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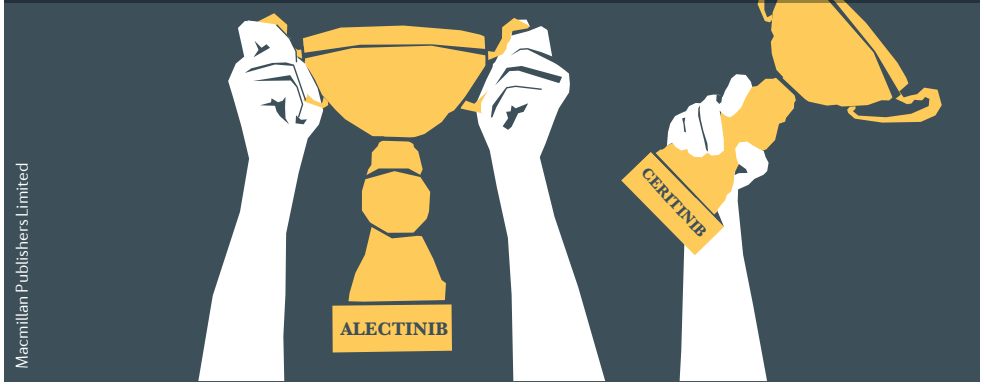
TARGETED THERAPIES

Defining the best-in-class in NSCLC



For patients with ALK-positive non-small-cell lung cancer (NSCLC) the standard first-line therapy is crizotinib. Resistance to first-line ALK inhibitors is common — inevitably, patients relapse, and can develop metastases in the central nervous system (CNS). The second-generation ALK inhibitor alectinib is able to penetrate the CNS, and the welcome results of the recent J-ALEX study have confirmed that alectinib is more efficacious and tolerable than crizotinib in Japanese patients with NSCLC. Now, the results of the ALEX trial, published in the *New England Journal of Medicine*, illustrate that the results observed in J-ALEX are generalizable to other patient populations.

In the international, open-label, phase III ALEX trial, alectinib was compared with crizotinib in patients with previously untreated advanced-stage ALK-positive NSCLC. Tony Mok and co-authors reported a significantly higher progression-free survival (PFS) with alectinib compared with crizotinib (68.4% versus 48.7%). Grade 3 to 5 adverse events were reported less frequently with alectinib than with aoutcomes.

Mok elaborates, "we took great effort to follow disease progression in patients with and without CNS metastases at trial enrolment. We have demonstrated greater CNS control with alectinib, as noted by the improvement of median PFS to 25.7 months, more than double the 10.1 months PFS duration noted with crizotinib." The implications of these data are obvious: "there is high likelihood that alectinib will supersede crizotinib to become the new standard first-line therapy for ALK-positive NSCLC. The outstanding issue, however, relates to drug sequence. Some would argue it is better to give crizotinib in the first line and reserve alectinib or ceritinib for the second line. It will be difficult to perform a comparative study in this regard."

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Other ALK inhibitors have been shown to be active in patients with ALK-independent mechanisms of resistance to crizotinib, including ceritinib. In the phase III ASCEND-5 trial, Alice Shaw and investigators explored the efficacy of ceritinib in patients with *ALK*-rearranged NSCLC who had disease progression following treatment with crizotinib and platinum-based chemotherapy. In this trial, the median PFS was significantly improved with ceritinib compared with chemotherapy (5.4 months versus 1.6 months). Moreover, control of brain metastases was better with ceritinib than with chemotherapy, and patient-reported outcomes, in general, favoured ceritinib, with the median time to deterioration of symptoms being significantly longer than the timeframe noted with chemotherapy.

Collectively, these data establish next-generation ALK inhibitors as the preferable treatment option for patients with *ALK*-rearranged NSCLC. Future trials should no longer compare ALK tyrosine-kinase inhibitors (TKIs) with chemotherapy, but instead assess the next-generation of these agents against standard-of-care TKIs. Ongoing trials of various ALK TKIs should provide the data to confirm that next-generation ALK inhibitors are better than crizotinib in patients who have not received TKI therapy. Although ceritinib has not been compared to crizotinib, recent results from the ASCEND-4 trial showed that ceritinib prolonged responses and doubled median PFS to over 16 months compared with chemotherapy in TKI-naive patients.

Acquired resistance owing to additional ALK mutations or activation of alternative bypass pathways will need to be addressed. In the future, key research avenues should determine the variant *ALK* mutations by genomic analysis to define the best therapy. A promising approach includes plasma-based genomic monitoring of ALK status to help decide whether and when to switch to an alternative TKI. Finally, in the immunotherapy era, it will be important to define optimal combinations of immunotherapy with TKI therapy.

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ORIGINAL ARTICLES Peters, S. *et al.* Alectinib versus crizotinib in untreated ALK-positive NSCLC. *N. Engl. J. Med.* http://dx.doi.org/10.1056/NEJMoa1704795 (2017) | Shaw, A. T. *et al.* Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol.* http://dx.doi.org/10.1016/S1470-2045(17)30339-X (2017)
FURTHER READING Hutchinson, L. J-ALEX hints at new first-line in NSCLC. *Nat. Rev. Clin. Oncol.* **14**, (2017)