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# A prospective, phase II, open-label study (JO22903) of first-line erlotinib in Japanese patients with epidermal growth factor receptor (*EGFR*) mutation-positive advanced non-small-cell lung cancer (NSCLC)☆

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ABSTRACT

*Introduction:* The epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor erlotinib is associated with survival benefits in patients with *EGFR* mutation-positive non-small-cell lung cancer (NSCLC). This phase II, single-arm study examined the efficacy and safety of first-line erlotinib in Japanese patients with *EGFR* mutation-positive NSCLC.
*Methods:* Eligible patients received erlotinib 150 mg/day until disease progression or unacceptable toxicity. The primary endpoints were progression-free survival (PFS) and safety.
*Results:* A high degree of concordance was observed between different mutation testing methodologies, suggesting feasibility of early, rapid detection of *EGFR* mutations. Median PFS was 11.8 months (95% confidence interval [CI]: 9.7–15.3) at data cut-off (1 June 2012) ($n = 102$). Exon 19 deletions seemed to be associated with longer PFS compared with L858R mutations; T790M mutations were tentatively linked with shorter PFS. The safety profile was as expected: rash (any grade; 83%) and diarrhea (any grade; 81%) were most common. Six interstitial lung disease (ILD)-like cases were reported, and 5 were confirmed as ILD-like events by the extramural committee. Two patients died of treatment-related pneumonitis (JAPIC Clinical Trials Information number: Japic CTI-101085).
*Conclusion:* Erlotinib should be considered for first-line treatment in this subset of Japanese patients, with close monitoring for ILD-like events.


## 1. Introduction

Non-small-cell lung cancer (NSCLC) remains a significant global health burden, with high mortality and poor prognosis for patients diagnosed at an advanced stage. Erlotinib is an epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor (TKI), which has been approved for the treatment of advanced NSCLC. Originally approved as second- or third-line treatment in patients refractory to chemotherapy, erlotinib showed overall survival (OS) and progression-free survival (PFS) improvements compared with


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placebo in a large phase III trial (OS: 6.7 vs. 4.7 months, respectively, hazard ratio [HR] = 0.7, 95% confidence interval [CI]: 0.58–0.85, $p < 0.001$; PFS: 2.2 vs. 1.8 months, respectively, HR = 0.61, 95% CI: 0.51–0.74, $p < 0.001$) [1]. Further trials have expanded its use to maintenance therapy (SATURN) [2] and to first-line treatment of *EGFR* mutation-positive disease (OPTIMAL and EURTAC) [3,4]. The latter 2 studies reported significant PFS benefits with erlotinib as first-line treatment for *EGFR* mutation-positive NSCLC compared with chemotherapy in Chinese and European populations (OPTIMAL: 13.1 vs. 4.6 months, respectively, HR = 0.16, 95% CI: 0.10–0.26, $p < 0.0001$; EURTAC: 9.7 vs. 5.2 months, respectively, HR = 0.37, 95% CI: 0.25–0.54, $p < 0.0001$).

Until now, erlotinib has not been prospectively evaluated in Japanese patients with *EGFR* mutation-positive NSCLC. This prospective, phase II, open-label study (JO22903) was initiated to obtain confirmatory efficacy and safety data in the first-line setting for Japanese patients with *EGFR* mutation-positive NSCLC, in order to corroborate data from Chinese and Caucasian populations.

## 2. Materials and methods

### 2.1. Study design and patients

JO22903 was a phase II, multicenter, open-label, non-randomized study conducted at 25 centers in Japan. Eligible patients were aged ≥20 years with advanced, untreated, metastatic (stage IIIB/IV), or relapsed NSCLC, with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 and tumors harboring confirmed activating mutations of *EGFR* (exon 19 deletion or L858R point mutation in exon 21), with at least 1 measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0. Staging was assessed by TNM classification (7th edition). The study was carried out in accordance with the Declaration of Helsinki and Japanese Good Clinical Practice guidelines. The protocol was approved by ethics committees and all patients gave informed consent for study participation.

### 2.2. Procedures

Eligible patients received oral erlotinib 150 mg/day until disease progression (PD) or unacceptable toxicity (Fig. 1). Dose reductions (in 50-mg decrements) and/or interruptions (of up to 2 weeks) were permitted to manage adverse events (AEs) related to erlotinib treatment. Treatment was interrupted if interstitial lung disease (ILD) was suspected; for patients with confirmed ILD diagnosis, erlotinib was discontinued immediately. In cases of gastrointestinal perforation or any grade 4 AE, erlotinib was discontinued.

Patients were screened for *EGFR* mutations in a local or central laboratory. In the central laboratory, *EGFR* mutation status was determined using Scorpion ARMS [5]. For exploratory analyses, tumor samples were obtained from hospital archives for patients who were screened in their local laboratory to confirm the concordance between several local methods and Scorpion ARMS. In addition, serum samples were collected at screening from all patients who provided informed consent to participate in the exploratory research ($n = 95$). DNA was isolated from serum with the QIAmp MinElute Virus Spin kit (Qiagen, Hilden, Germany). Scorpion ARMS was used for *EGFR* mutation testing for circulating DNA in the serum.

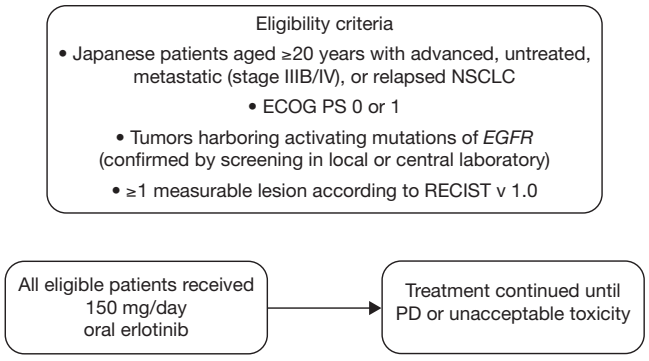


**Fig. 1.** Study design and eligibility criteria.

Tumor response was assessed by an independent review committee (IRC) using RECIST version 1.0. Tumor response evaluation was scheduled every 6 weeks. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTC AE) version 4.0.

At baseline mandatory lung and abdominal scans (CT/MRI), brain scans (CT/MRI) and bone scans (bone scintigraphy, PET, CT and MRI) were performed. During treatment until disease progression, lung and abdominal scans were mandatory. Brain scans were required for those patients who revealed brain metastases at baseline. When confirming complete or partial tumor response, bone scans were required for patients with bone metastases at baseline.

### 2.3. Study endpoints

Primary endpoints were PFS, as assessed by an IRC, and safety profile. Secondary endpoints included overall response rate (ORR), disease control rate (DCR), and OS. Exploratory analyses examined concordance between different *EGFR* mutation testing methodologies, and concordance between serum and tumor tissue at screening. *EGFR* mutation status alterations in serum before and after treatment were observed.

### 2.4. Statistical analyses

The statistical plan assumed a median PFS of 7 months in the historical control group and 11 months in the erlotinib treatment group. The primary analysis was planned for 11 months after the last patient was enrolled to confirm superiority of erlotinib over the historical control.

Given an expected median PFS of 11 months, 93 patients were necessary to provide statistical power of 80% to confirm the superiority of the lower confidence boundary of the observed median PFS compared with the threshold median PFS of 7 months. The target sample size was 100 patients, taking into consideration patients who would prove to be ineligible for the study. For PFS (the primary efficacy endpoint), OS, and duration of response, median and 95% CIs were estimated using Kaplan–Meier survival methodology. CI limits were calculated according to the Greenwood method. Response rate and DCR were summarized by presenting the rate and 95% CIs according to Pearson–Clopper.

The analysis of safety parameters (co-primary endpoint) was descriptive: all AEs were converted to MedDRA preferred terms and summary tables were produced. For laboratory parameters, descriptive summary tables or graphs of change over time were produced.

According to the statistical analysis plan, all patients who received at least 1 dose of study treatment would be included in the safety population. The modified intention-to-treat (ITT) population for the efficacy analysis excluded all patients with major protocol violations.

## 3. Results

### 3.1. Patient population

Between 8 April 2010 and 6 October 2010, 103 patients with confirmed *EGFR* mutations were enrolled and received erlotinib,