



Encouraging data out of the 2010 Congress of the European Society for Medical Oncology with respect to non-small-cell lung cancer

KEY WORDS

Metastatic NSCLC, third- or fourth-line treatment, afatinib, LUX-Lung 1

The Editor,
Current Oncology
October 15, 2010

Lung cancer continues to be the leading cause of cancer-related mortality worldwide¹. Most patients present with locally advanced or metastatic disease. Although targeted treatment advances have been made in recent years, lung cancer remains a stubborn cancer to treat, and there is still no approved, standard therapy for patients with metastatic non-small-cell lung cancer (NSCLC) in whom chemotherapy has failed and who have progressed after therapy with an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI).

I recently attended the European Society for Medical Oncology (ESMO) congress in Milan, Italy, and I can report some encouraging data. Findings from the LUX-Lung 1 (phase IIB/III) trial studying afatinib—a next-generation irreversible dual inhibitor of EGFR and human epidermal growth factor receptor 2 (HER2) tyrosine kinase—in patients with advanced NSCLC suggest that afatinib has significant activity in that patient population².

The study involved 585 patients with advanced NSCLC whose cancer had progressed after receiving 1 or 2 lines of chemotherapy and a first-generation EGFR-TKI (gefitinib or erlotinib). The participants were randomly assigned to either best supportive care (BSC) plus placebo or to BSC plus afatinib. The patient characteristics were balanced in both arms: median age (58 years), women (60%), East Asian ethnicity (58%), performance status 0–1 (92%), more than 24 weeks of prior erlotinib or gefitinib (81%), and a complete or partial response on prior EGFR-TKI treatment (45%).

Afatinib significantly extended progression-free survival (PFS), unprecedentedly tripling it over PFS with placebo (3.3 months vs. 1.1 months; $p < 0.0001$;

hazard ratio: 0.38), confirmed by independent review². However, at primary analysis, median overall survival (OS), the primary endpoint, was not statistically significantly different: 10.78 months with BSC plus afatinib versus 11.96 months with BSC plus placebo (hazard ratio: 1.08; 95% confidence interval: 0.86 to 1.35; $p = 0.74$)².

The rate of disease control was also significantly higher in patients who took afatinib than in those who took placebo (58% vs. 18%, $p < 0.0001$), also independently verified². Moreover, afatinib significantly improved symptoms related to lung cancer (such as cough, dyspnea, and pain) and significantly delayed time to deterioration of cough, to individual dyspnea items, and to chest pain². There were no new or unexpected safety findings; the main side effects were diarrhea and rash.

In lung cancer patients with advanced disease, maintaining quality of life for as long as possible and managing debilitating symptoms is of high relevance. Although treating the cancer in these patients is important, it is equally important that the therapeutic agents control symptoms and be well tolerated.

The tripling of PFS is a clear indicator of the activity of afatinib; however, because of the unexpected use of additional (confounding) treatments in the study, the effect could not translate into a difference in OS prolongation in the afatinib arm as compared with the placebo arm (79% patients received further treatment). This use of further treatments had not been anticipated at the time of trial design. The lack of survival benefit may also be related to the probable high enrichment of the trial population with EGFR-mutated patients having an outstanding median survival time of approximately 12 months in the third- and fourth-line settings in the placebo arm. Such survival is unprecedented in NSCLC and highlights the intrinsic good prognosis of EGFR-mutated NSCLC patients. Elimination of patients whose first- and second-line treatments failed, and who were not eligible for more treatments, contributes further to the selection of biologically better patients.

Interestingly, in a patient subgroup that did not receive any treatments subsequent to afatinib or placebo (given that no further treatment was available in some countries), a benefit in OS could be shown for afatinib versus placebo (hazard ratio: 0.65). However, that analysis was not formally planned as a subgroup analysis, and the results are therefore exploratory only.

The fact that afatinib induced objective regressions, delayed progression of the cancer, and improved cancer-related symptoms cannot be minimized in a population with no further standard treatment options. The results from LUX-Lung 1 have substantially contributed to a better understanding of the EGFR-mutated patient population. Conclusions from the trial will be relevant for the design of further clinical studies.

Encouraging results were also presented from LUX-Lung 2, a phase II trial studying patients in first- and second-line treatment for advanced NSCLC who harbour EGFR mutations, showing that patients with common EGFR mutations receiving afatinib have a median PFS of approximately 14 months and a median OS of about 2 years³.

Afatinib is taken in tablet form and, unlike first-generation TKIs, irreversibly binds to EGFR and HER2. The compound is under development for advanced NSCLC and several solid tumour types.

CONFLICT OF INTEREST DISCLOSURES

Dr. Vera Hirsh is a co-author of the LUX-Lung 1 trial and chair of the Lung Cancer Committee, McGill University, Montreal, QC. She received an honorarium for advisory board work with Boehringer Ingelheim.

Vera Hirsh MD FRCP(C)
Associate Professor, Departments of Medicine
and Oncology
McGill University
Chair, Lung Cancer Committee
McGill University
Chair, Lung Administrative Tumor Group
McGill University Health Centre (MUHC)
MUHC Royal Victoria Hospital
Department of Medical Oncology
A3.04 – 687 Pine Avenue West
Montreal, Quebec H3A 1A1
E-mail: vera.hirsh@muhc.mcgill.ca

REFERENCES

1. Cancer Research UK. Home > CancerStats > 26 Types of Cancer > Lung Cancer and Smoking > Lung Cancer and Smoking Statistics—Key Facts [Web page]. London, UK: Cancer Research UK; July 2010. [Available at: info.cancerresearchuk.org/cancerstats/types/lung/; cited October 13, 2010]
2. Miller VA, Hirsh V, Cadranet J, *et al*. Phase II/III double-blind randomized trial of afatinib (BIBW 2992, an irreversible inhibitor of EGFR/HER1 and HER2) + best supportive care (BSC) versus placebo + BSC in patients with NSCLC failing 1–2 lines of chemotherapy and erlotinib or gefitinib (LUX-Lung 1) [abstract LBA1]. *Ann Oncol* 2010;21(suppl 8):viii1. [Available online at: annonc.oxfordjournals.org/content/21/suppl_8/NP.full.pdf+html; cited October 20, 2010]
3. Yang C, Shih J, Su W, *et al*. A phase II study of BIBW 2992 in patients with adenocarcinoma of the lung and activating EGFR/HER1 mutations (LUX-Lung 2) [abstract 367PD]. *Ann Oncol* 2010;21(suppl 8):viii123. [Available online at: annonc.oxfordjournals.org/content/21/suppl_8/viii122.full.pdf+html; cited October 20, 2010]