

Trial Offers Early Test Case for Personalized Medicine

By Ken Garber

Personalized medicine in cancer took a great leap forward a decade ago. In September 1998, the U.S. Food and Drug Administration (FDA) approved trastuzumab to treat metastatic breast cancer in patients whose tumors overexpressed the HER2 protein. Today, breast tumors are automatically screened for HER2 overexpression and treated accordingly, since only HER2-positive patients are likely to benefit from the drug. Trastuzumab was to have been the first in a series of designer drugs selected for patients on the basis of the molecular profile of their tumors—an entirely new way to attack cancer, instead of the traditional “one size fits all, hope for the best” approach.

But, despite much hype, personalized medicine in cancer has stalled since trastuzumab’s approval. A few other examples do exist: Mutations in the epidermal growth factor receptor (EGFR) predict one’s response to gefitinib in lung cancer, and colorectal cancer patients with mutations in the KRAS gene are resistant to cetuximab and panitumumab and should not receive those drugs (*see* JNCI 2008; 100:1667–9). These are helpful developments, but they came about by retrospectively analyzing clinical trial data for already approved drugs (gefitinib and cetuximab) or they predicted drug resistance only (cetuximab and panitumumab). The trastuzumab model is more revolutionary, informative and, in theory, faster: Conduct clinical trials only in a select population that is likely to respond to the drug, in order to include more responders, speed drug approval, and rescue an otherwise ineffective drug candidate for the subgroup that can benefit.

This model has not been successfully repeated. In fact, no prospective clinical trial has yet taken place that

selected only patients whose tumors contain somatic mutations that, based on preclinical models, predict drug response.

Such a trial, finally, is pending. Plexxikon, a biotech company in Berkeley, Calif., plans to give its anti-BRAF drug, PLX4032, only to melanoma and colorectal cancer patients with mutations in their tumors’ BRAF gene. David Solit, M.D., a researcher at the Memorial Sloan-Kettering Cancer Center in New York, calls the Plexxikon trial “a landmark event.” In theory, the trial could speed PLX4032’s journey to market, since the success rate should be higher if the drug is only given to patients likely to benefit.

Fateful Mutation

There are good reasons to think Plexxikon’s strategy could work. To begin with, BRAF, one of three RAF family members, is a key target in cancer. RAF is a downstream effector of the RAS oncogene, which is altered in about a quarter of all human cancers, leading to uncontrolled growth signaling. RAF, in turn, activates MAPK kinase (MEK), which activates MAPK, also known as ERK. The RAS-RAF-MEK-ERK pathway is one of the best understood signaling pathways in cancer, and drug companies have amassed a collection of compounds targeting it.

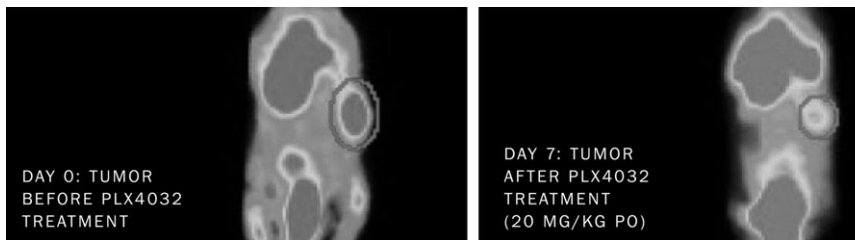
Patient selection seems to offer a clear path to success. In 2002, researchers at the Wellcome Trust Sanger Institute in Great Britain found that mutations in the BRAF gene were present in about two-thirds of

malignant melanomas. Smaller proportions of thyroid, colorectal, and lung tumors also bear the mutations. Plexxikon’s compound targets the most common BRAF mutation, known as V600E. “All our preclinical data suggests that... only tumors with the mutation are affected by the compound,” said Gideon Bollag, Ph.D., senior vice president for research at Plexxikon. Hence Plexxikon’s plans to select mutation-positive patients in the next phase of its ongoing phase I clinical trial.

Such a strategy might seem obvious, but it has been neglected so far by the pharmaceutical industry. In 2005, researchers led by Neal Rosen, M.D., Ph.D., at Memorial Sloan-Kettering Cancer Center reported in *Nature* that BRAF-mutant tumors were highly dependent on RAF signaling and extremely sensitive to MEK-inhibiting compounds. (Specific MEK inhibitors were much further along in development than selective RAF inhibitors.) The last sentence of the paper was a clear call to action: “We therefore propose clinical trials of MEK inhibitors in which patients are stratified based on BRAF mutational status.”

AstraZeneca and Pfizer, two companies with MEK inhibitors already in development, did not follow Rosen’s advice. Instead, they enrolled melanoma patients in clinical trials regardless of mutation status. “We know now that was a mistake,” said Judith Sebolt-Leopold, Ph.D., a former Pfizer scientist who led the company’s MEK inhibitor preclinical development efforts. She left Pfizer last year.

The AstraZeneca and Pfizer clinical results, Sebolt-Leopold said, help make the case for selection in the future. Once a maximum tolerated dose for the drugs is established from



PET scan of mouse tumor before and after treatment with BRAF inhibitor.

early trials, Sebolt-Leopold said, “I feel strongly that only BRAF-mutated tumors, and possibly N-RAS-mutated melanoma patients, should be entered into MEK inhibitor trials.”

Doomed To Fail?

The AstraZeneca and Pfizer trials, without selection, did not succeed. Overall survival for patients in phase II taking AstraZeneca’s MEK inhibitor, AZD6244, was no better than for those taking temozolomide, which is often used to treat metastatic melanoma. Pfizer has not published any phase II results but investigators did report ocular toxicity, and the company has apparently dropped the drug. The compound, PD-325901, has disappeared from Pfizer’s development pipeline on its website.

Patients with BRAF mutations did do better, as preclinical models predicted: In the AstraZeneca phase II trial, five of the six partial responders were mutation-positive, confirming that this group was the most likely to respond. But not enough patients responded: Only 12% of mutation-positive patients had a partial response to the MEK

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inhibitor, based on standard imaging response criteria. Once again, promising preclinical results had failed to translate to an improved benefit to patients.

Was failure inevitable? Solit pointed out that AZD6244 did no worse than standard of care. Had the trial enrolled only mutation-positive patients, the drug might have shown superiority. “We’ve never done a prospective study of just BRAF mutant patients in different tumor types, to see what the response rate would be first,” he said. Not only would such a trial have greater statistical power to detect a difference, Solit said, but it would be far more informative. “Get tumor tissue on those patients who respond and don’t, and try and figure out what’s different in their tumors,” he urged. “Are there second and

third hits in the tumors that don’t respond, which diminish dependence on RAF?” Such secondary mutations could be used to further stratify patients, or, Solit pointed out, to select combination therapy. “We’re not really doing it (now) in a logical way,” he said.

Astra-Zeneca defends its trial design. (Pfizer did not respond to phone and email queries.) The company “believes that there was no strong reason to exclude non-BRAF patients who might have shown benefit,” wrote Lynn Grant, Astra-Zeneca’s global PR director, in an email. Astra-Zeneca plans to test AZD6244 in combination with chemotherapy, although the company hasn’t decided which patient populations will be included.

Sebolt-Leopold sees combinations of targeted agents as the optimal future use of these drugs. In the meantime, she stressed, companies should select mutation-positive patients up front for clinical trials to increase the odds of response for everyone, as long as the preclinical models show a clear benefit, as they did for MEK inhibitors. And selection implies exclusion. “If I were the patient and knew that my genetics did not support all that we know about the pathway... I wouldn’t want to be on that trial,” she said. Despite the AstraZeneca and Pfizer results, Sebolt-Leopold is optimistic that newer MEK inhibitors can win FDA approval. “The trials just have to be done right,” she said. In her view, casting a broad net early on is reasonable for multi-targeted kinase inhibitors because responders are harder to predict, but not for highly selective MEK and BRAF inhibitors. There, selection will be crucial.

The Case Against Selection

Others disagree. Rich Buller, M.D., Ph.D., head of translational medicine for Exelixis, a biotech company in South San Francisco, Calif., argued against narrowly selecting patients in early clinical trials. “Our approach is to try to cast a fairly broad net initially,” Buller said. “If you just focus in on mutation-positive groups, you may miss a lot of other opportunities, and you may find that your agent only works some percentage of the time... You want to have the broadest potential group that could derive benefit.” Exelixis is testing a BRAF inhibitor in patients with

tumors likely to be dependent on activated RAS or RAF, especially melanoma and colon cancer, but is not restricting enrollment to mutation-positive patients. “We don’t limit enrollment prospectively,” said Dana Aftab, Ph.D., Exelixis’ vice president for translational research. “We look at the genotype of these patients retrospectively and annotate the data accordingly. And then based on the complete package of clinical data from that trial, we decide how we want to move forward.” If the results warrant a mutation-restricted pivotal trial, Aftab added, selection at that point is a possibility.

But selection should only happen late in the process, Buller and Aftab stressed. That’s because the diagnostic test used to select patients must prove itself along with the drug, and they say the FDA strongly encourages randomized trials that include both biomarker-positive and biomarker-negative patients before the agency will approve the test. “You can’t simply select on the basis of having a positive test,” said Buller. “Because the agencies want to prove that patients that test negative aren’t being deprived of a potential benefit.” The FDA confirmed this.

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“Although the FDA in the past has approved drugs that have been tested on mostly or only marker positive patients, CDRH [the FDA Center for Devices and Radiological Health] would suggest that a trial design that includes a bio-marker-negative population (where ethical) is a better choice,” wrote Alberto Gutierrez, Ph.D., deputy director of the FDA’s office of in vitro diagnostics, in response to a JNCI query.

There are also practical obstacles to genotyping patients in advance. For example, for every patient who qualified for the trastuzumab trials, Genentech needed to test four for HER2 expression—an enormous additional expense that drug companies are now hesitant to take on. Retrospective genotyping is much

cheaper, since only enrolled patients are tested. That's the strategy, for better or worse, that most companies have adopted.

It's a shortsighted policy, in Solit's view. Ultimately, he said, all patients will need their tumors genotyped up front, at the time of diagnosis, in order to select the right treatment or clinical trial for them. Colon and lung cancers will be first, he predicted, because mutations can already be used to predict response to EGFR inhibitors, and insurance companies already reimburse doctors who genotype these tumors. But no insurer will pay to sequence the DNA for other tumor types. "There's no reason for someone to pay me to do a BRAF test in melanoma right now," Solit said.

The only way to get the genetic information to validate DNA biomarkers in advance, he added, is to test everybody. "We're just

going to have to start genotyping every single patient who walks in the door for these things, not knowing what you're going to use that information for. Because BRAF-mutant colon cancer is a different disease than RAS-mutant colon cancer. And you need to start characterizing these patients as having a different disease, if you're ever going to be able to develop effective targeted therapy for these patients." Despite the large expense involved, Memorial Sloan-Kettering recently made the institutional commitment to begin such universal DNA testing, Solit said, beginning with lung cancer.

Getting Personal

It's a necessary first step, but only that. "To start moving combinations forward, we're really going to have to start genotyping and doing selective trials," said Solit. "It's been slower than you would have hoped."

The Plexikon BRAF inhibitor trial will set an important precedent. And MEK inhibitors, despite the Astra-Zeneca and Pfizer setbacks, are far from through. GlaxoSmithKline and AstraZeneca, among others, have new MEK inhibitors in the pipeline, in addition to the Exelixis/Genentech compound. Sebolt-Leopold expects at least some of these drugs to be tried prospectively in mutation-positive patient populations, given the preclinical evidence that they're only effective in these populations, and considering the ease of obtaining tumor samples from melanoma patients and the target specificity of the drugs. These factors make MEK inhibition an ideal test case for personalized medicine. "The world no longer needs a more potent MEK inhibitor," she said. "What's needed now is the right trial design to get one of them approved."

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