Editorial

Osimertinib—first or second line for epidermal growth factor (EGFR) mutation-positive non-small cell lung cancer?

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Epidermal growth factor (EGFR) M+ non-small cell lung cancer (NSCLC) accounts for about 10% of non-squamous NSCLC in Europe and North America and as much as 40% in women in Asian countries (1). For advanced disease, chemotherapy was commonly employed and achieved remission durations of 12 months at a cost of considerable toxicity, but with the development of the EGFR tyrosine kinase inhibitors gefitinib and erlotinib, targeted therapy gradually replaced chemotherapy in second line and more recently first line in EGFR M+ cancer, although the majority of the initial studies were carried out in Asian patients (2). In general these therapies were associated with a lower incidence of side effects compared to chemotherapy.

The irreversible tyrosine kinase inhibitor afatinib has become the most widely used targeted agent in advanced EGFR M+ NSCLC following the Lux-lung phase IIB trial which showed a 2.2 m gain in time to treatment failure compared to gefitinib (3). The principal side effects of afatinib were skin rash and diarrhoea compared to liver function abnormalities with gefitinib. However, earlier systematic reviews including one network meta-analysis had not shown differences in progression free survival between afatinib, gefitinib and erlotinib (2,4). A recent head to head comparison of the other second generation tyrosine kinase inhibitor dacomitinib (unlicensed September 2018) with gefitinib showed a 5.5 m benefit in progression free survival in favour of dacomitinib (5). The main side effects of dacomitinib were again skin rash and diarrhoea. These first line studies were performed in patients with the common mutations exon 19 deletion or L858R mutation, and patients with brain metastases were excluded. Exon 19 deletion tumours show an improved outcome compared to cancers with the L858R mutation and with afatinib treatment the median survival of patient with Del 19 mutant tumours has been in excess of 30 months a combined analysis of in two trials with a significant benefit in overall survival compared to chemotherapy (6). In common with many studies of targeted therapy across different tumour types, a gain in overall survival has been elusive in comparison with standard therapy, which may in part be due to the majority of studies allowing crossover from the control arm and the data in some cases remains immature. However, the EGFR-TKIs have largely replaced chemotherapy as the first line therapy for advanced EGFR M+ lung cancers (2).

Between 50% and 60% of acquired resistance to first and second generation tyrosine kinase inhibitors in EGFR M+ NSCLC has been found to be associated with the T790M mutation, based on tumour biopsies at relapse compared to an incidence of around 1% in pre-treatment biopsies (7). Two third generation tyrosine kinase inhibitors currently have accelerated FDA approval, osimertinib and olmutinib (a third drug rociletinib had its application for phase II/III status rejected by the FDA and its EMA application has been withdrawn). In addition to increased potency against the T790M mutation, these drugs have reduced activity against wild type EGFR compared to the second generation agents and hence the potential for less severe side skin side

effects (8). Osimertinib is the most clinically advanced of these drugs and in the second-line setting showed an overall response rate of 70% out of 199 patients (9). In addition, a response rate to CNS metastases of 54% out of 50 patients was shown. A phase III comparison has recently been published for osimertinib against gefitinib or erlotinib in a 556 patient study in first line (10). The FLAURA trial showed an 8.7 month gain in progression-free survival (HR 0.46, CI: 0.37–0.57) in favour of osimertinib from 10.8 to 18.7 months and a similar effect was seen in all predefined subgroups including race (one third of patients were of non-Asian origin). Skin rash occurred in 58% of patients with osimertinib compared to 78% with gefitinib or erlotinib, and the rate of permanent discontinuation was lower at 13% compared to 18% for the standard drugs. Both these observations are important as with improving progression free survivals patient tolerability is important. Survival data was immature but showed a HR of 0.63 (CI: 0.45–0.88, P<0.007) compared to standard therapy which the authors report as approaching statistical significance.

Crossover was allowed from the control arm in the FLAURA trial at relapse, and 43% of those retreated with a targeted agent were given osimertinib. However, the results of these second treatments were not given either in terms of response rate or duration but the overall time to second relapse was longer in the osimertinib arm than in the standard TKI arm.

Out of 116 patients with brain metastases at the start of therapy, the median progression-free survival was 15.2 months for osimertinib compared to 9.6 months for standard TKI therapy. Of the more serious adverse events, prolongation of QT interval occurred in 10% of patients and interstitial lung disease in 4% of patients on osimertinib, although none were fatal in this trial, but cardiac and lung toxicity remain concerns with this group of agents. CNS progression, irrespective of baseline status, was seen in 6% of the osimertinib patients compared to 15% in the EGFR-TKI group.

The FLAURA trial demonstrates impressive results for osimertinib therapy in EGFR M+ NSCLC. However, it should be noted there are no data on patients with the less common mutations in codon 19 as well as those in codons 18 and 20, which together may account for 12–14% of the overall mutations (9). These rare mutations do show differential sensitivity to the available drugs and further information should become available with wider availability of these agents. Secondly, the trial was conducted against the comparator gefitinib and not the more widely used afatinib, which has a broader spectrum of activity against EGFR mutations as does the other second generation drug dacomitinib. Many clinicians will continue to use the drugs they have experience with, particularly for those patients with Del19 mutations, and reserve osimertinib for T790M positive relapse. Thirdly these therapies are palliative and resistance develops to third generation drugs. A range of mechanisms including amplification of EGFR or MET, and mutations in the C797S EGFR site and KRAS (8) have been shown to account for this resistance, and a number of treatment options proposed. A small proportion show transformation to small cell lung cancer. Fourth generation drugs are under development which can overcome C797S mutations (11), and it is clear these approaches will require molecular testing at the time of relapse.

However, overall EGFR targeted therapy remains a major step forward with some cases of advanced NSCLC demonstrating response durations and survival of 3–5 years, a situation which would have been unheard of until recently. At 18 months in the FLAURA trial, the estimated survival in the osimertinib group was 83% (CI: 78–87%) out of 279 patients, 19% of whom had brain metastases at presentation.

A further point is that not all EGFR mutations are the same—while these may be grouped for common clinical characteristics, both the response and the resistance patterns demonstrate heterogeneity which will take time, sequential biopsies and careful follow-up to resolve (12). A meta-analysis of seven trials showed that the HR for EGFR-TKI compared to chemotherapy was 50% greater for Del 19 mutations than for L858R mutations (13), and emerging data will rank and quantify the probability of response of tumours harboring each mutation to each licensed drug. To date this has only been carried out for the 50 different variants of Del19 (14,15). These structural alterations to the EGFR molecule alter the binding site and may prevent or limit drug access, leading to differential response to drug therapy.

Current sequencing technologies in widespread use achieve good sensitivity and specificity, but are not as good for T790M alterations as for the common mutations. Next generation sequencing is more promising but has yet to become cost effective for routine use. The FLAURA trial and the majority of studies to date have relied on tumour biopsy testing, but cell free DNA in plasma offers the prospect of doing this in a non-invasive manner as many patients are not suitable for repeat bronchoscopic biopsy. However, liquid technology has not been widely accepted based on concerns about false positives (poor specificity), but a number of commercial tests are now available (16).

The question remains precisely where adoption of

osimertinib into clinical practice will take place. The FLAURA trial shows a clear rationale for use of osimertinib first line in patients with brain metastases and the small number of cases where T790M is demonstrated at the outset, which assumes the ready availability of reliable molecular testing. Serial monitoring of molecular changes may assist determination of the optimum sequencing of TKIs, but will require funding and development of guidelines. Cost effectiveness analyses will determine if the drug will be employed first line across the board in EGFR M+ tumours by health care funders at present, or if the present policy, currently adopted by NICE in the UK and under review in 2019, of reserving it for second line in T790M+ patients will continue.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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