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Editorial Comment

Targeted kinase inhibitors in lung cancer: From EGFR to patients

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The classification of solid tumours masks heterogeneous molecular components, that cause considerable differences in response to treatment and survival [1]. This might explain the conflicting results regarding the effectiveness of two "targeted" kinase inhibitors (gefitinib and erlotinib) in non-small-cell lung cancer (NSCLC) [2–9].

Gefitinib (*Iressa*), after promising results in phase II studies in terms of safety and response rate in chemotherapy-refractory advanced patients [7], showed no benefit when added to traditional chemotherapy in phase III confirmatory studies [8,9]. Thus, after accelerated approval in the US, it has recently received a new restrictive labelling from the US Food and Drug Administration (FDA) stating that gefitinib should be restricted to cancer patients who have already taken the drug and where some benefit is seen. New patients should not be given gefitinib as other drugs for NSCLC have shown longer survival rates [10]. In Europe, the drug is not available.

Erlotinib (*Tarceva*) prolongs survival in patients with NSCLC after first or second line chemotherapy when compared to placebo (median survival: 6.7 months versus 4.7 months) [4], but the results from the molecular analyses are difficult to interpret [5,6]. The expression of epidermal growth factor receptor (EGFR) increased the responsiveness to erlotinib (i.e., response rate), but none of the molecular findings (EGFR expression, number of copies and mutational status) were significantly associated with survival. In addition, after adjusting for the molecular profile, some prognostic or predictive clinical features such as smoking status, sex, race and type of tumour were still significantly associated to the responsiveness to erlotinib. Further, the paper reporting the associations between molecular and clinical predictors of outcome [5] did not include any analysis on safety and toxic effects. Consequently, it lost the opportunity to clarify some intriguing findings from the randomized controlled trial (RCT) such as: the lower proportion of fatigue and infection in the erlotinib arm; and mostly, the opportunity to evaluate the risk/benefit ratio for this "targeted" treatment in clinically and molecularly identifiable group of patients. Thus, the recent clinical and molecular results with erlotinib in NSCLC are encouraging [4,5], but should be treated with caution in the interpretation of results from research and prudence in its translation to clinical management [6]. Erlotinib *was* granted marketing authorization by the FDA and European Medicines Agency (EMEA) for the treatment of NSCLC patients with locally advanced or metastatic disease after failure of at least one prior chemotherapy [11,12]. This was because it showed a modest survival benefit when compared to placebo and an

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acceptable risk profile, despite the fact that the mechanism of action was not fully understood. Most patients in the placebo arm could have received some alternative active treatments, and the results from molecular analysis could not identify patients in whom treatment with erlotinib was more appropriate.

Thus, despite progress in understanding the molecular factors underlying the development of cancer and the improvement in response rates with some new drugs, long-term survival is still disappointing. Since the late 1980s, cancer mortality has decreased by over 10% in Europe [13] and North America [14]. However, most of the improvement in age-standardized mortality in Europe and the USA is attributable to primary and secondary prevention, the contribution of advancements in (medical) therapy being restricted to lymphoid neoplasms, germ cell cancers and a few selected epithelial neoplasms, such as breast cancer [15,16]. Survival gains with pharmacological treatments for most other common advanced/metastatic cancers are measured in months, not years, and little of such a modest gain is the result of the new compounds discovered and marketed recently.

In the context of an assessment of the activity of the EMEA using the European Public Assessment Report (EPAR) that contains documents describing the steps, reasons, scientific summary, technical documents and commitment for approval of a given drug [17], we identified 14 anticancer drugs for 27 different indications (14 new applications and 13 extensions). Overall, 48 clinical studies were used as the basis for approval; RCT and response rate were the study design and endpoints most frequently adopted (respectively, 25/48 and 30/48). In 13 cases, the EPAR explicitly reported differences between arms in terms of survival: the range was 0–3.7 months, and the mean and median differences were 1.5 and 1.2 months. A recent report from the FDA described a similar scenario [18]. Drugs should be rapidly released for patients who need them but not at the expense of adequate knowledge about real benefit. The pharmaceutical industry's objective to obtain a slice of the market should be balanced by the need to provide drugs that are supported by good evidence without posing an undue burden on European national health services.

Conflict of interest statement

All Authors do not have any financial or personal relationships with other people or organizations that could be considered conflicts of interest for the present work.

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