European Journal of Cancer (2013) 49, 1205–1215

Available at www.sciencedirect.com

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journal homepage: www.ejcancer.info

Effects of erlotinib first-line maintenance therapy versus placebo on the health-related quality of life of patients with metastatic non-small-cell lung cancer

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Available online 7 March 2013

KEYWORDS
Health-related quality of life
Metastatic non-small-cell lung cancer
Erlotinib

Abstract ***Introduction:*** Maintenance therapy can delay progression and prolong survival in metastatic non-small-cell lung cancer (mNSCLC). As treatment for mNSCLC is non-curative, its impact on patient health-related quality of life (HRQoL) is an important consideration. SATURN (Sequential Tarceva in Unresectable NSCLC) was a randomised, double-blind, placebo-controlled, multicentre study investigating the impact of erlotinib maintenance therapy on HRQoL in patients with locally advanced or recurrent NSCLC.

Patients and Methods: Eligible patients who had previously completed four cycles of platinum-based chemotherapy were randomised 1:1 to receive erlotinib 150 mg/day or placebo until disease progression, unacceptable toxicity or death. Patient HRQoL was assessed using the Functional Assessment of Cancer Therapy-Lung questionnaire, in terms of time to symptom progression (TSP), time to deterioration (TTD) in Trial Outcome Index (TOI) and TTD. Exploratory analysis was based on time to analgesia and appearance of key symptoms (pain, cough and dyspnoea).

Results: Compared with placebo, erlotinib maintenance therapy prolonged progression-free and overall survival by 41% and 23%, respectively. At baseline, HRQoL measures were comparable between the two treatment groups. Maintenance therapy with erlotinib did not impact on deterioration in HRQoL: TSP (hazard ratio [HR] = 0.91 [95% confidence interval (CI) 0.74–1.12]; $n = 785$), TTD in TOI (HR = 1.06 [95% CI 0.87–1.31]; $n = 781$) and TTD in HRQoL (HR = 0.96 [95% CI 0.79–1.16]; $n = 776$). Time to pain and time to analgesic use were significantly delayed in patients receiving erlotinib compared with placebo (HR = 0.61

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0959-8049/$ - see front matter © 2012 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.ejca.2012.11.006

[95% CI 0.42–0.88]; $p = 0.0080$ and HR = 0.66 [95% CI 0.46–0.94]; $p = 0.0199$, respectively). A non-significant trend towards delayed time to cough and time to dyspnoea (HR = 0.77 [95% CI 0.49–1.21] and HR = 0.75 [95% CI 0.48–1.17], respectively) was also observed.

Conclusions: Erlotinib maintenance therapy significantly extends progression-free survival without compromising patient HRQoL in comparison with placebo, with some improvement in symptoms.

1. Introduction

An estimate of the cancer burden in Europe in 2006 revealed that lung cancer was the most common cause of death from cancer (estimated 334,800 deaths [19.7% of total]).[1] Lung cancer can be broadly divided into two categories based on histology: small-cell lung cancer and non-small-cell lung cancer (NSCLC). Metastatic NSCLC is largely incurable using current treatment strategies due to the frequent presence of occult metastases by the time of diagnosis. Less than 1% of patients with metastatic NSCLC are alive after 5 years.[2] A biological and genetic differentiation of lung cancer is NSCLC-bearing epidermal growth factor receptor (EGFR)-activating mutations. Overexpression of EGFR is a common observation in NSCLC[3–8] and in some tumours; its expression has been associated with poor clinical outcome.[9]

The symptomatic burden of NSCLC is high. In addition to concerns over reduced life expectancy, patients can experience debilitating symptoms such as dyspnoea, cough, pain, loss of appetite and haemoptysis, which may adversely affect the health-related quality of life (HRQoL) of patients.

Patients who respond to, and tolerate, chemotherapy can receive only a limited number of cycles due to a plateau in effectiveness and cumulative treatment-limiting adverse events (AEs),[10] which can impinge on HRQoL. Furthermore, treatment is largely palliative and improvement in overall survival (OS) is often modest.[11]

Addition of bevacizumab to four to six cycles of doublet chemotherapy and its continuation until progressive disease (PD) has been shown to improve progression-free survival (PFS)[12,13] and OS in patients with non-squamous metastatic NSCLC.[13,14] These findings support the concept of active treatment between completion of first-line chemotherapy and initiation of second-line treatment. However, there remains an unmet need for further treatment options that extend survival in patients with advanced or metastatic NSCLC.

One strategy currently under investigation for improving survival in metastatic NSCLC is first-line maintenance therapy. This is initiated after first-line chemotherapy and before second-line treatment. Maintenance therapy (sometimes referred to as 'consolidation therapy') is the prolongation of treatment duration or administration of an additional treatment at the end of a defined number of initial chemotherapy cycles, after maximum tumour response has been achieved (this may be complete response, partial response or stable disease).[15–17] With the exception of unacceptable toxicity, maintenance therapy can be continued for a defined time or until PD occurs.

As first-line maintenance therapy for locally advanced or metastatic NSCLC is not curative, the goals are to improve survival and manage symptoms. An important consideration in a patient population for whom HRQoL is already compromised is that maintenance treatment should be associated with as few AEs as possible, in order to minimise any negative impact on HRQoL.

Erlotinib (Tarceva®; F. Hoffmann-La Roche Ltd., Basel, Switzerland) is described as a potent oral EGFR tyrosine kinase inhibitor.[18] It is one of only two treatments approved by the European Medicines Agency for use as monotherapy in Europe for first-line maintenance therapy for patients with locally advanced or metastatic NSCLC with stable disease after four cycles of standard platinum-based first-line chemotherapy[19] and by the United States (US) Food and Drug Administration for use in the United States of America (USA) for maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.[20]

In a phase III, double-blind, randomised, placebo-controlled, multicentre study (SATURN), the effects of first-line maintenance therapy with erlotinib following four cycles of platinum-based chemotherapy were investigated in patients with locally advanced or metastatic NSCLC (stage IIIB or IV). Patients who had not experienced PD after initial chemotherapy were randomised 1:1 to receive erlotinib orally plus best supportive care (BSC) or placebo plus BSC until PD, unacceptable toxicity or death. The primary end-point was investigator-assessed PFS. The primary efficacy parameter was duration of PFS, defined as the time from randomisation to PD or death, whichever occurred first. PD was defined according to Response Evaluation Criteria In Solid Tumours (RECIST). Secondary end-points were OS and HRQoL, in terms of time to symptom progression (TSP), time to deterioration (TTD) and TTD in Trial Outcome Index (TOI). Poor performance status has been linked with a higher incidence of clinically significant symptoms related to poor HRQoL in patients with advanced lung cancer.[21] However, the observed clinical