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# Lung Cancer: One Therapy is better than Two Sequential Therapies

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## Editorial

Lung cancer is the leading cause of cancer death among men and women, accounting for about one-third of all cancer deaths, more than breast, prostate and colorectal cancers combined [1]. 10% to 15% of these are EGFR mutation-positive. Approximately two-thirds of patients treated with EGFR TKI therapy will acquire resistance related to the T790M mutation. Further investigations demonstrated that the highest response rates to these TKIs were seen in patients with somatic mutations within the EGFR-TK domain, particularly exon 19 deletion, exon 21 L858R, and exon 18 G719X [2].

By contrast, the exon 20 T790M mutation is associated with acquired resistance to TKI therapy Osimertinib is an oral, potent, irreversible EGFR-TKI selective for EGFRm and T790M mutations. Osimertinib had significantly greater efficacy in the form of PFS and ORR than platinum therapy plus pemetrexed in patients with T790M-positive advanced non–small-cell lung cancer who had disease progression after first-line EGFR-TKI therapy as it achieved median PFS (10.1 months vs. 4.4 months; hazard ratio; 0.30; 95% confidence interval [CI], 0.23 to 0.41; P<0.001). Preliminary data from a Phase I/II study demonstrated clinical activity and a manageable tolerability profile for AZD9291 (osimertinb) as first-line treatment of patients with EGFRm advanced NSCLC.

This Phase III, double-blind, randomized study (FLAURA, NCT02296125) is designed to assess the efficacy and safety of AZD9291 (80 mg qd, orally) versus standard of care (SoC) EGFR-TKI (gefitinib [250 mg qd, orally] or erlotinib [150 mg qd, orally]) in treatment-naïve patients with locally advanced or metastatic EGFRm NSCLC. Osimertinib significantly improved PFS compared to erlotinib or gefitinib in previously untreated patients with locally advanced or metastatic EGFRm NSCLC. Median PFS was nearly doubled at 18.9 months for osimertinib compared with 10.2 months for the EGFR-TKI comparator arm (PFS, hazard ratio [HR] 0.46; 95% confidence interval [CI] 0.37-0.57; p<0.001).

Osimertinib was well tolerated, with less frequent grade 3 or higher adverse events (AEs) than with standard EGFR-TKIs (34% vs. 45%). In all patients, the most common AEs were rash or acne (58% [1% Grade ≥3] for osimertinib vs. 78% [7% Grade ≥3] for the comparator arm), diarrhoea (58% [2% Grade ≥3] for osimertinib vs. 57% [2% Grade ≥3] for the comparator arm), and dry skin (36% [<1% Grade ≥3] for osimertinib vs. 36% [1% Grade ≥3] for the comparator arm) [2]. So, as we seen previously osimertinib can achieve a better ORR, PFS and lesser adverse events than gefitinib or erlotinib

On the other hand, 2-7% of NSCLC patients exhibit rearrangement of the ALK gene which plays a dominant oncogenic driver that can be targeted by TKIs like crizotinib. Crizotinib, a first-generation ALK inhibitor, has been the standard of care for patients with newly diagnosed advanced ALK-positive NSCLC. Crizotinib can be very effective in this setting, achieving an ORR of 74% and a median PFS of 10.9 months vs. 45% and 7.0 months with platinum/pemetrexed chemotherapy in the first-line PROFILE 1014 trial (P < .001 for both) Alectinib, a second-generation ALK inhibitor, is currently approved for patients with ALK-positive NSCLC who have failed crizotinib based on phase II study results that showed an ORR of approximately 50% and median PFS of 8-9 months with second-line alectinib.

Primary results of the global phase III ALEX study presented at ASCO in June 2017 comparing alectinib versus crizotinib in the first-line setting have now established alectinib as a new standard of care for newly diagnosed ALK-positive NSCLC, The primary endpoint of PFS by investigator review was not reached with alectinib vs. 11.1 months with crizotinib (HR for progression: 0.47; 95% CI: 0.34-0.65; P < .0001). Similarly, the secondary endpoint of PFS by independent review was 25.7 months with alectinib vs. 10.4 months with crizotinib (HR: 0.50; 95% CI: 0.36-0.70; P < .0001). Hence, the magnitude of the PFS improvement with first-line alectinib shown in the ALEX study suggests that patients may benefit from receiving

alectinib as initial therapy vs. receiving sequential crizotinib followed by alectinib, In addition to the more efficacious role of alectinib than crizotinib, also alectinib showed more safety profile with fewer grade 3-5 AEs and fewer AEs leading to treatment discontinuation, dose interruption or dose reduction vs. crizotinib.

## Conclusion

So, generally we can assume that one TKI is better than two sequential TKIs regarding its efficacy in management of NSCL cancer.


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