LUNG CANCER IN FOCUS

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Combining Inhibitors of ALK and ROS1 With Other Agents for the Treatment of Non–Small Cell Lung Cancer

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H&O How common are rearrangements of anaplastic lymphoma kinase (ALK) and ROS1 in non–small cell lung cancer (NSCLC)? Do they ever co-occur?

AS ALK and ROS1 rearrangements define relatively small subsets of patients with NSCLC. ALK rearrangement is identified in 3% to 5% of patients, whereas ROS1 rearrangement is identified in approximately 1% of patients. Although the percentages are small, the total number of patients diagnosed each year with advanced NSCLC is very large, so small percentages still translate into a sizable number of patients.

The clinical features of patients with ALK- or ROS1-rearranged lung cancers are very similar. Both ALK- and ROS1-rearranged patients tend to be younger than average, they usually are never or light smokers, and they almost always have adenocarcinoma histology. Nonetheless, these are distinct subsets of lung cancer patients, and we rarely if ever see overlap of ALK and ROS1 rearrangement. We did recently report a case in which a tumor tested positive for both ALK and ROS1 using fluorescence in situ hybridization assays. However, confirmatory next-generation sequencing demonstrated that the tumor harbored only ALK rearrangement, and not ROS1 rearrangement.[1]

H&O What makes ALK and ROS1 important therapeutic targets in NSCLC?

AS ALK and ROS1 testing in NSCLC is critically important because highly active targeted therapies exist for both of these subsets. Because of the similarity between the tyrosine kinase domains of ALK and ROS1, many ALK inhibitors also inhibit ROS1. For example, crizotinib (Xalkori, Pfizer) is a standard therapy for advanced ALK-rearranged NSCLC, with a demonstrated response rate in the 60% to 70% range and a median progression-free survival of approximately 8 to 11 months.[2-4] Crizotinib is also highly effective in advanced ROS1-rearranged NSCLC. Among 50 patients with ROS1-rearranged NSCLC, the response rate was 72% and the median progression-free survival exceeded 19 months.[1]

In addition, for ALK-rearranged NSCLC, there are numerous next-generation inhibitors that are highly active after crizotinib has failed. Thus, the importance of these targets lies in the availability of multiple therapies that can be very effective and are generally much better tolerated than cytotoxic chemotherapy.

H&O How is ALK- or ROS1-rearranged NSCLC currently treated, and what are the limitations of treatment?

AS Patients with advanced ALK- or ROS1-rearranged NSCLC are usually treated with crizotinib as first-line therapy. Two randomized phase 3 studies of crizotinib in advanced ALK-rearranged NSCLC have established that crizotinib is superior to standard chemotherapy in both the first- and second-line settings.

Recently, several studies have demonstrated that more potent ALK inhibitors (so-called next-generation inhibitors) can overcome crizotinib resistance in the majority of

patients who relapse on crizotinib.[5-7] The next-generation ALK inhibitor ceritinib (Zykadia, Novartis) was recently approved for patients who were previously treated with crizotinib, and 2 other next-generation ALK inhibitors, alectinib and brigatinib, have received US Food and Drug Administration (FDA) Breakthrough Therapy Designation for patients who were previously treated with crizotinib. We have shown that some patients can benefit from another ALK inhibitor after their disease has failed to respond to crizotinib and a next-generation ALK inhibitor; these patients tend to have acquired ALK resistance mutations and their tumors are still ALK-dependent.

Outside of targeted therapies, patients with ALK-rearranged NSCLC typically receive standard platinum-based combination chemotherapy if they are appropriate candidates. Platinum/pemetrexed or single-agent pemetrexed are commonly used, and may have slightly better efficacy in ALK-rearranged NSCLC compared with unselected NSCLC.[2]

For patients with ROS1-rearranged NSCLC, the preclinical and emerging clinical data with crizotinib are extremely compelling.[1] Previously, we treated patients with advanced ROS1-rearranged NSCLC with crizotinib in the phase 1 PROFILE 1001 study (NCT00585195). However, the ROS1 expansion cohort within that study has closed, and we now prescribe commercial crizotinib for these patients. As with ALK-rearranged patients, ROS1-rearranged patients also typically receive standard chemotherapy when there are no other targeted therapy options.

The major limitation with all targeted therapies is the emergence of resistance. With crizotinib and ALK-rearranged NSCLC, resistance often emerges in the first or second year of treatment. Resistance also emerges with crizotinib in ROS1-rearranged NSCLC, but often later than seen with ALK-rearranged NSCLC (median progression-free survival of 19 months vs 8-11 months). Crizotinib does not penetrate well into the central nervous system (CNS), so relapses often occur in the CNS. For patients with ALK-rearranged NSCLC, next-generation ALK inhibitors have shown promising activity in the CNS and can reinduce intracranial responses, even in a patient whose disease has failed to respond to crizotinib.

H&O What is the rationale behind combining inhibitors of ALK or ROS1 with other targeted agents or immunotherapies?

AS Almost all patients with ALK- or ROS1-rearranged NSCLC will relapse on crizotinib and other ALK/ROS1 inhibitors. In some cases, resistance may be due to a new (ie, secondary) mutation within the target kinase, and tumors will remain dependent on that kinase. Treatment with another inhibitor that can overcome that mutation is often effective. However, tumors also can become resistant through a number of mechanisms that allow the cancer to bypass ALK or ROS1 inhibition. For example, in some cases, the endothelial growth factor receptor (EGFR) pathway can be activated through upregulation (not mutation) of EGFR, and targeting both ALK and EGFR can overcome resistance, at least in preclinical models. Over the years, a number of different signaling pathways have been shown to function as bypass tracks mediating resistance to crizotinib and other ALK inhibitors. This is the rationale for pursuing combinations of targeted therapies. In a number of cases, we and others have observed multiple mechanisms of resistance emerging in a single patient in response to crizotinib, particularly in response to next-generation ALK inhibitors. Given this potential heterogeneity, combinations that include agents with broader activity (eg, chemotherapy, immunotherapy) are also being pursued in the clinic.

H&O What are the more common mechanisms of resistance in ALK- and ROS1-rearranged disease?

AS Cancer cells can become resistant to crizotinib in many different ways. The best-understood mechanism of resistance is genetic alteration of the target kinase itself. Resistant cells can acquire a new mutation within the tyrosine kinase domain that hinders drug binding (such as the gatekeeper L1196M mutation in ALK, or the highly refractory solvent front mutation G2032R in ROS1). In the case of ALK-rearranged NSCLC, we have observed many different resistance mutations in addition to the L1196M gatekeeper mutation; next-generation ALK inhibitors can overcome many of these resistance mutations. In the case of ROS1-rearranged NSCLC, we have identified only 1 resistance mutation so far (G2032R), but this appears to be the most common mechanism of resistance to crizotinib.

As mentioned earlier, resistance to targeted therapies can also be mediated by other important signaling pathways that function independently of ALK or ROS1. Examples of these bypass pathways include EGFR, c-KIT, Src, insulin-like growth factor 1 receptor, c-MET, and mitogen-activated protein kinase (MAPK).

H&O Should patients be routinely biopsied at the time of disease progression?

AS Obtaining repeat biopsies at the time of progression is very important because it may allow identification of the resistance mechanism and help select the next therapy. In ALK-rearranged NSCLC, most patients will respond once again to a next-generation ALK inhibitor after relapsing on crizotinib. However, occasionally patients

will develop a highly resistant mutation, such as ALK G1202R, after crizotinib. For this particular mutation, none of the most advanced next-generation ALK inhibitors—alectinib, ceritinib, or AP26113—are effective. These patients either should be directed to a clinical trial of PF-06463922, which is the only ALK inhibitor with preclinical activity against this particular resistance mutation, or should receive standard chemotherapy.

H&O What ALK and ROS1 inhibitors are available or in development?

AS Numerous ALK and ROS1 inhibitors are available in the clinic. Some (but not all) ALK inhibitors also inhibit ROS1, such as crizotinib and PF-06463922. Crizotinib, which is the most advanced ALK inhibitor in the clinic, is now widely available in many countries for advanced ALK-rearranged NSCLC. Ceritinib, which was approved by the FDA 1 year ago for ALK-rearranged NSCLC patients who were previously treated with crizotinib, has been recommended by the European Medicines Agency for conditional approval for the same indication in Europe. Alectinib has already been approved in Japan, and has FDA Breakthrough Therapy Designation in the United States. The Ariad compound AP26113 also has FDA Breakthrough Therapy Designation.

In addition, other potentially active next-generation ALK inhibitors are in earlier development, including X-396, TSR-011, PF-06463922, and RXDX-101 (entrectinib). Of all the ALK inhibitors, PF-06463922 appears to cover the broadest spectrum of ALK resistance mutations, based on preclinical studies. PF-06463922 is also a highly potent inhibitor of ROS1.

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