Editorial

The evolving first-line treatment of advanced non-small cell lung cancer harbouring epidermal growth factor receptor mutations

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The current standard first-line treatment for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harbouring an epidermal growth factor receptor (EGFR) mutation is a first or second-generation EGFR tyrosine kinase inhibitor (TKI) (1,2).

The first-generation EGFR TKIs, gefitinib and erlotinib, reversibly and competitively inhibit the tyrosine kinase domain of EGFR. Both have shown significant improvements for response rate, progression-free survival (PFS) and quality of life (QOL) when compared to chemotherapy in this selected EGFR mutant NSCLC population (3-5). However, none of these trials have shown an overall survival (OS) benefit, possibly because of cross-over treatments and the relatively high efficacy of chemotherapy in this type of lung cancer. In a head-to-head phase III comparison, both first-generation EGFR TKIs demonstrated comparable efficacy for median PFS (13 *vs.* 10.4 months, HR: 0.81, P=0.108), response rates (56.3 *vs.* 52.3%, P=0.503) and median OS (22.9 *vs.* 20.1 months, HR: 0.84; P=0.250) (6). In addition, toxicity was comparable between the two drugs.

The second-generation EGFR TKIs, namely afatinib and dacomitinib, are irreversible, covalent inhibitors of EGFR and other human epidermal growth factor receptor (HER) family members (pan-HER inhibitors). As a consequence, both dacomitinib and afatinib also have some therapeutic value in HER2 driven NSCLC (7-9). Although the magnitude of the benefit is modest, these drugs offer some prolonged relieve to individual patients when they have become resistant to chemotherapy (9).

In phase III trials in EGFR mutant lung cancer, afatinib has demonstrated response rates and PFS superior to chemotherapy in the first-line treatment of EGFR mutant NSCLC (10,11). In a pooled analysis of these two phase III trials, afatinib showed a significant improvement of OS in patients with an exon 19 deletion compared to chemotherapy (12).

The phase IIb Lux-Lung 7 study was the first to compare a second-generation EGFR TKI (afatinib) with a first-generation EGFR TKI (gefitinib) in the first-line setting for NSCLC harbouring an activating EGFR mutation (13). In this study afatinib lead to a statistically significant, but clinically insignificant improvement of median PFS (11 *vs.* 10.9 months, HR: 0.73, P=0.017). Interestingly, PFS curves did further separate beyond the median PFS (≥10% improvement in 18- and 24-month PFS with afatinib *vs.* gefitinib), possibly reflecting the broader and more durable inhibitory profile of afatinib, which may also delay the emergence of acquired resistance. However, no difference in OS was observed between afatinib and gefitinib (27.9 *vs.* 24.5 months, HR: 0.86, P=0.258) (14). In addition, toxicity was higher for patients treated with afatinib.

Dacomitinib, despite its preclinical potency as a pan-HER TKI, much like afatinib failed to show a clinically meaningful activity in second line after failure of first-line EGFR TKI's that would weigh against the increased toxicity, mainly rash and diarrhoea (15).

The ARCHER 1050 study, recently published in

the *Lancet Oncol* by Wu *et al.*, is a phase III study which compares dacomitinib and gefitinib (16) in the first-line setting. In this study dacomitinib significantly improved PFS from 9.2 to 14.7 months (HR: 0.59 and P<0.0001) when compared to gefitinib. OS data are still immature. Treatment with dacomitinib was associated with increased grade 3/4 toxicity and a substantial need for dose reductions (66% *vs.* 8% respectively). Dacomitinib is thus the first EGFR TKI to demonstrate a significant and clinically meaningful superior activity regarding PFS when compared to gefitinib, a first-generation TKI. However, given the increased toxicity, more data will be required on OS benefit and/or a quality of life advantages to impact clinical practice.

These results should also be evaluated in the context of the recent development of osimertinib, a third generation, irreversible EGFR TKI that selectively inhibits both EGFR TKI sensitizing and EGFR T790M resistance mutations, with lower activity against the wild type EGFR (17). On the basis of positive results from the AURA3 study, osimertinib is currently approved worldwide for the treatment of patients with metastatic T790M positive NSCLC who have disease progression during treatment with a first or second-generation EGFR TKI (18). Osimertinib, like the other EGFR TKIs, has a high probability of passing the blood-brain barrier and penetrating the central nervous system resulting in high response rates in brain metastases (19,20).

In the FLAURA phase III study, osimertinib was compared with upfront gefitinib/erlotinib in patients with EGFR mutant NSCLC (19). Osimertinib significantly improved PFS (median 18.9 *vs.* 10.2 months, HR: 0.46; P<0.0001), but OS data are immature and eagerly awaited. Importantly, osimertinib was associated with significant lesser toxicity than erlotinib/gefitinib. Based on these data, osimertinib is close to becoming a preferred first line EGFR TKI for EGFR mutant NSCLC.

With the availability of multiple agents for EGFR mutated NSCLC, treatment options need to be considered in terms of a long-term plan to maximize survival and QOL. Physicians should therefore consider different factors before selecting a treatment option for EGFR mutant NSCLC, including possible mechanisms of resistance and subsequent treatment options, the management of brain metastases and the tolerability profile of different EGFR TKIs. Patients with EGFR mutated NSCLC are particularly prone to the development of brain metastases, which makes efficacy in patients with brain metastases an important asset for an EGFR TKI. Both afatinib and osimertinib have demonstrated activity in patients with asymptomatic brain metastases. In the LUX-Lung 3 and 6 trials, afatinib improved PFS versus chemotherapy in patients with asymptomatic brain metastases (HR: 0.50) and delayed central nervous system progression (21). Equally, osimertinib significantly prolonged PFS compared with erlotinib/gefitinib in patients with asymptomatic brain metastases (HR: 0.47) and resulted in a lower proportion of *de novo* central nervous system progression (6% *vs.* 15%) (19).

In the choice of the optimal treatment sequence it is important to realize that the majority of patients with EGFR mutated NSCLC treated with first or second-generation EGFR TKIs will develop resistance due to a T790M mutation, which makes them eligible for second-line treatment with osimertinib, while the resistance mechanisms after first line osimertinib are not fully understood so far and appear to be heterogeneous including novel but also mechanisms of resistance shared with the first-generation TKI's. One resistance mechanism is the acquisition of a tertiary C797S mutation, which may occur in cis or in trans. For mutations that occur in trans, combination therapy of first and third generation EGFR TKIs appear to be feasible and active, but mutations that occur in cis with T790M are likely resistant to first and second-generation (22,23) and fourth generation EGFR TKI are being investigated (24).

In the absence of an available molecular therapy for most of these first-and second line TKI resistance mechanisms, platinum doublet chemotherapy should be the offered as the optimal second line after osimertinib failure or after a first-line TKI failure not related to a T790M mutation.

There might be some interest for a comparison of upfront osimertinib with dacomitinib or afatinib with a cross-over between the two arms to compare the single and combined PFS in both arms as well as toxicity. However, EGFR mutant NSCLC patients treated with first or second-generation EGFR TKIs will develop mechanisms of resistance other than T790M, such as HER2 amplification, MET amplification, etc. Therefore, the design of such a comparative trial might be too complicated with second line branching based on diverse acquired resistance mechanisms.

Perhaps there is no need for such a trial. Cross-trial comparison indicates a similar hazard ratio for both dacomitinib and osimertinib compared to first-line reversible EGFR TKI treatment. But osimertinib has a more favourable toxicity profile (6,13,16,19), which has an important impact on the QOL of the patients.

The first-line treatment of cancer patients has the highest impact on outcome. A fundamental principle in oncology therefore is that patients should get the best first-line treatment option available, defined as the most effective treatment and, if equally effective, the best tolerated. Today it seems that the direct and cross-trial comparisons of PFS and tolerance in the first-line studies today guide us towards osimertinib as the preferred first-line treatment for EGFR mutant lung cancer.

In the future, the possible role of immunotherapy should also be further investigated in EGFR mutant NSCLC. Current results suggest that patients with an EGFR mutation do not seem to benefit from single agent programmed cell death-1 (PD-1) inhibitors such as nivolumab and pembrolizumab (25), but efforts should be undertaken to investigate methods that could enhance the immunogenic potential or immune priming of these cancers including the exploration of therapeutic vaccines and adoptive cell therapies together with existing and novel immune checkpoint inhibitors.

In conclusion, oncologists now have an expanding number of first line options available for advanced EGFR mutant NSCLC and need to consider how to use these agents to provide the best chance of long-term progression and overall survival while considering the relative toxicities.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Hanna N, Johnson D, Temin S, et al. Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology Clinical Practice Guideline update. J Clin Oncol 2017;35:3484-515.
2. Novello S, Barlesi F, Califano R, et al. Metastatic non-small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27:v1-27.
3. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib of carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57.
4. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase III study. Lancet Oncol 2011;12:735-42.
5. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239-46.
6. Yang JJ, Zhou Q, Yan HH, et al. A Phase III randomised controlled trial of erlotinib vs gefitinib in advanced non-small cell lung cancer with EGFR mutations. Brit J Cancer 2017;116:568-74.
7. Kris MG, Camidge DR, Giaccone G, et al Targeting HER2 aberrations as actionable drivers in lung cancers: phase II trial of the pan-HER tyrosine kinase inhibitor dacomitinib in patients with HER2-mutant or amplified tumors. Ann Oncol 2015;26:1421-7.
8. De Grève J, Moran T, Graas MP, et al. Phase II study of afatinib, an irreversible ErbB family blocker, in demographically and genotypically defined lung adenocarcinoma. Lung Cancer 2015;88:63-9.
9. De Grève J, Teugels E, Geers C, et al. Clinical activity of afatinib (BIBW 2992) in patients with lung adenocarcinoma with mutations in the kinase domain of HER2/neu. Lung Cancer 2012;76:123-7.
10. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3327-34.
11. Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung ancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised Phase III trial. Lancet Oncol 2014;15:213-22.
12. Yang JC, Wu YL, Schuler M, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase III trials. Lancet Oncol 2015;16:141-51.
13. Park K, Tan EH, O'Byrne K, et al. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase IIB, open-label, randomised controlled trial. Lancet Oncol 2016;17:577-89.
14. Paz-Ares L, Tan EH, O'Byrne K, et al. Afatinib versus

gefitinib in patients with EGFR mutation-positive advanced non-small-cell lung cancer: overall survival data from the phase IIb Lux-Lung 7 trial. Ann Oncol 2017;28:270-7.
15. Zugazagoitia J, Díaz A, Jimenez E, et al. Second-line Treatment of Non-Small Cell Lung Cancer: Focus on the Clinical Development of Dacomitinib. Front Med (Lausanne) 2017;4:36.
16. Wu YL, Cheng Y, Zhou X, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. Lancet Oncol 2017;18:1454-66.
17. Cross DA, Ashton SE, Ghiorghiu S, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. Cancer Discov 2014;4:1046-61.
18. Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med 2017;376:629-40.
19. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med 2018;378:113-25.
20. Watanabe S, Hayashi H, Nakagawa K. Is afatinib a treatment option for brain metastases in patients with EGFR mutation-positive non-small cell lung cancer? Ann Transl Med 2016;4:225.
21. Schuler M, Wu YL, Hirsh V, et al. First-line afatinib versus chemotherapy in patients with non-small-cell lung cancer and common epidermal growth factor receptor gene mutations and brain metastases. J Thorac Oncol 2016;11:380-90.
22. Niederst, MJ, Hu H, Mulvey HE, et al. The allelic context of the C797S mutation acquired upon treatment with third-Generation EGFR inhibitors impacts sensitivity to subsequent treatment strategies. Clin Cancer Res 2015;21:3924-33.
23. Wang Z, Yang JJ, Huang J, et al. Lung adenocarcinoma harbouring EGFR T790M and in trans C797S responds to combination therapy of first- and third-generation EGFR TKIs and shifts allelic configuration at resistance. J Thorac Oncol 2017;12:1723-7.
24. Lu X, Yu L, Zhang Z, et al. Targeting EGFRL858R/T790M and EGFRL858R/T790M/C797S resistance mutations in NSCLC: Current developments in medicinal chemistry. Med Res Rev 2018. [Epub ahead of print].
25. Lee CK, Man J, Lord S, et al. Checkpoint Inhibitors in Metastatic EGFR-Mutated Non-Small Cell Lung Cancer-A Meta-Analysis. J Thorac Oncol 2017;12:403-7.

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