Erlotinib as the 2nd/3rd line treatment in advanced or recurrent non-small cell lung cancer with wild type epidermal growth factor and negative expression of c-Met: an open, single arm, phase II trial.（CTONG 1306）

Li Zhang*, Ting Zhou, Yan Huang, Hongyun Zhao, Yunpeng Yang, Cong Xue, Yuxiang Ma, Xuan Wu, Wenhua Liang, YuanYuan Zhao, Wenfeng Fang and Tao Qin

[1]Sun-YatSen University Cancer Center, [2]State Key Laboratory of Oncology in South China, Guangzhou, China, [3]Collaborative innovation Center for Cancer Medicine

*Corresponding Author: Li Zhang, M.D., E-mail: zhangli6@mail.sysu.edu.cn

Background

Given excellent clinical benefits and increased use of Erlotinib in epidermal growth factor receptor (EGFR) mutant non-small cell lung cancer (NSCLC) patients, the question of its benefits in patients who do not have EGFR mutations has gained increasing attention since EGFR wild type constitutes approximately 70% NSCLC.

Preclinical study shows that overexpression of c-Met could cause EGFR-TKI primary and secondary resistance. Therefore, negative expression of c-Met might be feasible to increase EGFR TKIs sensitivity in NSCLC, which could be considered as 2nd biomarker, as so called “bi-biomarker”. This concept is supported by a phase II study (OAM4558g, ASCO2011) which showed Erlotinib treatment in patients with EGFR wild type and c-met negative expression had a longer duration of PFS versus Erlotinib plus Onartuzumab (2.7 vs. 1.4 months, stratified HR = 1.82; 95% CI: 0.99, 3.32).

The aim of this study is to evaluate the efficacy and safety of Erlotinib as the 2nd/3rd line treatment in stage IV NSCLC patients with EGFR wild type and c-met negative expression.

Study objectives

- **Primary Objective**
  - To assess 6-monts progression free survival (PFS) rate of patients taking Erlotinib 150mg/day, which evaluated by RECIST criteria 1.1, defined as the interval from randomization to investigator-assessed progression or death.
- **Secondary Objectives**
  - To calculate objective response rate (ORR)
  - To calculate progression free survival(PFS)
  - To calculate overall survival (OS)
  - To evaluate the safety profile using NCI CTCAE version 4.02
  - To evaluate health-related quality of life
  - To assess biomarker data on tumor specimens and blood samples

Study design

- This is an open, single arm, phase II clinical trial to evaluate the efficacy and safety of Erlotinib as 2nd/3rd line in advanced NSCLC patients with EGFR WT and c-Met negative expression.
- Fifty-four advanced NSCLC patients will be enrolled and each patient will take Erlotinib 150mg/day orally until disease progression or intolerable toxicities
- The duration of the trial will be 30 months (12 months recruitment and 18 months follow-up). Up to now, one patient has been recruited. The trial will be finished at July 2016.

Study population

Inclusion criteria
Age ≥ 18 and ≤ 75 years ; Eastern Cooperative Oncology Group (ECOG) performance status 0~2;
Histologically or cytologically documented metastatic (stage IV) or recurrent NSCLC;
Being characterized according to the response evaluation criteria in solid tumors(RECIST1.1) criteria；having at least one prior platinum-based chemotherapy regimen for advanced NSCLC and now exhibiting progressive disease (PD); having recovered from any serious treatment related toxicities.
Neither with EGFR mutation nor c-Met expression detected in Ventana Benchmark instrument (definition of c-Met negative expression: ≥50% cells with no staining or weak intensity staining (clinical score 0 or 1+));
Adequate hematological function: Neutrophil count ≥ 1.5 × 109/L, Platelets ≥ 100 × 109/L and Hemoglobin ≥9 g/dL (may be transfused to maintain or exceed this level).
Adequate liver function: Total bilirubin ≤ 1.5 × upper limit of normal (ULN); AST (SGOT) and ALT (SGPT) < 2.5 × ULN in the absence of liver metastases, or < 5 × ULN in case of liver metastases. Adequate renal function: Serum creatinine ≤ 1.25 x ULN, and creatinine clearance ≥ 60 ml/min.
Patients must sign study specific informed consent prior to enrollment; Able to comply with study and follow-up procedures.
Exclusion criteria
Patients with prior exposure to agents targeting at the HER axis (e.g. erlotinib, gefitinib, cetuximab, trastuzumab)
Patients with brain metastasis or spinal cord compression have not yet been definitively treated with surgery and/or radiation; previously diagnosed and treated CNS metastases or spinal cord compression without evidence of stable disease (clinically stable imaging) for at least 2 months
History of another malignancy in the last 5 years with the exception of other malignancies cured by surgery alone and having a continuous disease-free interval of 5 years or cured basal cell carcinoma of the skin or cured in situ carcinoma of the uterine cervix.
Receiving treatment with any other investigational agents, or participating in other clinical trial;
Females who are pregnant or breast-feeding; patients who are hypersensitive to erlotinib; patients who have any unstable systemic disease.
Any significant ophthalmologic abnormality, especially severe dry eye syndrome, keratoconjunctivitis sicca, Sjögren syndrome, severe exposure keratitis or any other disorder likely to increase the risk of corneal epithelial lesions.
Chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD) and any other active lung diseases.

In 2nd/3rd line of advanced NSCLC with EGFR WT and c-Met negative → Erlotinib 150mg/day taken orally → until disease progression or intolerable toxicities

Sample size

The 6 month PFS rate of experimental arm is estimated to be 35%(refer to OAM4558g, 2011ASCO), and historical control is estimated to be 20%(refer to BR.21,SATURN and TAILOR), considering 10% total dropout rate, adjusting two-sided α=0.05,power 80%, a sample size of 54 is needed

Statistical analysis plan

- The time to event data (OS, PFS, etc.) will be summarized with Kaplan-Meier analysis. The median times to event and 95% confidence limits will be calculated if applicable. Results from a two-sided log-rank test at the 5% significance level will be presented. The Cox regression model will also be applied, if applicable.
- The categorical data (including binary data) will be summarized by presenting the rate and 95% confidence limits according to Pearson-Clopper. Two-sided chi-squared test or Fisher exact test at the 5% significance level will be presented for comparison analysis. Logistic regression adjusting confounders will also be considered, if applicable

Acknowledgments

This study is supported by Shanghai Roche Pharmaceuticals Limited. The authors thank in advance all the patients and investigators who will be involved in this study.

Reference

1. Ciuleanu T .et. al; Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-smallcell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study; Lancet Oncol. 2012 Mar;13(3):300-8.
2. Garassino MC, Martelli O, Bettini A, et al (2012). TAILOR: A phase III trial comparing erlotinib with docetaxel as the second-line treatment of NSCLC patients with wild-type (wt) EGFR. J Clin Oncol, 30, abstr LBA7501.
3. Okano Y, et al. 2013 ASCO Abstract 8006