EGFR tyrosine kinase inhibitor combined with synchronous or sequential chemotherapy for advanced NSCLC patients of gradual progression after first-line EGFR-TKI therapy: a randomized controlled study

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Abstract

Research topic	EGFR tyrosine kinase inhibitor combined with synchronous or sequential chemotherapy for advanced NSCLC patients of gradual progression after first-line EGFR-TKI therapy: a randomized controlled study
Purpose	The purpose of this study is to investigate whether concurrent use of EGFR-TKI and chemotherapy can achieve better response than sequential use of EGFR-TKI and chemotherapy in advanced EGFR-activating NSCLC patients who occurred gradual progression after first-line EGFR-TKI treatment and to investigate genetic alteration and peripheral blood immune cell phenotype change during the EGFR-TKI therapy.
Endpoints	Primary endpoints: progression-free survival (PFS) Secondary endpoints: objective response rate (ORR), disease control rate (DCR), overall survival (OS), safety index
Study design	Single center, randomized, open-label
Enrollment	Patients who occurred gradual progression on first-line EGFR-TKI therapy are randomly assigned 1: 1 to synchronous therapy group or sequential therapy group.

Inclusion criteria (Details see page 9 to 10):

1) Signed informed consent for the study
2) Histologically or cytologically stage IIIB or IV adenocarcinoma
3) Sensitive EGFR mutations (19 del, 21L858R)

4) With measurable lesions

5) Patients achieved the gradual progression after first-line EGFR-TKI therapy

6) Able to comply with study and follow-up procedures

7) Age >=18 years, ECOG PS: 0~2, estimated survival duration more than 3 months;

Exclusion criteria (Details see page 10 to 12) :

1) Evidence of non-adenocarcinoma histology

2) EGFR wild-type patients, or patients with rare EGFR mutations or complex EGFR mutations

3) Symptomatic or untreated brain metastases

4) Unstable systemic disease

5) History of other unstable diseases.

6) Pregnancy or lactation

1 Background

Lung cancer is the most common cause of cancer-related deaths worldwide[1], and approximately 85 to 90% of all lung cancer cases are non-small cell lung cancer (NSCLC). More than 70% of lung cancer cases are diagnosed at an advanced stage, which means that surgery is not an option for most of these patients. EGFR mutations are one of the most common lung cancer-driven genes. In particular, as many as 51.4% of EGFR mutations occur in Asian patients with adenocarcinoma.[2]It has been absolutely confirmed that compared with the traditional chemotherapy treatment, EGFR tyrosine-kinase inhibitors (TKIs) can significantly improve the objective response rate (ORR) and progression free survival(PFS), and become a standard first-line treatment for NSCLC patients with EGFR mutation-positive.[3-11]

However, it is unavoidable that almost all patients develop acquired resistance to EGFR-TKI with a median progression-free survival time of only 8 to 13 months[3-11]. The concept of acquired resistance for EGFR-TKI was defined by Jackman[12] according to Response Evaluation Criteria in Solid Tumors (RECIST) or the World Health Organization definition of progression[13]. However，we can see that the RECIST is increasingly showing the limitation of EGFR-TKI evaluation in clinical work. Wu et al demonstrated clinical modes of EGFR-TKI failure could favor strategies for subsequent treatment and predicting a survival benefit in advanced NSCLC. For those patients with gradual progression in clinical practice, continuation of EGFR-TKI would be an optimal treatment strategy after failure. Also several studies[14-16] have reported continuation of EGFR-TKI may delay second-line therapy.

Besides a second mutation, such as T790M and c-MET amplification is related to the failure of EGFR-TKI therapy, nearly 40% of acquired resistance mechanism is remain unknown. Thus, the way that prolong the duration from gradual progression to eventual failure seems to be optimal strategy.

Although there is no evidence whether additional chemotherapy can further delay acquired EGFR-TKI resistance for gradual progression patients. We once found[17] first line treatment with chemotherapy (pemetrexed plus cisplatin) combined with EGFR-TKI could provide better survival benefits for patients with lung adenocarcinoma harboring sensitive EGFR mutations. Therefore, this study would investigate for patients with EGFR-TKI gradual progression, whether chemotherapy combined with TKI could provide more benefit than first continuing EGFR-TKI and then chemotherapy alone.

In order to further understand the mechanism of drug resistance, this study would conduct some exploratory analyses by using mass spectrometry technology to detect genetic alteration and peripheral blood immune cell phenotype change during the EGFR-TKI therapy.

2 Study purpose

To directly compare different strategy (concurrent use of EGFR-TKI and chemotherapy or sequential use of EGFR-TKI and chemotherapy) in terms of efficacy and safety in advanced EGFR-activating NSCLC patients who occurred gradual progression after first-line EGFR-TKI treatment and to investigate genetic alteration and peripheral blood immune cell phenotype change during the EGFR-TKI therapy.

2.1 Primary objective

PFS, PFS is defined as the time from the date of randomization to the first date of disease progression or death from any cause. For patients who don't have objective progressive disease or don't know whether or not have died at the cut-off date, PFS is censored at the date of the last objective progression-free disease assessment.

For the sequential therapy group, PFS is defined as PFS1(from gradual progression to discontinue EGFR-TKI) plus PFS2(chemotherapy alone).

2.2 Second objective

1)ORR, ORR is defined as the percentage of patients with complete remission and partial remission and maintaining the number of evaluable patients over 4 weeks.

2)DCR, DCR is defined as the percentage of patients with complete remission, partial remission, and disease stabilization and maintaining the number of evaluable patients over 4 weeks.

3)OS, OS is 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.

4)Safety index (National Cancer Institute Common Terminology Criteria for adverse events, version 4·0.)

3 Study participants

3.1 Inclusion criteria

1) Patients had to voluntarily join the study and give written informed consent for the study

2) Histologically documented, unresectable, inoperable, locally advanced, recurrent or metastatic stage IIIB or IV adenocarcinoma.

3) A cytologic diagnosis is acceptable (i.e., FNA or pleural fluid cytology)

4) Sensitive EGFR mutations (19del, 21L858R)

5) At least one unidimensionally measurable lesion meeting Response Evaluation Criteria in Solid Tumours (RECIST) criteria.

6) Patients achieved the gradual progression after first-line EGFR-TKI therapy.

   The criteria of gradual progression[18]:

   (1) disease control≥6 months with EGFR-TKI treatment;

   (2) compared with the previous assessment，no significant increment of tumor burden and progressive involvement of non-target lesions with a score ≤2;

   (3) symptom scored≤1.

7) Patients did not receive any chemotherapy previously.

8) Able to comply with study and follow-up procedures

9) Age >=18 years, ECOG PS: 0~2, estimated survival duration more than 3 months；

10) Major organ function

   （1） For regular test results（no blood transfusion within 14 days）：

a) Hemoglobin（HB）≥90g/L；

b) Absolute neutrophils count（ANC）≥1.5×10^9/L；

c) Blood platelets（PLT）≥80×10^9/L

（2） Biochemical tests results defined as follows：

a) Total bilirubin（TBIL）≤1.5 times the upper limit of normal (ULN)；

b) Alanine aminotransferase（ALT）and aspartate aminotransgerase AST≤2.5×ULN，liver metastases，if any，ALT 和 AST≤5×ULN；

c) Creatinine（Cr）≤1.5×ULN or Creatinine Clearance rate (CCr)≥60 ml/min；

（3）Doppler ultrasound assessment：left ventricular ejection fraction (LVEF) ≥the lower limit of normal value (50%).

3.2 Exclusion criteria：

1) Other types of non-small cell lung cancer except adenocarcinoma and Small cell lung cancer（including patients with mixed small cell lung cancer and non-small cell lung cancer）；
2) Evidence of other types of non-small cell lung cancer except adenocarcinoma, small cell, carcinoid, or mixed small cell/non-small cell histology
3) EGFR wild-type patients, or patients with rare EGFR mutations or complex EGFR mutations
4) Patients achieved the dramatic progression after first-line EGFR-TKI therapy.

The criteria of dramatic progression[18]:

(1) disease control lasting ≥3 months with EGFR-TKI treatment;

(2) compared with the previous assessment, rapid progression of multiple target lesions, or progressive involvement of non-target lesions with a score >2;

(3) symptom scored 2.

5) Patients achieved the local progression after first-line EGFR-TKI therapy.

The criteria of local progression[18]:

(1) disease control lasting ≥3 months with EGFR-TKI treatment;

(2) PD due to solitary extracranial lesion or limitation in intracranial lesions (covered by a radiation field);

(3) symptom scored≤1.

6) Previously (within 5 years) or presently suffering from other malignancies

7) A in situ，non-melanoma skin cancers and superficial bladder cancer [Ta (noninvasive carcinoma)，Tis (carcinoma in situ) and T1 (invasion into lamina propria)]；

8) [19]Unstable systemic disease, including active infection, uncontrolled hypertension, unstable angina, congestive heart failure, or myocardial infarction within 6 months prior to Day 1, or serious cardiac arrhythmia requiring medication (patients with chronic atrial arrhythmia, i.e., atrial fibrillation or paroxysmal supraventricular tachycardia, are eligible)

9) History of other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect the

interpretation of the results of the study or render the patient at high risk from treatment complications

10) Gastrointestinal tract disease resulting in an inability to take oral medication or a requirement for intravenous (IV) alimentation, or prior surgical procedures affecting absorption

11) Pregnancy or lactation

3.3 Stop criteria (The reasons for withdrawal will be specified and recorded.**)**

1) Disease progression or death from any cause
2) In case patient is allergic to pemetrexed, cisplatin or icotinib
3) The patient is noncompliant with study procedures.
4) Unacceptable toxicity (The investigator decides that whether the patient should be withdrawn from study treatment. If this decision is made because of toxicity, a serious AE (SAE), or a clinically significant laboratory value, the study drug is to be discontinued, and appropriate measures are to be taken.)
5) The patient has had 2 (Day 1) dose reductions and experiences an AE that would cause a third dose reduction.
6) The patient becomes pregnant or fails to use adequate birth control (for those patients who are able to conceive).
7) According to the informed consent form, the subjects have the right to withdraw from the trial. Subjects who do not accept treatment or re-examinations will be withdrawn.

3.4 Standards for discontinued testing

The following standards for discontinued testing will be applied:

1) a serious safety problem occurs

2) major mistakes are found in the designed clinical protocol during the trial

3) The sponsor of this trial requests discontinued testing because of a lack of funds or poor management.

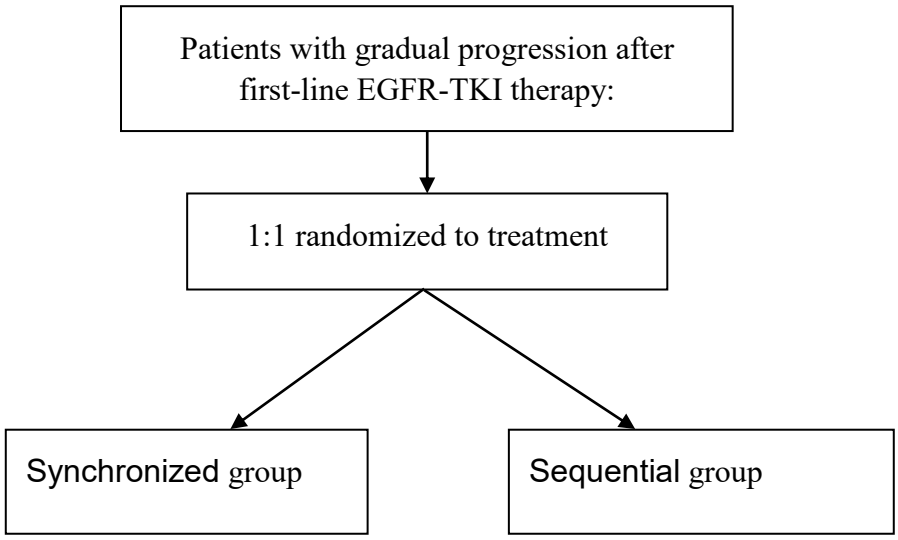
4 Study design

4.1 Sample size

The sample size was set at 120 patients in total on the basis of several assumptions: a median PFS of 5 months with chemotherapy alone beyond first-line EGFR TKI therapy, 8.5 months for chemotherapy combined with EGFR TKI; and 80% power to detect a hazard ratio (HR) of 0.50 with an overall a level of 5%.

4.2 Randomization

Patients were allocated in a 1:1 ratio using minimization software. Randomization was stratified by EGFR mutation status.



Synchronized group

Continued using the initial EGFR-TKI (icotinib (125 mg/time, 3 times/day every day)) combined with Pemetrexed (500 mg/㎡ on day 1) plus cisplatin (75mg/m^2 on day 1) and repeat every four weeks for up to six cycles and then continue to receive pemetrexed combined with EGFR-TKI every four weeks.

Sequential group

Continued using the initial EGFR-TKI (icotinib (125 mg/time, 3 times/day every day)) alone until the investigator judged that continuation was adiaphorous, and switched to Pemetrexed (500 mg/㎡ on day 1) plus cisplatin (75mg/m^2 on day 1) alone, repeat every four weeks for up to six cycles and then continue to receive pemetrexed every four weeks.

4.3 Supportive Care Guidelines

If the patient experiences nausea or vomiting despite the above-mentioned pre-medications, appropriate anti-nausea and anti-emetic therapy may be administered at the discretion of the investigator.

The use of erythrocyte colony stimulating factors (erythropoeitin or darbapoeitin) is allowed.

Other medication other than that described above, which is considered necessary for the subject safety and well being, may be given at the discretion of the investigator.

4.4 Dosing delays/dose modifications

Assuming that there is a normal proportion of granulocytes, the chemotherapy will be allowed to continue if the WBCC is within the range of 3.0 to 4.0×10^9/l. If the WBCC falls within the range of 2.0 to 3.0×10^9/l, chemotherapy will be stopped until the WBCC increases to 3.0 × 109/l, or above. Granulocyte colony-stimulating factor will be used for supportive treatment if WBCC decreases to 2.0×10^9/l or below. The

doses of chemotherapy drugs will be decreased by 25% in the next cycle if IV degree toxicity (including fever-induced neutropenia syndrome) emerges. Chemotherapy will be stopped in advance in cases of disease progression, or unacceptable AEs, even the patient may not finish the chemotherapy plan.

If a patient experiences a grade 3 or higher unacceptable toxicity, which the investigator considers to be associated with EGFR-TKI, dosing will be interrupted, and relevant supportive treatment will be administered.

Treatment may be delayed for up to 49 days to allow a patient sufficient time for recovery from study drug-related toxicity. Patients should be removed from study if treatment is delayed more than 3 weeks due to toxicity or if more than two dose reductions are necessary.

Any patient who requires a dose reduction will continue to receive the reduced dose for the remainder of the study. Any patient who has had 2 dose reductions and who experiences a toxicity that would cause a third dose reduction must be discontinued from study therapy.

5 Observation

5.1 Before enrollment (before the start of treatment, the patients should complete the following tests)

1. History & physical examination, including measurement of height, weight, vital signs and performance status
2. Blood chemistry: bilirubin, alkaline phosphatase, ALT, AST, BUN, creatinine, total protein, albumin, calcium, phosphorus, electrolytes, glucose
3. CT scan of chest, The abdomen ultrasonic.
4. Electrocardiogram
5. Blood CEA, Cyfra21-1, NSE, SCC, Ca125 test
6. MRI or CT scan of brain
7. Radionuclide bone scan (if PET scan available [within 4 weeks], bone scan not necessary)

5.2 Duration of Therapy

1. History & physical examination, including measurement of height, weight, vital signs and performance status (Before every cycle).
2. Blood chemistry: bilirubin, alkaline phosphatase, ALT, AST, BUN, creatinine, total protein, albumin, calcium, phosphorus, electrolytes, glucose (Before every cycle).
3. CT scan of chest, the abdomen ultrasonic (Before every two cycles).
4. Blood CEA, Cyfra21-1, NSE, SCC, Ca125 test (Before every cycle).

5. Electrocardiogram (Before every cycle).
6. MRI or CT scan of brain every 3 months.
7. Radionuclide bone scan every 6 months.

5.3 After disease progression

All of the Patients who arrived the criteria of disease progression will be suggested to detect the most common resistant mutation-EGFR T790M mutation by biopsy or blood sample, but whether to conduct the EGFR mutation analysis is determined by the patient.

Biopsy sample will be used to detect the EGFR T790M mutation by amplification refractory mutation system(*ARMS*), and blood sample will be detected by digital droplet polymerase chain reaction (ddPCR) technology.

5.4 Sample collection (use to exploratory analysis)

1. ctDNA- to detect immune cell phenotype and gene state: collect 8ml peripheral blood (collecting by tube with EDTA-K2 anticoagulant) at prior treatment, one month and every 2 months later.

2. Immune cell phenotype- to detect immune cell phenotype: collect 5ml peripheral blood (collecting by tube with heparin sodium) at prior treatment, one month and every 2 months later.

6 Test method for EGFR mutations

The highly sensitive method termed Amplification Refractory Mutation System (ARMS) was used to detect mutations in the EGFR gene according to the manufacturer's protocol of the DxS EGFR mutation test kit.

7 Efficacy evaluation (RECIST guideline 1.1)

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10mm

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on

study

Special notes on the assessment of target lesions and non-target lesions

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = invaluable.

8 Safety assessments

8.1 Adverse events

Adverse events are development of an undesirable medical condition following or exposure to treatment agents. An undesirable medical condition includes symptoms, or abnormal laboratory findings. The adverse events were graded according to National Cancer Institute Common Terminology Criteria for adverse events, version 4.0.

8.2 Time period for collection of adverse events

Adverse events will be collected from the start of therapy throughout the treatment period and including the safety follow-up period. The follow-up period is defined as 28 days after study treatment is discontinued. All the AEs after starting the trial should be followed until satisfactory resolution, or the primary researcher should determine if the AEs have stabilized.

8.3 Judgement of relationship between drug and adverse events

The determination of whether an adverse event is related to a medical treatment is categorized as one of five associations. The definition of “related” is that there is a reasonable possibility that the drug caused the adverse experience.

Definite - The adverse event is clearly related to the medical treatment.

Probable - The adverse event is likely related to the medical treatment.

Possible - The adverse event may be related to the medical treatment.

Unlikely - The adverse event is doubtfully related to the medical treatment.

Unrelated - The adverse event is clearly NOT related to the medical treatment.

8.4 Serious adverse event

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose results in:

1. death
2. life-threatening
3. requires inpatient hospitalization
4. prolongation of existing hospitalization
5. persistent or significant disability/incapacity
6. a congenital anomaly/birth defect

Serious adverse events will be captured from first dose of any study treatment to 30 days after last dose of the study treatment, unless deemed as related to the study treatment by the Investigator.

If serious AEs occur, corresponding countermeasures will be conducted by researchers according to the drug-induced symptoms to ensure patient safety.

8.5 Reporting serious adverse events

Adverse events classified as serious require expeditious handling and reporting to comply with regulatory requirements. Any serious adverse event or death must be reported independent of the circumstances or suspected cause if it occurs or comes to

the attention of the investigator at any time during the study through 30 days after the last administration of study drug. Any serious adverse event occurring beyond 30 days after last administration of study drug must be promptly reported if a causal relationship to study drug is suspected.

9 Follow up

Post-Treatment: The follow-up schedule is the same for both arms of the study. Follow up visits are to be conducted every 16 weeks (+/-30 days) after the start of therapy. Patient will be monitored for progression until death.

Suggested disease assessments in response to symptoms:

- If the patient has new symptoms of bone or back pain, a bone scan should be done
- If the patient has symptoms of abdominal pain or if the physician notes jaundice, hepatomegaly, or an elevation in the liver function tests, a CT scan of the abdomen should be done.
- If the patient exhibits a change in mental or neurologic status, A CT scan or MRI of the brain should be done.

10 Statistical analysis

The data will be collected and analyzed according to the intention-to-treat principle. Standard statistical techniques will be used to describe characteristics of patients in both groups.

PFS and OS will be analyzed by using the Kaplan-Meier method and performed the multivariate analysis using the Cox proportional hazards model, included the following covariates: gender, age, smoking history, EGFR mutations status (deletions in exon 19 vs. L858R), tumor stage and previous response to TKI. ORR and DCR will be analyzed by chi-square statistics or Fisher's exact tests. A significance level of 5% will be used throughout the analysis. All statistical analyses will be conducted using the SPSS software, version 23 (IBM, Armonk, NY).

11 Reference

[1] Mok TS, Wu Y-L, Thongprasert S, Yang C-H, Chu D-T, Saijo N, et al. Gefitinib or Carboplatin–Paclitaxel in Pulmonary Adenocarcinoma[J]. New England Journal of Medicine. 2009,361(10):947-57.

[2] Shi Y, Au JS-K, Thongprasert S, Srinivasan S, Tsai C-M, Khoa MT, et al. A Prospective, Molecular Epidemiology Study of EGFR Mutations in Asian Patients with Advanced Non–Small-Cell Lung Cancer of Adenocarcinoma Histology (PIONEER)[J]. Journal of Thoracic Oncology. 2014,9(2):154-62.

[3] Fukuoka M, Wu YL, Thongprasert S, Sunpaweravong P, Leong SS, Sriuranpong V, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS)[J]. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011,29(21):2866-74.

[4] Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study[J]. The Lancet Oncology. 2011,12(8):735-42.

[5] Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a

multicentre, open-label, randomised phase 3 trial[J]. The Lancet Oncology. 2012,13(3):239-46.

[6] Wu YL, Zhou C, Liam CK, Wu G, Liu X, Zhong Z, et al. 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[J]. Annals of oncology : official journal of the European Society for Medical Oncology. 2015,26(9):1883-9.

[7] Shi YK, Wang L, Han BH, Li W, Yu P, Liu YP, et al. 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[J]. Annals of oncology : official journal of the European Society for Medical Oncology. 2017,28(10):2443-50.

[8] Han JY, Park K, Kim SW, Lee DH, Kim HY, Kim HT, et al. First-SIGNAL: first-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung[J]. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012,30(10):1122-8.

[9] Mok TSK, Kim SW, Wu YL, Nakagawa K, Yang JJ, Ahn MJ, et al. Gefitinib Plus Chemotherapy Versus Chemotherapy in Epidermal Growth Factor Receptor Mutation-Positive Non-Small-Cell Lung Cancer Resistant to First-Line Gefitinib (IMPRESS): Overall Survival and Biomarker Analyses[J]. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2017,35(36):4027-34.

[10]Inoue A, Kobayashi K, Maemondo M, Sugawara S, Oizumi S, Isobe H, et al. Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naive non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002)[J]. Annals of oncology : official journal of the European Society for Medical Oncology. 2013,24(1):54-9.

[11]Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial[J]. The Lancet Oncology. 2010,11(2):121-8.

[12]Jackman D, Pao W, Riely GJ, Engelman JA, Kris MG, Janne PA, et al. Clinical definition of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer[J]. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010,28(2):357-60.

[13]Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)[J]. European journal of cancer (Oxford, England : 1990). 2009,45(2):228-47.

[14]Park K, Yu CJ, Kim SW, Lin MC, Sriuranpong V, Tsai CM, et al. First-Line Erlotinib Therapy Until and Beyond Response Evaluation Criteria in Solid Tumors Progression in Asian Patients With Epidermal Growth Factor Receptor Mutation-Positive Non-Small-Cell Lung Cancer: The ASPIRATION Study[J]. JAMA oncology. 2016,2(3):305-12.

[15]Nishino K, Imamura F, Morita S, Mori M, Komuta K, Kijima T, et al. A

retrospective analysis of 335 Japanese lung cancer patients who responded to initial gefitinib treatment[J]. Lung cancer. 2013,82(2):299-304.

[16]Soria J-C, Wu Y-L, Nakagawa K, Kim S-W, Yang J-J, Ahn M-J, et al. Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial[J]. The Lancet Oncology. 2015,16(8):990-8.

[17]Han B, Jin B, Chu T, Niu Y, Dong Y, Xu J, et al. Combination of chemotherapy and gefitinib as first-line treatment for patients with advanced lung adenocarcinoma and sensitive EGFR mutations: A randomized controlled trial[J]. International journal of cancer. 2017,141(6):1249-56.

[18]Yang J-J, Chen H-J, Yan H-H, Zhang X-C, Zhou Q, Su J, et al. Clinical modes of EGFR tyrosine kinase inhibitor failure and subsequent management in advanced non-small cell lung cancer[J]. Lung cancer. 2013,79(1):33-9.

[19]Li L, Wang H, Li C, Wang Z, Zhang P, Yan X. Transformation to small-cell carcinoma as an acquired resistance mechanism to AZD9291: A case report[J]. Oncotarget. 2017,8(11):18609-14.