Editorial

Improved overall survival following tyrosine kinase inhibitor treatment in advanced or metastatic non-small-cell lung cancer—the Holy Grail in cancer treatment?

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Abstract: Advanced or metastatic non-small-cell lung cancer (NSCLC) is characterized by a poor prognosis and few second- or third-line treatments. First-generation epidermal growth factor receptor tyrosine kinase inhibition has paved the way for targeted therapies in lung cancer. Although these drugs result in excellent responses [and significantly improved progression-free survival (PFS)] in patients with activating EGFR mutations, none of these randomized studies has yet demonstrated a statistically significant improvement of overall survival (OS). PFS is often used as a predictor for improved OS since it is independent of subsequent treatment, but OS is acknowledged as the key clinical outcome in the treatment of advanced NSCLC. When effective treatment is given as post therapy, it will be difficult to distinguish the treatment effect of original and subsequent treatments because differences in OS are potentially confounded by crossover, and a relevant number of patients assigned to chemotherapy arms received tyrosine kinase inhibitors (TKIs) as second- or third-line treatment after disease progression. The high proportion of crossover may extend the benefit associated with the administration of TKIs to patients assigned to the control arm, and its "salvage"-effect may compensate for the relevant differences in PFS of first-line treatment consistently demonstrated in all TKI trials. Results for the INFORM trial (maintenance therapy with gefitinib following platinum-based chemotherapy) provided evidence that maintenance therapy with gefitinib significantly improved PFS, with greatest benefit in patients harboring EGFR mutation. Despite a high crossover rate (53%) final OS results of this study have now demonstrated a significant survival benefit for the gefitinib-treated EGFR mutation-positive patients (46.9 *vs.* 21.0 months, P=0.036). This is the first randomized clinical trial that showed a significant and clinical meaningful OS benefit in EGFR mutation-positive NSCLC patients following maintenance therapy with gefitinib as compared to placebo. It remains to be seen whether further exploration of this treatment strategy will confirm these promising results.

Keywords: Gefitinib; non-small-cell lung cancer (NSCLC); maintenance therapy; overall survival (OS); editorial

Submitted Jan 27, 2015. Accepted for publication Feb 02, 2015.
doi: 10.3978/j.issn.2218-6751.2015.03.01
View this article at: http://dx.doi.org/10.3978/j.issn.2218-6751.2015.03.01

The introduction of the epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) gefitinib (Iressa®, AstraZeneca, UK), erlotinib (Tarceva®, Roche, Switzerland), and afatinib (Giotrif®, Boehringer Ingelheim, Germany) and the anaplastic lymphoma kinase (ALK) inhibitors crizotinib (Xalkori®, Pfizer, USA) and ceritinib (Zykladia®, Novartis, Switzerland) represent the most important innovations in non-small-cell lung cancer (NSCLC) treatment over the past ten years (1). By targeting the main pathways of NSCLC signal transduction, these drugs significantly improved progression-free survival (PFS) and quality of life in a highly selected subgroup of NSCLC (harbouring EGFR mutations), sparing them from toxic chemotherapy approaches. However, for the vast majority of patients platinum-based chemotherapy remains the only potential treatment and has led to significantly improved survival outcomes with a "plateau" of about 10-11 months median survival (2). Subsequently, significant advances have been made with the introduction of pemetrexed, especially against the non-squamous cell subtype. The addition of this agent led to a further improvement in survival to 12-13 months (3) and up to 14 months with the introduction of maintenance therapy (4).

Maintenance therapy is a treatment strategy that has been investigated extensively in NSCLC and has been the subject of considerable recent debate. Options for maintenance include continuing the initial combination chemotherapy regimen, continuing only single agent chemotherapy ('continuation maintenance') or introducing a new agent ('switch' maintenance therapy). Therapies that have been studied in this setting in randomized trials to date include chemotherapy, molecularly targeted agents and immunotherapy approaches (5).

The outstanding results of the JMEN study proved that maintenance of pemetrexed (for patients with tumours of non-squamous histology) significantly improved the overall survival (OS) in advanced NSCLC patients was a proof of principle (6). Subsequently, the results of the SATURN study also showed a significant prolongation of PFS and OS with maintenance erlotinib (for patients with stable disease) compared with placebo (7). Despite considerable controversy, it has become an acceptable treatment paradigm and both drugs are approved for maintenance therapy of advanced NSCLC patients in Europe (EMA) and the USA (FDA) and this has certainly shifted the pendulum towards maintenance therapy.

Zhang and colleagues (8) first presented results from the INFORM trial evaluating gefitinib in the maintenance setting in 2012 (8). In this large phase III multicentre, double-blind trial patients (Asian ethnic origin, n=296) with stage IIIb or IV NSCLC after four cycles of platinum-based doublet chemotherapy were randomized either to placebo or maintenance therapy with gefitinib (250 mg/d) until progression or unacceptable toxic effects. Primary endpoint was PFS as assessed in the intent-to-treat population, whereas OS was a secondary endpoint. Assessment of PFS according to the tumour EGFR mutation status was also a pre-planned exploratory objective [highlighted in a previous editorial in this journal by Dempke (9)].

Median duration of treatment was 148 [49-467] days with gefitinib and 73 [42-127] days with placebo. PFS was significantly longer with gefitinib than that with placebo [median PFS 4.8 (95% CI: 3.2-8.5) *vs.* 2.6 (1.6-2.8) months; hazard ratio 0.42; 95% CI: 0.33-0.55; P<0.0001]. OS did not differ between both treatment groups [hazard ratio 0.84; 95% CI: 0.62-1.14; P=0.26; median OS 18.7 (95% CI: 15.6-22.2) *vs.* 16.9 (14.5-19.0) months]. Moreover, the greatest PFS benefit with gefitinib was found in the subgroup positive for EGFR mutations [hazard ratio 0.17; 95% CI: 0.07-0.42; median PFS 16.6 (9.4-22.7) *vs.* 2.8 (1.3-4.1) months].

In a most recently published update of the INFORM trial OS results were detailed (10). The median duration of follow-up for OS was 17.83 months (95% CI: 15.43-20.23). At the time of data cut-off for OS (June 17, 2014), 230 patients (78%) had died. In the subgroup positive for EGFR mutation, a higher OS was observed in patients treated with gefitinib than the placebo arm (HR 0.39; 95% CI: 0.15-0.97; P=0.036; median OS 46.87 *vs.* 20.97 months). In contrast, there was no significant difference in OS for gefitinib *vs.* placebo in patients negative for EGFR mutations (HR 1.27; 95% CI: 0.7-2.3; P=0.431; median OS 10.9 *vs.* 14.0 months). In the subgroup with unknown EGFR mutation, OS was numerically but not statistically longer with gefitinib *vs.* placebo (HR 0.92; 95% CI: 0.68-1.25; P=0.603; median OS 20.6 *vs.* 16.8 months). However, it is worth noting that a large proportion of patients (73%) had insufficient tumour samples to perform a mutation analysis.

Targeted therapies are currently being evaluated in a variety of treatment settings in NSCLC and novel strategies of disrupting tyrosine kinase-controlled pathways have been investigated. However, almost all of the recently reported trials have failed to improve OS for which there may be several key reasons.

Firstly, without a validated biomarker, specific subgroups of patients who are more likely to respond cannot be selected. Furthermore, the redundancy in tyrosine kinase-triggered

Table 1 Crossover rates (control → TKI) and median OS for selected clinical trials with gefitinib, erlotinib, and afatinib in EGFR mutation-positive NSCLC

Study	Design	Cross-over rate (%)	Median OS	References
SATURN	Platinum-based chemotherapy followed by erlotinib or placebo	67	12.0 *vs*. 11.0 months (P=0.0088)	Cappuzzo *et al*. (7)
EURTAC	Erlotinib *vs*. platinum-based chemotherapy	76	19.3 *vs*. 19.5 months (NS)	Rosell *et al*. (13)
OPTIMAL	Erlotinib *vs*. carboplatin/gemcitabine	68	PFS: 13.1 *vs*. 4.6 months (P<0.0001); OS: no differences	Zhou *et al*. (14)
IPASS	Gefitinib *vs*. carboplatin/paclitaxel	64	18.6 *vs*. 17.3 months (NS)	Mok *et al*. (15)
NEJ002	Gefitinib *vs*. carboplatin/paclitaxel	95	27.7 *vs*. 26.6 months (NS)	Inoue *et al*. (16)
FIRST-SIGNAL	Gefitinib *vs*. cisplatin/gemcitabine	75	22.3 *vs*. 22.9 months	Han *et al*. (17)
WJTOG3405	Gefitinib *vs*. cisplatin/docetaxel	91	34.8 *vs*. 37.3 months (NS)	Yoshioka *et al*. (18)
INFORM	Platinum-based chemotherapy followed by gefitinib or placebo	53	46.9 *vs*. 21.0 months (P=0.036)	Zhao *et al*. (10)
LUX-Lung 3 (LL-3)	Afatinb *vs*. cisplatin/pemetrexed	65	28.2 *vs*. 28.2 months (NS)	Sequist *et al*. (19)
LUX-Lung 6 (LL-6)	Afatinib *vs*. cisplatin/gemcitabine	48	23.1 *vs*. 23.5 months (NS)	Wu *et al*. (20)
LL3 and LL-6	Pooled analysis	–	27.2 *vs*. 24.3 months (del19 only, P=0.037)	Yang *et al*. (21)

TKI, tyrosine kinase inhibitor; EGFR, epidermal growth factor receptor; NS, not significant; PFS, progression-free survival; OS, overall survival; NSCLC, non-small-cell lung cancer.

pathways leads to primary and secondary resistance to an agent that targets a specific signal transduction cascade; as a result, agents that target multiple pathways are currently under investigation. Finally, it is unlikely that any TKI could achieve complete inhibition of its target(s), which may result in reduced but not completely abrogated signalling (11). Moreover, the reasons that TKIs have failed to improve survival when added to chemotherapy remain far from clear. A possible potential mechanism for the lack of synergy between these agents and chemotherapy may be the G_1 phase cell-cycle arrest caused by TKIs, which then may interfere with the cell cycle-dependent cytotoxicity of chemotherapy (12).

The question remains whether the benefit of targeted therapy for NSCLC may be best defined by PFS since in this regard published data are still inconclusive. Truly, PFS is regarded as a good predictor for improved OS (and is independent of subsequent treatment), but OS is acknowledged as the key clinical outcome in the treatment of advanced NSCLC. All large previous randomized phase III trials assessing first-line treatment demonstrated a significantly higher response rate and longer PFS in patients treated with first- and second-generation EGFR-TKIs, including gefitinib, erlotinib, and afaftinib than in patients treated with standard platinum-based combination chemotherapy. Although these trials met their primary endpoint with significantly longer PFS, no significant difference was observed in terms of OS. However, no restrictions were imposed on treatment after the end of protocol therapy in any of these trials and the majority of patients in the control arm received EGFR-TKI therapy at least once (*Table 1*).

None of these randomized trials has yet demonstrated a statistically significant improvement with these TKIs in terms of OS, which is of course the strongest endpoint for clinical research in oncology, in a condition of no effective treatment afterwards. When effective treatment is given as post therapy, it will be difficult to distinguish the treatment effect of original and subsequent treatments because differences in OS are potentially confounded by crossover, and a relevant number of patients assigned to chemotherapy arms received TKIs as second- or third-line treatment after disease progression (*Table 1*). Intuitively, the high proportion of crossover may extend the benefit associated with the administration of TKIs to patients assigned to the control arm, and its "salvage"-effect may compensate for the relevant differences in PFS of first-line treatment consistently demonstrated in all TKI trials.

However, a most recently published joint analysis of the LUX-Lung trials 3 and 6 revealed that afatinib prolonged survival of patients with NSCLC with common EGFR

mutations compared with standard chemotherapy by a median of 3 (27.3-24.3) months, significantly reducing the risk of death by 19% (HR =0.81, CI =0.66-0.99; P=0.037). The most pronounced reduction in risk of death, by 41% (HR =0.59, CI =0.45-0.77; P<0.001), was noted for patients whose tumors have the most common type of EGFR mutation (namely deletion in exon 19), which is present in approximately 48% with an EGFR mutation. For patients with the exon 21 (L8585R) mutation, there was no impact on OS (HR =1.25, CI =0.92-1.71; P=0.160) (21). From a methodological point of view, subgroup and post-hoc analyses can be informative, but should be interpreted with caution since PFS was chosen as the primary endpoint in both trials

Moreover, crossover was high for afatinib and erlotinib, and very high for gefitinib in all studies (*Table 1*) making the statistical power for analysis of OS very low (22,23).

In conclusion, the updated results of the INFORM trial clearly do not support the routine use of gefitinib for maintenance therapy as standard of care in NSCLC patients with advanced or metastatic NSCLC following treatment with platinum-based chemotherapy. However, to our knowledge the INFORM study is the first randomized clinical trial that shows a significant OS benefit in the EGFR mutation-positive population following maintenance therapy with gefitinib as compared to placebo. It remains to be seen whether further exploration of this treatment strategy will confirm these promising data.

Acknowledgements

Disclosures: Klaus Fenchel and Ludger Sellmann declare no conflicts of interest. Wolfram Dempke is an employee of AstraZeneca Ltd (UK).

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Cite this article as: Sellmann L, Fenchel K, Dempke WC. Improved overall survival following tyrosine kinase inhibitor treatment in advanced or metastatic non-small-cell lung cancer—the Holy Grail in cancer treatment? Transl Lung Cancer Res 2015;4(3):223-227. doi: 10.3978/j.issn.2218-6751.2015.03.01

