Future of ALK inhibition in non-small-cell lung cancer

Progress in defining molecular targets of oncogenesis and drugs to inhibit cancer growth in specific populations has led to augmented outcomes for patients and new expectations in the development of treatments. The EML4–ALK fusion protein was identified in patients with non-small-cell lung cancer (NSCLC) in 2007.1 Rearrangements in the ALK gene lead to constitutive signalling, triggering transforming properties. Up to now, two drugs have been approved by the US Food and Drug Administration for ALK-rearranged NSCLC—crizotinib and ceritinib. ALK inhibitors vary in potency against their target and in ability to overcome resistance; moreover, CNS activity differs between agents. Crizotinib is an oral tyrosine kinase inhibitor that targets ALK, MET, and ROS1. It has an objective response of 61% and results in median progression-free survival of 9.7 months.2 Activity was similar between crizotinib and chemotherapy as second-line treatment for ALK-positive NSCLC.3 Despite exceptional responses, all patients develop resistance and progression due to second-site mutations or activation of bypass pathways.

Several second-generation ALK inhibitors can overcome resistance to crizotinib, including ceritinib and alectinib. Ceritinib is a selective small-molecule tyrosine kinase inhibitor of ALK with an objective response of 56% in patients who previously progressed on crizotinib.4 Alectinib is a highly selective ALK inhibitor with an objective response of 94% in patients with ALK-rearranged NSCLC who have never received an ALK inhibitor before.5

In The Lancet Oncology, Shirish Gadgeel and colleagues present results of the phase 1 part of a phase 1/2 study of alectinib in patients with ALK-rearranged NSCLC who were resistant to crizotinib.6 24 (55%) of 44 patients had an objective response, although nine (20%) responses remain unconfirmed because of limited follow-up. These data confirm the activity of alectinib in patients with ALK-rearranged NSCLC and suggest that second-generation ALK inhibitors might be able to overcome some forms of resistance to crizotinib.

The CNS is a common site of progression in patients with ALK-rearranged NSCLC treated with crizotinib,7 findings suggest that penetrance of the drug into the CNS is limited.7 With ceritinib, 64 patients had CNS metastases, with progression-free survival of 6-9 months.4 Gadgeel and colleagues assessed 21 patients with CNS metastases; 11 (52%) had an objective response. Nine patients had measurable CNS lesions at baseline, and five (56%) of these had a partial response. Furthermore, five patients with CNS metastases at baseline had paired cerebrospinal fluid (CSF) and plasma samples available; measurable concentrations of alectinib in the CSF were seen. These early results indicate some CNS activity from second-generation ALK inhibitors, but the number of patients with untreated brain metastases and measurable disease are small.

Most patients who receive crizotinib have a good quality of life and remain active.3 When transitioning to a second-generation ALK inhibitor, patients will expect to maintain their quality of life, but toxic effects could be increased with more potent ALK inhibitors. At a ceritinib dose of 750 mg, 62% of patients needed dose reduction and 6% discontinued because of an adverse event.4 This high level of toxicity is concerning because continued daily grade 1 or 2 toxic effects can lead to dose reductions and discontinuations that might affect efficacy in clinical trials.8 In ALK inhibitor-naive patients receiving alectinib,3 37% had grade 3 adverse events; a similar proportion in the study by Gadgeel and colleagues (36%, n=17) had grade 3 and 4 adverse events.5 12 patients (26%) needed a dose reduction or interruption because of adverse events. In this small sample, the tolerability of alectinib might be more favorable than ceritinib, but data from larger cohorts are needed. Alectinib has clear activity in crizotinib-resistant ALK-rearranged NSCLC, but a place for this agent in the treatment plan for patients remains to be established.

Despite drugs approved for ALK-rearranged NSCLC having exceptional activity, patients are not cured and resistance ultimately develops. A new paradigm in drug development must incorporate activity, tolerability, sequencing, and potential combinations. For example, the tyrosine kinase inhibitors sunitinib and pazopanib have been compared in patients with metastatic renal-cell carcinoma. In a non-inferiority trial,9 these agents had similar efficacy, and adverse events were reduced with pazopanib. In a novel crossover trial,10 patients were assigned either pazopanib followed by
sunitinib or sunitinib followed by pazopanib; patients’ preference was assessed as the primary endpoint, with pazopanib the preferred drug on the basis of quality of life and adverse events. Trial designs must also assess efficacy within the CNS, and innovative methods will be needed to address heterogeneity in treatment of CNS metastases and difficulties in measurement of response. Ultimately, patients and clinicians will ascertain the value of these types of drugs as researchers establish the best timing, sequence, and possible combinations.

Karen L Reckamp
City of Hope Comprehensive Cancer Center, Duarte, CA 91010, USA
kreckamp@coh.org
I have been an institutional principal investigator on trials for Ariad, Pfizer, GlaxoSmithKline, and Novartis.