Treating Anaplastic Lymphoma Kinase–Positive Lung Cancer in the Weeks After the US Food and Drug Administration Approval of Crizotinib

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On August 26, 2011 the US Food and Drug Administration (FDA) approved the anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor crizotinib (Pfizer; New York, NY) for the treatment of patients with advanced non–small-cell lung cancer (NSCLC) with translocations of the *ALK* gene as determined by an FDA-approved companion genetic test.¹ The approval was based on a high response rate in 255 patients with ALK-positive NSCLC treated with the drug as part of two early-phase trials.^{2–3} This is the first new FDA-approved drug for advanced NSCLC in the last 5 years, to our knowledge, and there is much enthusiasm about the approval among patients and practitioners.

As an oncologist specializing in the treatment of patients with lung cancer, I had suspected that crizotinib would be approved sometime in 2011. However, I also worried that there would be growing pains in prescribing this new (and expensive) drug for a small, genetically defined subpopulation. When a new drug is approved, the pharmaceutical company usually does not yet have mass production up and running and starts out with a limited supply produced for research purposes. For crizotinib the drug was initially made available only through three specialty mail-order pharmacies. In addition, insurance companies need time to develop policies for coverage of crizotinib in a molecularly defined (*ALK*-positive) patient population. As it turns out, all of my concerns would come to life in the form of three young men in just the first couple of weeks after the approval.

One Story of Frustration

The first patient was a 35-year-old male neversmoker who was referred in mid-August 2011 after his local oncologist discovered that his tumor was *ALK* positive. My institution had been participating in the phase II clinical trial of crizotinib in patients with *ALK*-positive NSCLC, and we had several patients on this trial—some referred from many hours away. This patient was quite symptomatic, with a cough and increasing shortness of breath, having rapidly progressed through first-line chemotherapy. In this setting, second-line chemotherapy has only a small chance of helping, and patients with *ALK*-positive disease tend not to respond to erlotinib, the only other approved second-line drug.⁴ Fortunately, we had an alternative.

There was an issue with his enrollment when his tumor tissue came back negative for the *ALK* translocation by the company's central laboratory. The trial was originally designed to only enroll patients who were confirmed to have *ALK*-positive disease by the central laboratory, which was using the com-

panion diagnostic test eventually submitted and approved by the FDA (Vysis *ALK* Break Apart Fluorescent In Situ Hybridization [FISH] Probe Kit; Abbott Molecular, Des Plaines, IL). However, there are several different ways to test for *ALK* positivity: immunohistochemistry (IHC), which detects expression of the fusion protein; reverse transcriptase polymerase chain reaction, which identifies the fusion gene transcript with high sensitivity; and break apart FISH, which visually detects the chromosomal translocation and is the technology used in the FDA-approved test.² This patient's *ALK* translocation was initially detected by reverse transcriptase polymerase chain reaction.

In 2010, the clinical trial, which allowed any previously treated patient with NSCLC with an *ALK* translocation to receive crizotinib, was amended to allow all patients who were determined to be *ALK*-positive by any of the above tests to enroll, even if they failed central laboratory confirmation. We had more than one patient who was enrolled on the basis of local testing, so we knew this process well and were preparing to submit our patient's outside test for approval when crizotinib's FDA approval was announced, and the trial was immediately closed to new enrollment.

In theory, it should have been simple at this point: write a prescription for crizotinib and order it from one of three approved specialty pharmacies. However, the approved indication was specific—crizotinib was only approved in patients found to have *ALK*-positive disease by the FDA-approved FISH assay, which our patient had failed. And we rapidly discovered that his insurance company (one of the top five largest insurers in the United States) had not prepared its frontline people to address claims for crizotinib at all. Our request disappeared into the ether without even the option of a direct peer-to-peer review, and one week of frustrating silence ensued while we waited for some response. We were eventually told that it would be up to 30 days for the claim to be reviewed, by which time the patient would likely have died. The published price of the drug without insurance coverage was \$9,600 per month so I could not ask the patient to pay for it out of pocket.

At this point, I appealed directly to Pfizer to see whether they could help, and they put my team in touch with the patient assistance program, which initiated contact with the insurer directly. Pfizer appears to have anticipated issues such as these and had a rapid response team in place; we heard back from the insurer quickly this time. They actually did have a policy that *ALK*-positivity required the FDA-approved companion test, but on appeal, they approved the coverage. In the end, it took

11 days, countless phone calls and emails, and more than a few extra gray hairs for the patient to receive his treatment. This is about 10 days too long for a seriously ill patient to wait, and I was hoping this would not be a harbinger of things to come.

Cooperation Saves the Day

The week before crizotinib's approval, I met a 24-year-old man, again a neversmoker, who had been diagnosed with metastatic adenocarcinoma of the lung. He is to date the youngest patient I have personally cared for with this disease. He was quite fit and otherwise healthy, and his only symptoms were a persistent dry cough and some fatigue. We discussed that his tumor would be tested for both epidermal growth factor receptor (*EGFR*) mutations and *ALK* translocations (both commonly found in neversmokers), but he did not want to wait for the testing, so I set him up to return the following week to initiate chemotherapy.

When he showed up for chemotherapy, though, he had taken a turn for the worse. He was having difficulty breathing and was admitted to the hospital. Within 24 hours, he had been admitted to the medical intensive care unit and, over the week-end, was intubated, suffered cardiac arrest resulting from a malignant pericardial effusion causing tamponade, had bilateral chest tubes placed for large malignant effusions, and suffered a large pulmonary embolus requiring anticoagulation. Only his youth and vigor allowed him to make it through the weekend alive, and by Monday, he was extubated but still critically ill. He was started on chemotherapy urgently by the weekend on-call oncologist, but in my experience, cytotoxic chemotherapy for NSCLC does not work quickly enough to make a difference in these situations. Our primary hope was that his tumor would come back positive for a molecular marker that would allow us to treat him with either erlotinib or crizotinib, both of which can cause rapid tumor responses in the presence of the target.

After alerting our molecular pathologist to the urgency of the matter, the break-apart FISH assay for *ALK* was done in 48 hours and was strongly positive for the translocation (Fig 1). The following day, a prescription was written for crizotinib, which was not yet available at the hospital pharmacy and had to be ordered from one of the three mail-order specialty pharmacies. It turned out that his insurance company's specialty pharmacy was not one of the three approved initially to carry the drug, and his insurance would not approve shipment from an outside pharmacy. Even if this could be overcome, the drug was listed by the patient's insurance as "not an approved alternative" despite the fact that there is no alternative for this drug, and a 20% copayment (\$1,900, which exceeded this young man's net worth) was required. Our intrepid financial specialist sat down with the patient's frantic mother and spent an entire Friday on the phone with the patient's insurance company, the specialty pharmacies, and again Pfizer's copay assistance program, which expedited the process a great deal. Before the specialist left work on Friday evening, however, well after the workday had ended, arrangements had been made to have the drug shipped to the medical intensive care unit by the following morning.

In addition, at about 11 that night, I received a call directly from the head of medical affairs at Pfizer, who had somehow

Figure 1. Break-apart fluorescent in situ hybridization assay of cells from the patient's tumor, with 80% of cells positive for the *ALK* translocation signal. The white arrow shows the fused, wild-type yellow signal; whereas the yellow arrow shows the red and green probes separated in the presence of the gene translocation.

gotten wind through the copay assistance program that a young man was in extremis and needed crizotinib urgently; he personally offered to remove any barriers to allow our patient to get the drug as soon as possible and without cost, including the possibility of using some of our research stock of crizotinib from the trial. Although, this did not turn out to be necessary, it was a welcome offer.

The following morning, the drug arrived on schedule, and the patient started on crizotinib. Within 48 hours, his pericardial and pleural drainage had decreased enough to remove the drains with no further intervention. By day 5, he was ready to leave the intensive care unit with palpably smaller lymphadenopathy. On day 12 of crizotinib, the patient walked out of the hospital on his own two feet, off all oxygen. Follow-up computed tomography scans showed a complete response to therapy.

The medical intensive care unit staff, consulting oncologist, pathologists, inpatient and outpatient nurses and midlevels, insurance company, Pfizer, and especially the financial specialist who took it as a personal mission to get this man the potentially life-saving drug, all came together in one week and literally saved this patient's life.

And the Third Time Is the Charm

In the second week of September, while I was still negotiating with the first patient's insurance company, I met with a 48-year-old man, again a neversmoker, who had noticed a lymph node above his left clavicle. He had imaging and a biopsy done, which revealed lung adenocarcinoma with metastases to the bone and adrenal glands. He was completely asymptomatic, and his local doctor had astutely tested him for both *EGFR* mutation (wild type) and *ALK* translocations (positive by FISH).

This was a situation I had thought about but hadn't really yet decided what to do—namely the previously untreated pa-

tient with *ALK*-positive NSCLC. The FDA label does not specify what line of treatment crizotinib should be used, and the phase I trial included patients ranging from previously untreated up to those treated with three or more previous lines with no measurable difference in efficacy.² However, there is a difference between knowing there is a high response rate and knowing whether crizotinib improves survival compared with (or is even equivalent to) standard first-line chemotherapy. This is being tested in an ongoing phase III trial, but for now, it is an unknown. There is experience from several trials comparing first-line anti-*EGFR* therapy in patients with *EGFR*-mutant disease showing at least equivalence to chemotherapy with regard to survival,⁵ but whether this can be extrapolated to the patients with *ALK*-positive disease remains to be seen.

In this case, I advised platinum-doublet chemotherapy and to reserve crizotinib for progression. However, the patient had done extensive research on the matter and wanted to try the crizotinib first; he was willing to accept the risk that it would be worse than chemotherapy. I prescribed the drug with a plan to do a quick restaging scan in a month so we could switch to chemotherapy if it was ineffective. Prepared for the worst, we submitted the prescription to his insurance company (which was a different company than that of the previous two patients) and found that it was immediately covered with a \$70-per-month copayment, and the drug was shipped to him the next day.

He had a nice partial response to crizotinib on his 4-week computed tomography scan; however, on his 12-week scan, there was unequivocal progression in the liver, and the patient started platinum-doublet chemotherapy.

Summary

We are entering an exciting time in the lung cancer world, with not just one but two effective targeted therapies for molecularly defined lung cancer. With luck, we are only scratching the surface of personalized treatments, as a recent presentation at the 2011 Annual Meeting of the American Society of Clinical Oncology pointed out that 55% of patients with adenocarcinoma of the lung have potentially targetable genetic lesions for which drugs are in development.⁶ However, as we enter this brave new world of molecularly defined therapies, it will be critical for hospitals, drug companies, and insurance companies to work out the interplay of molecular testing (whom to test, which test to use, and when to test) and coverage for expensive therapies that are effective but only in smaller, defined groups of patients.

Although break apart FISH is currently the only FDA-approved companion diagnostic test for *ALK*, data are being collected regarding other potential assays in the phase II crizotinib trial, which continues to accrue worldwide and allows local and/or alternative tests for *ALK* if central laboratory testing fails. In addition, studies directly comparing alternative tests such as IHC with FISH are ongoing,⁷⁻⁸ including at my own institution (unpublished observation). The outcomes of these comparisons and the clinical data from the phase II trial need to be collected and carefully evaluated, perhaps in an inde-

pendent registry. We need to be certain that FDA approval on the basis of proprietary tests does not exclude patients who might benefit from targeted drugs if other validated tests emerge that reliably identify the target population. It is certainly understandable to limit coverage for expensive drugs to those who would be likely to benefit, but in this case, the jury is still out on the best available test for *ALK* translocations, and access to the drug should not be based on only one test until this is worked out.

Although it is not practical for pharmaceutical companies to go into full production of their drug before obtaining approval, there are ways to ensure that what quantity of the drug that is available makes it to those who qualify during this interim period. A readily available supply of crizotinib existed outside the commercial supply—namely the research stockpile from the phase II and III trials at the individual study sites. In the second situation I described, I was offered the chance to tap our existing research supply; although by that time, we had already made arrangements to obtain a shipment of the commercial drug. One solution to this temporary bottleneck would be for pharmaceutical companies to establish a central call center to track all the existing research supply and have procedures in place to obtain it in the event that commercial drug is unavailable. In all likelihood, this would only be necessary for a small number of patients, but for those patients, the time saved could make all the difference.

Now that a few months have passed, it is likely that processes are either in development or in place to more efficiently evaluate who will and will not be covered for crizotinib, which tests will be considered appropriate and which will not, and how to best get the drug to the people who need it. I have prescribed crizotinib more than once since this brief flurry of activity, and there have been no issues with coverage. As more and more oncology drugs are approved, however, issues will continue to arise during this unique period immediately after the drug's approval but before its place has been established. When this happens, the onus will be on the pharmaceutical companies to consult with insurers well ahead of time to help them understand the complexity of the patient population and the companion diagnostic test in question so that they are able to define coverage for the testing and the drug and so that this period of uncertainty can be avoided.

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