

ALK, Lung Cancer, and Personalized Therapy: Portent of the Future?

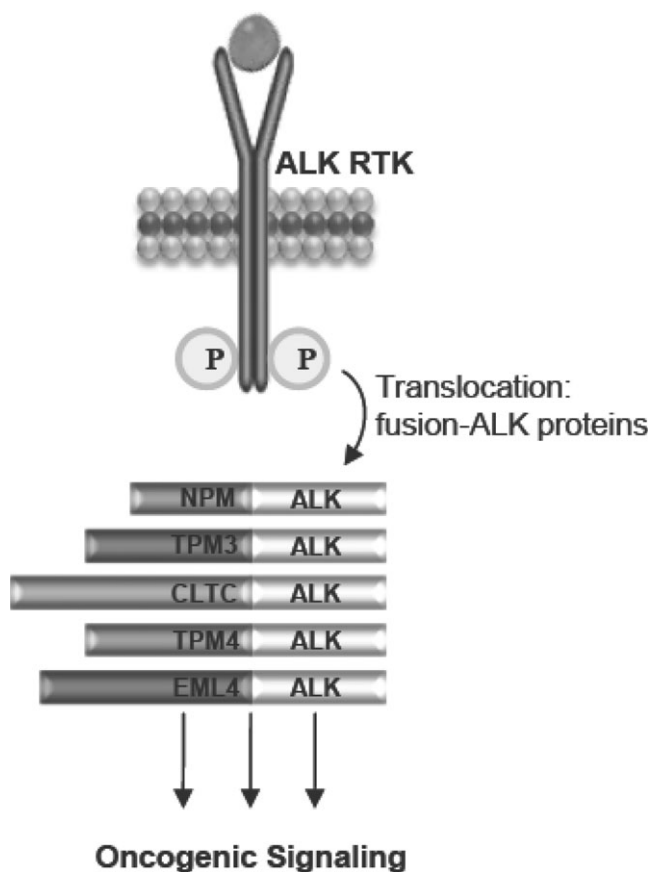
By Ken Garber

Despite much hope (and sometimes hype), personalized cancer therapy has progressed little since trastuzumab, the first genotype-specific molecular therapy, was approved for Her2-positive breast cancer in 1998. Most patients with a given cancer type and grade still receive the same treatment, regardless of genetic differences in their tumors.

After trastuzumab, genotype-based patient selection in trials was ignored as a strategy for common cancers. “Ten years go by, and then there aren’t any other examples of anybody actually doing that,” said Ross Camidge, M.D., Ph.D., a medical oncologist at the University of Colorado in Denver.

This situation is beginning to change. In 2007, AstraZeneca and KuDOS Pharmaceuticals launched breast cancer and ovarian cancer trials for the drug olaparib (a PARP inhibitor) only in patients with tumors bearing BRCA1 and BRCA2 mutations. And last year the biotech company Plexikon began a phase III trial of its BRAF inhibitor PLX4032 only in melanoma patients with BRAF gene mutations. Both drugs have shown notable activity in these genetically defined subpopulations. (See JNCI news, 2009;101:1230–2 and 2010;102:214–5.)

A third example now exists: anaplastic lymphoma kinase (ALK) inhibitors in lung cancer. In 2007, a group led by Hiroyuki Mano, M.D., Ph.D., at Jichi Medical University in Japan discovered a fusion gene, EML4-ALK, in a lung cancer patient and later in five others. The gene translocation activates ALK expres-



ALK fusions with various genes trigger a signaling cascade—and tumor growth in several cancers.

Courtesy Ariad Pharmaceutical

sion. First identified in 1994 as part of another translocation in anaplastic large-cell lymphoma, ALK is an oncogene that induces cell transformation in vitro and in vivo. About 12% of neuroblastomas, a rare pediatric cancer, exhibit ALK mutations.

Researchers now know that EML4-ALK is present in 3%–5% of North American non-small-cell lung cancer (NSCLC) patients, and two other ALK fusions in lung cancer have been reported. Among the 160,000 new cases of NSCLC each year in the U.S., at least 5,000 of them are ALK positive. Could ALK inhibitors work in these patients?

Rapid Translation

It didn’t take long to start investigating this question because an ALK inhibitor with good pharmaceutical properties already existed and was in the clinic. Pfizer’s crizotinib, an inhibitor of the Met oncogene, also has anti-ALK activity. A phase I trial in various cancers was under way when Mano reported his ALK fusions in lung cancer. Jeffrey Settleman, Ph.D., scientific director of the Massachusetts General Hospital Cancer Center in Boston, had been conducting cell line experiments with ALK inhibitors (among other kinase inhibitors) and found that lung cancer cell lines harboring ALK gene rearrangements were exquisitely sensitive to ALK inhibitors.

On the basis of the Settleman results and some of its own, Pfizer quickly opened the clinical trial to ALK-positive lung cancer patients. Camidge, who participated in the trial, reported that of 50 evaluable patients (all

ALK positive), 32 (64%) experienced an objective response by RECIST (response evaluation criteria in solid tumors) parameters, formalized rules for measuring tumor target lesions. Almost all patients in this heavily pretreated population experienced some tumor shrinkage, according to Camidge, who reported the results at the joint American Association for Cancer Research–International Association for the Study of Lung Cancer conference in January.

Median progression-free survival had not been reached, but crizotinib is not curative; patients eventually develop resistance and relapse. And although the result

is positive, the lack of a control group leaves open the possibility that later trials will not reproduce it.

But phase I vindicated the decision to select for ALK-positive patients. “It’s just another validation that the genotype or the genetic makeup of patients’ tumors has a high influence on the outcome,” said William Pao, M.D., Ph.D., assistant director of personalized medicine at the Vanderbilt–Ingram Cancer Center in Nashville. A phase III trial in ALK-positive patients is now under way.

Personal Problems

Lung cancer genotyping made sense even before the ALK fusion discovery. Mutations in the epidermal growth factor receptor (EGFR) and KRAS genes are much more common—about 10% and 25% of North American NSCLC patients, respectively—than ALK mutations. Most EGFR-positive patients respond dramatically to EGFR inhibitors like gefitinib and erlotinib, whereas KRAS-positive patients do not respond at all.

Yet EGFR and KRAS mutation testing of U.S. lung cancer patients at diagnosis isn’t yet standard practice in the community setting because of problems translating cancer genetics to routine practice. Most stage IV patients are diagnosed from a fine-needle biopsy, which allows identifying cancer cells but often doesn’t collect enough material even for histologic classification, much less mutation testing. Serial biopsies or a core biopsy are usually required. American Society for Clinical Oncology lung cancer guidelines do not mandate mutation testing, citing the need to balance the potential benefits of obtaining more tumor material against risk to the patient. So lung cancer patient tumors in the U.S. often do not get genotyped.

The U.S. Food and Drug Administration has also been slow to take action. In July 2009, the European Commission approved gefitinib for first-line treatment of NSCLC in patients with activating EGFR mutations, on the basis of two phase III trials showing markedly superior progression-free survival in these patients compared with chemotherapy. Other countries are

taking similar steps to require genotyping. “It’s only the U.S. that is behind,” said Pao.

Researchers are now solving the technical problems. Some academic centers are already routinely genotyping lung cancer patients at diagnosis for EGFR, KRAS, ALK, and other variants, using new assays that they hope the community will eventually adopt. Massachusetts General Hospital is now genotyping all lung and colorectal cancer tumors and plans to expand to all tumor types soon. Meanwhile, it has joined with 13 other institutions to form the Lung Cancer Mutation Consortium, which will genotype lung tumors free of charge. Using \$5.2 million in federal stimulus funds, the consortium will test for nine different mutations in 1,000 lung adenocarcinomas over the next 2 years, using a multiplex assay developed at Mass General, which has also developed an ALK translocation assay based on fluorescence in situ hybridization.

The mutation assay can test for 52 mutations from a small amount of DNA (fine-needle biopsy material is adequate), as well as common insertions and deletions. It tests standard formalin-fixed, paraffin-embedded tumor samples, even though formalin fragments DNA. “We actually have 1 year of experience with this, and I can say for sure this works,” said Dora Dias-Santagata, Ph.D., the Mass General pathologist who developed the assay. “And it doesn’t take more than your regular clinical lab already [has]: the expertise, the instrumentation.” To help other labs reproduce the assay, Dias-Santagata furnished the PCR “recipes” in an upcoming report in *EMBO Molecular Medicine*.

The consortium will genotype to guide treatment. ALK-positive patients will be offered enrollment in the phase III crizotinib trial (or a phase II trial designed for nonqualifiers). “There will also be a KRAS-specific study, an EGFR mutation-specific study, a PI3 kinase mutation-specific study,” said Camidge. “That’s going to roll out over the next few years.”

Overcoming Resistance

As Pfizer’s inadvertent ALK inhibitor moves through phase III, competition is emerging. New compounds may avoid or overcome the drug resistance that is causing Pfizer’s patients to eventually relapse. A compound from Ariad Pharmaceuticals, for example, has shown 10-fold greater potency and specificity for ALK in cell lines than the Pfizer compound. Potency should, in theory, overcome resistance because a single mutation is less likely to block the drug’s effects. “With a very potent compound, then it’s much harder for [ALK] to wriggle out of inhibition by mutating itself,” said Ariad chief scientific officer Tim Clackson, Ph.D., “as opposed to a rather modestly effective compound, where one mutation can blow away the benefit.”

Preclinical studies support this idea. In cell line experiments reported at the 2010 annual meeting of the American Association for Cancer Research, Ariad scientists identified six different ALK mutations that conferred resistance to crizotinib. In mouse models, crizotinib had no effect on these mutation-bearing xenografts, whereas the Ariad compound shrank the tumors.

Selected drugs targeting ALK

Drug	Company	Clinical stage
PF-2341066	Pfizer	Phase III and II for NSCLC; phase I/II in neuroblastoma and unspecified solid tumors; phase I in ALCL
GSK2141795	GlaxoSmithKline	Phase I, solid tumors or lymphomas
CEP-28122	Cephalon	Preclinical; IND expected 2010
AP-26113	Ariad Pharmaceuticals	Preclinical; IND expected 2011
Xcovery	X-276	Preclinical

ALCL: anaplastic large-cell lymphoma; IND, investigational new-drug application.

The biotech company Cephalon is also targeting ALK drug resistance. In preclinical models, its lead compound avoids multidrug resistance (the cell's ability to pump out the drug) that hinders crizotinib in these models, said Cephalon chief scientific officer Jeffrey Vaught, Ph.D. Cephalon used its compound in cell lines to identify a "gatekeeper mutation"—the same mutation in the active site of ALK that causes drug resistance in other kinases. The company's second-generation compound will

target such resistant tumor clones, if they exist in humans. Cephalon plans to test the first compound by early next year in lung cancer patients who can't tolerate crizotinib. Several other companies are also targeting ALK (*see sidebar*).

But whether ALK is the beginning or the end of a trend is not yet clear. Despite the EGFR, KRAS, and ALK success stories in lung cancer, widespread personalized therapy still seems a long way off. Mutation combinations for any given

tumor type vary widely by individual, and which are drivers and which are passengers is not always apparent. The Cancer Genome Atlas pilot project in 2008 sequenced 188 lung adenocarcinomas, revealing 26 cancer-related genes that were mutated at a statistically significant rate. But individual tumors had different sets of mutated genes, suggesting many small patient subsets, each with a different driver mutation presumably needing special treatment. And 13% of

tumors had no statistically significant mutations at all, leaving them a complete black box.

One ray of hope in this thicket of complexity comes from never-smoker lung cancer patients. According to composite data from various studies, research has identified 90% of the driver mutations in these patients, including ALK fusions (33% of patients) and EGFR mutations (40%), both of which occur much more often in nonsmokers than smokers. "We're going to understand never-smoking lung

cancer very, very soon, at least at the molecular level," said Pao.

But for the many patients bearing rare mutations, treatments may not arrive because the financial incentives are small. "I love the term[s] 'molecular medicine' and 'individualized medicine,' but the costs of [drug] development are staggering," said Cephalon's Vaught. "If this approach . . . can't be shown to be profitable, no one's going to do it." Whether ALK is just the first of many rare genes to be targeted, or is instead the last of the

low-hanging fruit, will say a lot about whether personalized cancer therapy becomes a reality for most people anytime soon.

Dr. Camidge is an investigator in the Pfizer-sponsored multicenter phase I and III crizotinib trials; Dr. Pao has done past consulting work with AstraZeneca, maker of gefitinib; and Dr. Dias-Santagata has submitted a patent application for her genotyping assay.

© Oxford University Press 2010. DOI: 10.1093/jnci/djq184