European Journal of Cancer (2014) **50**, 302–308

Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Dosing to rash: A phase II trial of the first-line erlotinib for patients with advanced non-small-cell lung cancer an Eastern Cooperative Oncology Group Study (E3503) ☆,☆☆

J.R. Brahmer [a,*], J.W. Lee [b], A.M. Traynor [c], M.M. Hidalgo [d], J.M. Kolesar [c], J.M. Siegfried [e], P.P. Guaglianone [f], J.D. Patel [g], M.D. Keppen [h], J.H. Schiller [i]

[a] *Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, United States*
[b] *Dana-Farber Cancer Institute, Boston, MA, United States*
[c] *University of Wisconsin, Madison, WI, United States*
[d] *Hospital Madrid Sanchinarro, Madrid, Spain*
[e] *University of Pittsburgh, Pittsburgh, PA, United States*
[f] *Decatur Memorial Hospital, Decatur, IL, United States*
[g] *Northwestern University, Chicago, IL, United States*
[h] *Sanford Cancer Center, Sioux Falls, SD, United States*
[i] *University of Texas Southwestern Medical Center, Dallas, TX, United States*

Available online 15 November 2013

KEYWORDS
Erlotinib
Phase II
NSCLC

Abstract ***Background:*** The development of a rash has been retrospectively associated with increased response and improved survival when treated with erlotinib at the standard dose of 150 mg per day. The objective of this trial was to evaluate the association of the activity of erlotinib in the first-line setting in patients with advanced non-small-cell lung cancer (NSCLC) with the development of a tolerable rash via dose escalation of erlotinib or tumour characteristics.

Methods: Patients, with advanced NSCLC without prior systemic therapy, were treated with erlotinib 150 mg orally per day. The dose was increased by 25 mg every two weeks until the development of grade 2/tolerable rash or other dose limiting toxicity. Tumour biopsy specimens were required for inclusion.

☆ This study was conducted by the Eastern Cooperative Oncology Group (Robert L. Comis, M.D., Chair) and supported in part by Public Health Service Grants CA23318, CA66636, CA21115, CA21076, CA16116, CA39229, CA17145 and from the National Cancer Institute, National Institutes of Health and the Department of Health and Human Services. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

☆☆ Clinicaltrials.gov identifier: NCT00085280.

* *Corresponding author:* Address: Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Bunting Blaustein Cancer Research Building, Room G94, 1650 Orleans Street, Baltimore, MD 21287-0013, United States. Tel.: +1 410 502 7159; fax: +1 410 614 9334.
E-mail address: brahmju@jhmi.edu (J.R. Brahmer).

0959-8049/$ - see front matter
http://dx.doi.org/10.1016/j.ejca.2013.10.006

Results: The study enrolled 137 patients, 135 were evaluable for safety and 124 were eligible and evaluable for response. Only 73 tumour samples were available for analysis. Erlotinib dose escalation occurred in 69/124 patients. Erlotinib was well tolerated with 70% of patients developing a grade 1/2 rash and 10% developing grade 3 rash. Response rate and disease control rate were 6.5% and 41.1% respectively. Median overall survival was 7.7 months. Toxicity and tumour markers were not associated with response. Grade 2 or greater skin rash and low phosphorylated mitogen-activated protein kinase (pMAPK) were associated with improved survival.

Conclusions: Overall survival was similar in this trial compared to first-line chemotherapy in this unselected patient population. Dose escalation to the development of grade 2 skin rash was associated with improved survival in this patient population.

1. Introduction

In 2003, gefitinib became the first oral epidermal growth factor receptor (EGFR) inhibitor approved for use which revolutionised care for patients with non-small-cell lung cancer [1]. Erlotinib is currently the only EGFR tyrosine kinase inhibitor (TKI) approved for use in the United States based on the only trial to show a survival advantage of an oral EGFR TKI compared to placebo in the second and third-line treatment setting in advanced disease [2]. These two drugs are widely used throughout the world in patients with advanced non-small-cell lung cancer (NSCLC). After the discovery of the epidermal growth factor receptor (EGFR) mutation and its association with tumour response [3,4], tumour EGFR mutation analysis has helped guide the use of EGFR TKIs in advanced NSCLC. Reports of improved progression-free survival (PFS) with EGFR tyrosine kinase inhibitors compared to chemotherapy in the first-line setting in patients with EGFR mutations have led to EGFR TKIs use restricted in the first-line setting to patients with EGFR mutation positive tumours [5,6]. Prior to these reports and the discovery of EGFR mutations, improved survival was linked retrospectively to clinical characteristics, EGFR signalling and the development of toxicities such as skin rash [2,7–9].

Many groups have attempted to unlock the answer why patients who do not have EGFR mutations benefit from erlotinib. EGFR amplification, as assessed by FISH, has been implicated [10], as well as other markers of the EGFR pathway or other linked pathways such as mitogen-activated protein kinase (MAPK) or AKT [11,12]. Investigators have also used protein expression patterns otherwise known as serum proteomics to predict benefit from EGFR TKIs. Carbone and colleagues previously published validation of VeriStrat™ which is a proteomic signature that retrospectively was associated with benefit to EGFR TKIs [13]. The Veristrat signature is undergoing prospective studies.

The development of a rash caused by the EGFR TKIs has been retrospectively associated with improved response and survival [9]. The hypothesis of the current study was that by increasing the dose of erlotinib until the development of a grade 2 or tolerable skin rash, response and survival would be improved. This study of erlotinib in the first-line setting of advanced NSCLC evaluated prospectively if increasing the dose of erlotinib until the development of a tolerable skin rash was associated with improved outcome. Given that this trial was designed prior to the discovery of EGFR mutations, this trial also set out to prospectively identify downstream markers of EGFR linked signalling pathways that could be predictive of response or survival to erlotinib.

2. Methods

Eastern Cooperative Oncology Group (ECOG) 3503 was a phase II trial of first-line erlotinib treatment in patients with advanced non-small-cell lung cancer. The trial was designed to evaluate downstream markers of EGFR linked signalling pathways that might be predictive of clinical benefit to erlotinib, particularly the MAPK/Erk pathway. Because rash had been retrospectively associated with increased response and survival in the past [9], this trial was designed to prospectively see if the development of grade 2 rash was a predictor of response to erlotinib and of patient survival. Other exploratory analyses of correlative biological markers of EGFR activation and EGFR TKI metabolism in an attempt to broaden our understanding of the impact of erlotinib on our patients were explored.

This trial included patients with previously untreated stage IIIB (with a pleural effusion) and stage IV or recurrent NSCLC. Trial eligibility required submission of an available paraffin-embedded tumour block from the diagnostic specimen. Patients had to have measurable disease, adequate major organ function and ECOG performance status (PS) of 0 to 2 [14]. Patients were required to discontinue known CYP3A4 inducers or inhibitors one week prior to starting erlotinib. Patients with active peptic ulcer disease, prior surgical procedures affecting absorption and non-healing wounds were not eligible.