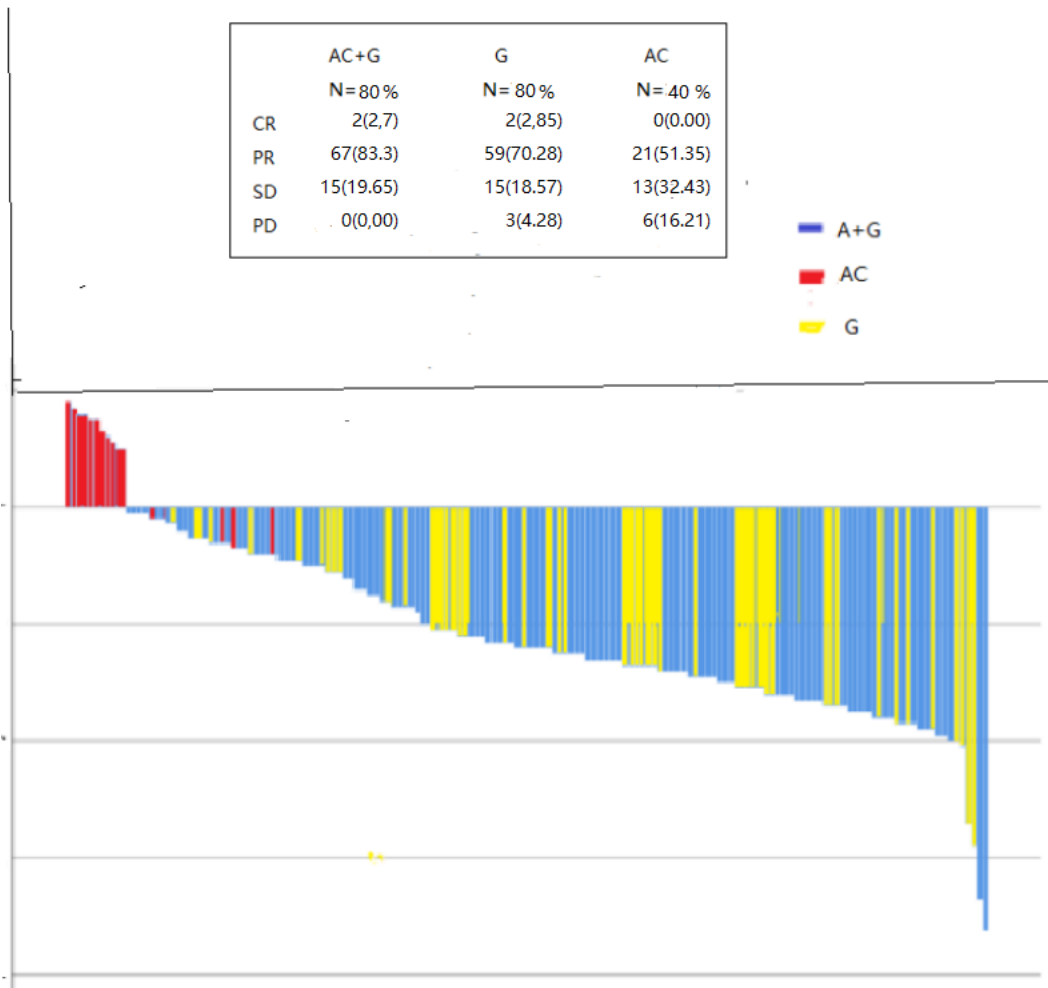


Figure 3
 Waterfall plot of the best percent change in target lesions from baseline for 200 patients based on investigator assessment. shows the best percent change from baseline in terms of size of target lesion for patients with measurable disease.AC+G:First generation Chemical-TKltherapy group+First-Third generation Chemical-TKltherapy group,G:First generation TKltherapy group+Third generation TKltherapy group,AC;Chemicaltherapy group.Tumor response was assessed as complete response (CR), partial response (PR), stable disease (SD), progression disease (PD) in accordance with the standard of RECIST [21]