LUNG CANCER IN FOCUS

Current Developments in the Management of Lung Cancer

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ALK Inhibitors in Non–Small Cell Lung Cancer: How Many Are Needed and How Should They Be Sequenced?

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H&O Which patients with non–small cell lung cancer (NSCLC) are candidates for treatment with crizotinib?

AS Crizotinib (Xalkori, Pfizer) is a multitargeted tyrosine kinase inhibitor that inhibits ALK, ROS1, and c-MET. It is approved by the US Food and Drug Administration (FDA) for patients with advanced *ALK*- or *ROS1*-rearranged NSCLC. Crizotinib is also being investigated for use in patients with an alteration in the *MET* gene—either *MET* amplification or *MET* exon 14 skipping mutations.

H&O What are the response rates to crizotinib, and how durable is the response?

AS Crizotinib is very active in *ALK*- and *ROS1*-rearranged lung cancer. For patients with ALK-positive lung cancer, which accounts for 3% to 7% of cases of NSCLC, the response rate with crizotinib is approximately 60% to 75%. Median progression-free survival (PFS) is in the range of 8 to 11 months.

The response rate in patients with ROS1-positive lung cancer, which occurs in 1% to 2% of cases of NSCLC, is approximately 70%. This is comparable to the response rate in ALK-positive patients. However, the median PFS appears to be significantly longer in ROS1-positive compared with ALK-positive patients; the registrational phase 1 study, which was published in the *New England Journal of Medicine* in 2014, found a median PFS of just over 19 months with crizotinib.

H&O What other agents are available as first-line treatment in patients who have ALK-positive NSCLC?

AS We now have data on 2 second-generation ALK inhibitors as first-line treatment in patients with ALK-positive NSCLC—ceritinib (Zykadia, Novartis) and alectinib (Alecensa, Genentech).

Ceritinib was compared head to head with platinum/pemetrexed (Alimta, Lilly) chemotherapy in the ASCEND-4 study (First-Line Ceritinib Versus Platinum-Based Chemotherapy in Advanced *ALK*-Rearranged Non-Small-Cell Lung Cancer), which was published in the *Lancet* by Soria and colleagues in early 2017. In that study, ceritinib was significantly superior to standard platinum combination chemotherapy as first-line treatment; the median PFS times were 16.6 and 8.1 months, respectively. As a result, ceritinib received

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FDA approval as first-line treatment for patients with ALK-positive lung cancer.

Alectinib has been compared with crizotinib in advanced ALK-positive NSCLC in 2 randomized phase 3 studies: the global ALEX study (Alectinib versus Crizotinib in Untreated *ALK*-Positive Non–Small-Cell Lung Cancer) and a Japanese study (J-ALEX: Alectinib Versus Crizotinib in *ALK*-Positive Lung Cancer). The results of the 2 studies were remarkably similar. In the phase 3 global ALEX study, which we presented at the 2017 annual meeting of the American Society of Clinical Oncology (ASCO) and published in the *New England Journal of Medicine*, alectinib was shown to be significantly superior to crizotinib as first-line treatment; the median PFS was more than 2 times longer than with crizotinib. On independent review, the median PFS was approximately 26 months with alectinib vs 10 months with crizotinib. In addition, we showed that alectinib significantly delayed time to central nervous system (CNS) progression. In a competing risk analysis, we showed that the cumulative incidence rate of CNS progression at 12 months was 9% with alectinib, vs 41% with crizotinib.

Alectinib has been granted FDA breakthrough therapy designation for first-line use. We anticipate that alectinib will soon receive approval as a first-line treatment for patients with advanced ALK-positive lung cancer. Because of the positive results of global ALEX and J-ALEX, we are already prescribing alectinib for the first-line treatment of advanced ALK-positive NSCLC.

H&O What options are available for patients in whom resistance to crizotinib or other ALK inhibitors develops in the first-line setting?

AS We are fortunate to have many options for patients with ALK-positive NSCLC if resistance to crizotinib develops. Most ALK-positive patients with relapse on crizotinib are still highly sensitive to the more-potent next-generation ALK inhibitors, which include the second-generation ALK inhibitors ceritinib, alectinib, and brigatinib (Alunbrig, Takeda), as well as the third-generation ALK inhibitor lorlatinib. All 3 of the second-generation ALK inhibitors are approved in the United States for patients who have ALK-positive disease previously treated with crizotinib. Moving patients from first-line crizotinib to a more potent, next-generation ALK inhibitor has become a standard approach to the treatment of ALK-positive patients.

What is more complicated is determining what to do when the disease becomes resistant to first-line ceritinib or first-line alectinib. Emerging data, most of which are in the setting of failure of sequential first- and second-generation inhibitors, suggest that in a significant proportion of patients whose disease recurs on a second-generation inhibitor, specific resistance mutations can develop within the ALK kinase domain. Each second-generation inhibitor is associated with a unique spectrum of *ALK* resistance mutations, but one mutation—*ALK* G1202R—is commonly seen after failure of second-generation inhibitors. Given the variable potencies of second-generation inhibitors against different resistance mutations, when resistance to a second-generation drug develops in a patient, we should not choose another second-generation ALK inhibitor at random. Ideally, we select another ALK inhibitor according to what is known about its potency against the identified resistance mutation.

For a patient in whom resistance to a second-generation ALK inhibitor has developed—whether that patient received first-line ceritinib or alectinib, or one of these agents as second-line treatment after crizotinib—I recommend re-biopsy of a resistant lesion. This allows us to do a histologic analysis (to confirm that the cancer still looks like NSCLC) and molecular profiling to determine whether the tumor contains specific *ALK* mutations that may confer sensitivity to a different ALK inhibitor.

H&O How effective are second-generation ALK inhibitors in patients in whom resistance to crizotinib has developed?

AS Second-generation ALK inhibitors are very effective in patients with crizotinib-resistant disease; we have seen response rates in the range of 40% to 60%. We know that the median PFS with alectinib after failure of crizotinib is approximately 8 to 9 months, and it may be even longer with brigatinib. Most patients do derive benefit from second-generation ALK inhibitors after crizotinib. However, the frontline alectinib studies suggest that patients may derive even greater benefit when second-generation ALK inhibitors are used up front rather than after crizotinib.

H&O Is there any reason to use crizotinib as first-line therapy at this point?

AS For patients who are ALK-positive, I would say no. The data supporting alectinib as first-line treatment are very strong in the global ALEX and J-ALEX studies. In both studies, the response rate was greater than 80% and the median PFS was approximately 26 months. In addition, alectinib was very well tolerated and may be associated with fewer serious side effects than crizotinib. For patients with ROS1-positive NSCLC, crizotinib remains the standard first-line therapy. However, new, next-generation, CNS-penetrant ROS1 inhibitors are currently in development.

H&O What are the differences between the various second-generation ALK inhibitors?

AS There are differences in terms of both efficacy and safety, but I should note that these differences are inferred from cross-trial comparisons, and no direct head-to-head comparisons of second-generation inhibitors have been conducted. Efficacy appears to be lower with ceritinib than with alectinib or brigatinib. The response rate with ceritinib may be slightly lower, and importantly, the PFS also appears to be shorter with ceritinib than with either alectinib or brigatinib. In separate trials, the median PFS was approximately 6 to 7 months with ceritinib, 8 to 9 months with alectinib, and 12 to 13 months with brigatinib. Again, a word of caution because these results are drawn from separate trials, each with its own eligibility criteria and study assessments.

All 3 second-generation ALK inhibitors have demonstrated efficacy in the CNS. Of the 3 drugs, alectinib has the most robust intracranial data. In the phase 2 and phase 3 studies of alectinib, all patients (even those without brain metastases at baseline) were required to have systematic brain magnetic resonance imaging (MRI) every 8 to 9 weeks. In contrast, for ceritinib and brigatinib, only those patients with known brain metastases at baseline were monitored regularly with brain MRI. Alectinib is very potent in the CNS, inducing CNS responses (including complete responses) in a significant proportion of patients. In addition, alectinib is active against traditionally refractory sites of CNS disease, including intramedullary metastases and leptomeningeal disease. This is a potent and highly CNS-penetrant drug.

Regarding safety, the side effect profiles vary significantly among the 3 second-generation inhibitors. Ceritinib is the most challenging to manage in terms of gastrointestinal side effects—nausea, vomiting, and diarrhea. We see these gastrointestinal side effects in the great majority of patients—about 80%—with the standard dose of 750 mg daily under fasting conditions. Most patients require dose interruptions and dose reductions, which may explain why the efficacy of ceritinib appears to be lower than that of alectinib and brigatinib. Fortunately, recent work has shown that a lower dose of ceritinib—450 mg—taken with food leads to plasma drug levels equivalent to those achieved with the standard 750-mg fasting dose. This lower dose is also associated with a more favorable side effect profile, with less frequent and less severe gastrointestinal toxicities.

Alectinib seems to be the most easily tolerated of the second-generation inhibitors. It does have some side effects, but they tend to be very mild. The most common are fatigue, constipation, edema, and muscle aches. But overall in my experience, patients usually tolerate alectinib very well.

Brigatinib is also relatively well tolerated, but I find that patients tend to have a few more side effects than with alectinib. The most important and worrisome side effect—and this is unique to brigatinib—is early pulmonary toxicity. Shortness of breath, cough, and in rare cases even respiratory failure will develop in some patients after a single dose of the drug. Fortunately, with the current schedule of brigatinib (lead-in dose of 90 mg daily for 7 days, then escalation to the standard dose of 180 mg daily), early pulmonary toxicity is less common (6% incidence in the phase 2 study of brigatinib). However, respiratory failure remains a potentially life-threatening reaction, so it's extremely important for oncologists to be aware of this toxicity and to counsel their patients about monitoring for early respiratory symptoms.

H&O Do you ever switch from one second-generation ALK inhibitor to another?

AS Yes, sometimes we do. We find that this strategy works best when we have identified a specific *ALK* mutation that causes resistance to one agent but not the other. For example, we have had patients whose disease relapsed on ceritinib because an *ALK* F1174 mutation developed in the cancer. This mutation happens to be very sensitive to alectinib, so we have moved these patients from ceritinib to alectinib and observed second responses.

The most common *ALK* mutation emerging in patients who have relapsed on a second-generation inhibitor—whether it be ceritinib, alectinib, or brigatinib—is the G1202R mutation in *ALK*. It causes cross-resistance to all the first- and second-generation inhibitors, so for this mutation, we need to consider a third-generation, pan-inhibitory compound, such as lorlatinib. In both preclinical and clinical studies, lorlatinib was shown to overcome the *ALK* G1202R mutation effectively. This finding again highlights the importance of performing another biopsy after failure of a second-generation inhibitor, rather than blindly moving from one drug to the next.

H&O What third-generation inhibitors are available?

AS The investigational agent lorlatinib, which was designed to overcome all the known crizotinib resistance mutations and penetrate the CNS, has FDA breakthrough therapy designation, and we hope the drug will be approved in early to mid 2018. Currently, lorlatinib is available to previously treated ALK- and ROS1-positive patients as part of an expanded-access protocol.

Another investigational ALK inhibitor is TPX-0005, which targets not only ALK but also ROS1 and TRK.

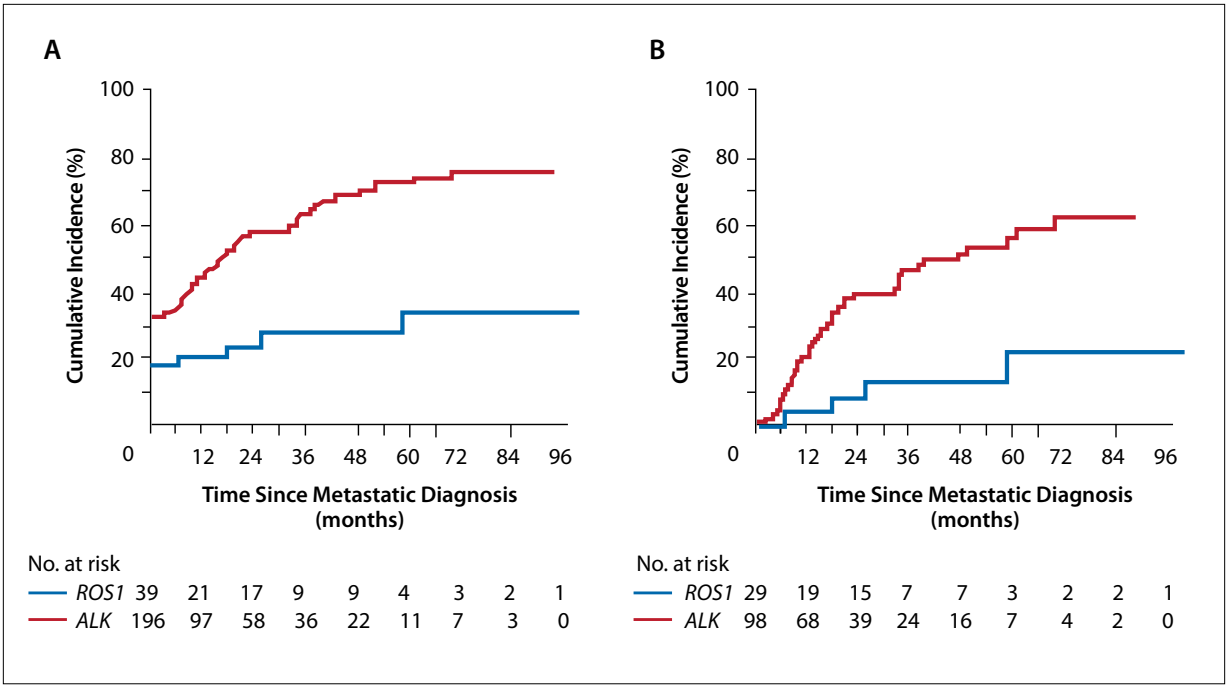

Figure. Cumulative incidence of brain metastases over time among (A) all patients with ALK- and ROS1-positive disease and (B) patients with ALK- and ROS1-positive disease with no known brain metastases at initial metastatic diagnosis.

Gainor JR, Tseng D, Yoda S, et al. Patterns of metastatic spread and mechanisms of resistance to crizotinib in ROS1-positive non–small-cell lung cancer. *JCO Precis Oncol*. 2017;1:1-13. Republished with permission.

This agent was designed to overcome the most refractory resistance mutations, including *ALK* G1202R and *ROS1* G2032R. This agent is currently in a phase 1 trial (NCT03093116). Based on the currently available data, lorlatinib would be the treatment of choice in patients with a documented G1202R *ALK* mutation.

H&O How many ALK inhibitors can be used in a single patient?

AS The number varies widely from 1 to many. I have seen many patients over the past decade who received multiple different ALK inhibitors—3 or even 4 ALK inhibitors—and derived benefit from each of them. There is no known limit to how many ALK inhibitors can be used, but I suspect that at some point, all tumors will develop ALK-independent mechanisms of resistance and so will no longer respond to further ALK inhibition.

H&O Can plasma-based biopsy be used in place of tissue biopsy to determine resistance mutations?

AS We are still determining whether plasma-based methods are sensitive enough to detect all the different *ALK* resistance mutations. The gold standard remains tissue, but I do have patients undergo plasma circulating tumor DNA (ctDNA) testing when I am unable to obtain tissue. Recently, my group conducted a study of serial ctDNA monitoring in ALK-positive patients as they moved from one ALK inhibitor to the next. The results will be published soon, but overall, we observed a high degree of concordance between tumor and liquid biopsies, and we showed that liquid biopsy could track the evolution of resistance in ALK-positive lung cancer. One of the objectives of the National Cancer Institute ALK Master Protocol is to establish the concordance between tumor and liquid biopsies, so we hope to know soon whether we can rely—at least initially—on plasma testing.

H&O Now that we have 4 approved ALK inhibitors and one that's available under certain protocols, is there a place for all these agents?

AS The second-generation ALK inhibitors have replaced crizotinib in ALK-positive NSCLC, although there could still be a role for crizotinib in these patients if resistance due to *MET* genetic alterations develops (eg, high-level *MET* gene amplification). In 2016, we reported in the *New England Journal of Medicine* a case in which resistance

to sequential treatment with crizotinib, ceritinib, and then lorlatinib developed. When the patient relapsed on lorlatinib, we identified a combination of 2 *ALK* resistance mutations that re-sensitized her cancer to crizotinib. She responded to crizotinib after lorlatinib and benefitted from 4 sequential ALK inhibitors—the first and last of them being crizotinib.

Recurrent *ALK* resistance mutations seem to develop in many patients, and their tumors remain dependent on ALK. These patients often derive benefit from 3 and sometimes 4 ALK inhibitors, especially when selection is tailored according to the underlying *ALK* resistance mutation.

H&O What else should oncologists consider when using ALK inhibitors?

AS Oncologists should be familiar with the different ALK inhibitors that are now available and understand how best to select among these therapies given the known efficacy and safety profiles of each drug. Oncologists should also recognize that patients with ALK-positive lung cancer can derive substantial benefit from ALK inhibitors that sometimes lasts for years.

As I mentioned earlier, brain metastases are very common in patients with ALK-positive NSCLC. Trials have shown that even at the time of diagnosis, between 30% to 40% of patients already have brain metastases (Figure). Thus, it's very important to be aware of drugs such as alectinib, brigatinib, and lorlatinib, all of which have potent CNS activity. Another important point is that with the increasing availability of CNS-penetrant targeted therapies, we can often defer or even avoid radiation treatments to the brain. These targeted therapies act very quickly, and patients with symptomatic CNS metastases often experience relief within a few days. If a patient has experienced relapse on crizotinib, including relapse in the CNS, the standard of care is to switch the patient to a second-generation, CNS-penetrant agent such as alectinib. Even when patients on alectinib relapse in the CNS, a significant proportion of them (~40%-50%) respond again to lorlatinib. If possible, we try to avoid whole-brain radiotherapy, especially early in the course of treatment, because whole-brain radiation can lead to progressive neurologic impairment over the years. Local approaches to radiation, such as stereotactic radiosurgery, are preferred over whole-brain radiation when radiation is required.

Disclosures

Dr Shaw has consulted for or received honoraria from Pfizer, Novartis, Ariad/Takeda, Roche/Genentech, Loxo Oncology, Blueprint Medicines, Ignyta, Foundation Medicine, EMD Serono, Daiichi-Sankyo, and Taiho Pharmaceutical.

Suggested Readings

ClinicalTrials.gov. A Study of TPX-0005 in Patients With Advanced Solid Tumors Harboring ALK, ROS1, or NTRK1-3 Rearrangements (TRIDENT-1). Identifier: NCT03093116. https://clinicaltrials.gov/ct2/show/NCT03093116. Accessed October 12, 2017.

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