Editorial

Improved overall survival following tyrosine kinase inhibitor (TKI) treatment in NSCLC—are we making progress?

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Non-small cell lung cancer (NSCLC; 80–85% of all lung cancers) continues to be one of the major causes of cancer related deaths around the world (1). The development of molecularly targeted therapies (small molecules and monoclonal antibodies) has, however, significantly improved outcomes in the metastatic setting for NSCLC patients harbouring activated oncogenes such as epidermal growth factor receptor (EGFR) and translocated anaplastic lymphoma kinase (ALK) (2). By targeting the main pathways of NSCLC signal transduction, these drugs dramatically improved progression-free survival (PFS) and quality of life (QoL) in this highly selected subgroup of NSCLC patients sparing them from toxic chemotherapy approaches (del16) (3).

The development EGFR tyrosine kinase inhibitors (TKIs) changed dramatically the history of NSCLC patients harbouring EGFR sensitive mutations. Several randomised prospective trials confirmed the superiority of these target agents about survival and response rate when comparing with platinum-based chemotherapy (4-6). Our knowledge about EGFR mutations increased gradually during the development of target agents and different clinical trials. EGFR mutations cannot be considered all equal, but different entities should be considered in our clinical practice: exon 19 deletions (del19), exon 21 mutation (L858R) and uncommon mutation (exon 20, exon 18 and double mutations) (7). Currently, of three different EGFR TKIs (afatinib, erlotinib, and gefitinib) approved for the treatment of NSCLC patients harbouring activating EGFR mutations, only results generated by indirect meta-analyses have been reported which were not always clear and convincing (7,8). In patients harbouring EGFR mutations, different randomised trials confirmed the significant superiority of EGFR TKIs *vs*. standard platinum-based chemotherapy in first-line settings in terms of PFS, QoL and safety profile. No randomised clinical trials evaluating erlotinib, gefitinib, or afatinib showed a statistical improving in overall survival (OS) for patients treated with EGFR TKIs, when considered individually and based on overall population (4-6). Although these trials seems to be very similar, exploring the same indications and end-points with different EGFR TKIs revealed many differences about study design, patient population and statistical analysis.

Recently, targeted therapies administered to patients selected by reliable and biologically relevant biomarkers (e.g., EGFR mutations, ALK rearrangement, PD-L1 expression) have produced substantial improvements in outcomes that have rapidly transformed patient care for several types of NSCLC (2).

Most recently, results from the first head-to-head comparison of two different TKIs (afatinib *vs*. gefitinib) have been reported (9). This multicentre, international, open-label, exploratory, randomised controlled phase 2B trial (LUX-Lung 7, NCT01466660) enrolled treatment-naive patients (N=319) with stage IIIB or IV NSCLC and a common EGFR mutation (del19 or L858R). Patients were randomly assigned (1:1) to receive afatinib (40 mg/d) or gefitinib (250 mg/d) until disease progression, or beyond if deemed beneficial by the investigator. Clinicians and patients were not masked to treatment allocation; independent review of tumour response was done in a blinded manner. Co-primary endpoints were PFD by independent central review, time-to-treatment failure (TTF), and OS. Efficacy analyses were done in the

intention-to-treat population and safety analyses were done in patients who received at least one dose of study drug.

PFS [median 11.0 months (95% CI: 10.6–12.9) with afatinib *vs*. 10.9 months (95% CI: 9.1–11.5) with gefitinib; HR 0.73 (95% CI: 0.57–0.95), P=0.017] and TTF [median 13.7 months (95% CI: 11.9–15.0) with afatinib *vs*. 11.5 months (95% CI: 10.1–13.1) with gefitinib; HR 0.73 (95% CI: 0.58–0.92), P=0.0073] were significantly longer with afatinib than with gefitinib. OS data are not yet mature. The most common treatment-related grade 3 or 4 adverse events were diarrhoea [20 (13%) of 160 patients given afatinib *vs*. two (1%) of 159 given gefitinib] and rash or acne [15 (9%) patients given afatinib *vs*. five (3%) of those given gefitinib] and liver enzyme elevations [no patients given afatinib *vs*. 14 (9%) of those given gefitinib]. Serious treatment-related adverse events occurred in 17 (11%) patients in the afatinib group and seven (4%) in the gefitinib group. Ten (6%) patients in each group discontinued treatment due to drug-related adverse events. Fifteen (9%) fatal adverse events occurred in the afatinib group and ten (6%) in the gefitinib group. All but one of these deaths were considered unrelated to treatment; one patient in the gefitinib group died from drug-related hepatic and renal failure. Overall, the frequency of severe adverse events was similar in both arms with slightly different toxicity profiles. The adverse events observed with both treatments were predictable and manageable, leading to an equally low rate of treatment discontinuation in both arms (6.3%).

Moreover, first-line afatinib treatment significantly reduced the risk of NSCLC progression by 27% *vs*. gefitinib. Interestingly, the improvement in PFS became more pronounced over time with a significantly higher proportion of patients alive and progression-free at 18 months (27% *vs*. 15%; P=0.018) and 24 months (18% *vs*. 8%; P=0.018), showing a greater long-term benefit for afatinib (9).

From this study it was concluded that afatinib significantly improved outcomes in treatment-naive NSCLC patients with activating EGFR mutations with gefitinib, with a manageable tolerability profile and may become the new first-line therapy of choice. However, tolerability also plays a determining role in the selection and dosing of a TKI. The tolerability profiles between gefitinib and afatinib are different and the selection of the therapy will still be based on the individual clinical decision.

Dacomitinib is another small molecule targeting EGFR (erbB1, erbB2, and erbB4) that had been tested in a head-to-head comparison with gefitinib (10). The drug binds irreversibly to cysteine-797. In a multinational, multicentre, randomized, open-labeled, phase III trial (ARCHER1050; NCT01774721) the efficacy and safety of treatment with dacomitinib (45 mg/d) *vs*. gefitinib (250 mg/d) in patients (N=440) with locally advanced or metastatic NSCLC with EGFR activating mutations was investigated. Primary endpoint is PFS, secondary endpoints include OS and safety. The study is ongoing, but not recruiting patients. Results are expected early 2017.

All large previous randomized phase III trials so far assessing first-line treatment demonstrated a significantly higher response rate and longer PFS in patients treated with EGFR TKIs, including gefitinib, erlotinib, and afatinib (4-6) 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. None of these randomized trials had 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. 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.

Considering individually the OS data coming out from all randomised clinical trials with erlotinib, gefitinib and afatinib so far it was not possible to found a statistically significant superiority of one drug on the other. The was mainly due to the facts that (I) no randomized head-to-head comparisons were available; and (II) indirect comparisons were derived from several meta-analyses (7,8).

Frankly, the goals of any new cancer treatment are to allow the patient to live longer and to live better. Therefore, clinical trials in NSCLC have two important endpoints: OS and the QoL of that survival. All other endpoints should be considered intermediate, becoming surrogates to those

Table 1 Overall survival (OS) of advanced or metastatic NSCLC patients following treatment with TKIs (phase IIB/III trials)

Drug	Study design	ΔOS (months)	Reference
Nintedanib	Docetaxel *vs*. docetaxel plus nintedanib (N=1,314; LUME-Lung 1)*	2.3 (HR =0.83)	Reck *et al*. (12)
Gefitinib	Platinium-based doublet chemotherapy, followed by either placebo or gefitinib (N=296; INFORM)	15.9 (HR =0.39)	Zhang *et al*. (13)
Afatinib	Cisplatin plus pemetrexate *vs*. cisplatin, pemetrexate plus afatinib (N=345; LUX-Lung 3)**	12.2 (HR =0.54)	Yang *et al*. (8)
Afatinib	Cisplatin plus gemcitabine *vs*. cisplatin, gemcitabine plus afatinib (N=364; LUX-Lung 6)**	13.0 (HR =0.64)	Yang *et al*. (8)
Afatinib	Afatinib *vs*. erlotinib (N=795; LUX-Lung 8)***	1.1 (HR =0.81)	Soria *et al*. (14)
Afatinib	Afatinib *vs*. gefitinib (N=319; LUX-Lung 7)****	Alive at 24 months: 18% *vs*. 8% (P=0.018)	Park *et al*. (9)
Dacomitinib	Dacomitinib *vs*. gefitinib (N=440; ARCHER1050)	Awaited Q1/2017	www.clinicaltrials.gov (10)

*, adenocarcinoma only; **, meta-analysis for del19 patients; ***, squamous histology only; ****, OS data not yet mature.

important two endpoints only if formally validated. Clinical trials in NSCLC have typically investigated agents or regimens in patients selected for study based primarily on histology, molecular biology (e.g., EGFR, ALK, c-MET, PD-1/PD-L1) and clinical characteristics (11). In the many of these cases this approach has resulted in only small incremental improvements in OS (*Table 1*) that probably reflect the impact of agents with modest efficacy in a subset of the study population that appears not to be readily identifiable. Although this work has certainly improved the lives of many patients with NSCLC, appears to be slow, costly, and empiric (15).

However, the results of pooled analysis showed that a significant improvement in OS with afatinib was achieved in NSCLC patients harboring the EGFR del19 mutations adding weight to the proposal that exon 19 deletions and L8585R mutations are two different disease entities (8).

While waiting for the results of the first randomised phase III trial, comparing two different EGFR TKIs (dacomitinib vs. gefitinib; ARCHER-1050), the LUX-Lung 7 study (phase IIb) may open the door towards a new era of clinical trials evaluating two different EGFR agents, and thereby reducing statistical issue developed from indirect comparison analyses. Moreover, it is conceivable that the choice of first-line EGFR-TKI has no effect on the subsequent therapy, considering that the development of EGFR T790M mutations (and c-MET amplifications) is one the major causes of resistance to first-generation TKIs (16) and also in patients treated with afatinib. In the era of precision medicine, it will be very interesting to understand the T790M rate in patients treated with afatinib as front-line therapy. Indeed, the only preliminary results of a prospective trial that evaluated the presence of T790M in TKI-naïve patients that progressing to afatinib, showed that the presence of T790M mutation was less common (33%) then is expected with first generation EGFR TKIs, however, these data are based on a small group of patients (17).

In addition, it remains to be seen whether combinations of TKIs with newly developed immune checkpoint inhibitors, targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death 1 (PD1) receptor and programmed cell death 1 ligand (PD- L1) might change current treatment paradigms in all NSCLCs (18). Only the identification of prognostic or predictive markers of response could help oncologists in choosing the most effective treatment (TKIs *vs*. chemotherapy *vs*. immunotherapy *vs*. combinations) for NSCLC patients.

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Footnote

Conflicts of Interest: Dr. Stephen P. Dale and Professor Wolfram C. M. Dempke are employees of Kyowa Kirin Ltd., UK. Dr. Klaus Fenchel has no conflicts of interest to declare.

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