

“This trial is proof of concept that HER2 mutations can be targeted, which could offer patients another treatment option.”

Research conducted with the Cancer Genome Atlas project identified HER2 mutations in a variety of solid tumors, including breast cancer. That finding led researchers to launch a multicenter, multinational phase II basket trial in 2013 to study neratinib in patients with any type of metastatic solid tumor with a HER2 mutation. Interim results on 19 metastatic breast cancer patients presented at the 2015 San Antonio Breast Cancer Symposium by David Hyman, M.D., director of developmental therapeutics at Memorial Sloan Kettering Cancer Center in New York, showed that six (32%) had a response at 8 weeks.

The adaptive I-SPY 2 trial found that giving neratinib and standard chemotherapy before surgery (called neoadjuvant treatment) was beneficial for high-risk patients with hormone receptor-negative, HER2-positive breast cancer. Those tumors were not tested for a HER2 mutation, so whether HER2-mutated pa-

tients would benefit from neratinib as adjuvant or neoadjuvant treatment is unknown, said I-SPY 2 investigator John W. Park, M.D., professor of medicine at the University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center.

“I think the idea that a HER2 mutation may be driving some tumors in the absence of a HER2 amplification is a reasonable hypothesis,” Park said.

Other tumors categorized as HER2 negative may respond to neratinib. Anthony Kong, Ph.D., clinical senior lecturer at the School of Cancer Sciences at the University of Birmingham, UK, will soon investigate neratinib, lapatinib (Tykerb), trastuzumab (Herceptin), and pertuzumab (Perjeta) in a panel of breast cancer cell lines with various levels of HER2 expression.

“The interpretation of some of the tests used to classify a tumor as HER2 positive is partly subjective and is influenced by many factors,” Kong said.

Some breast tumors have extra HER2 proteins but do not have them at a level high enough to be classified as HER2 positive. More patients have these types of tumors, Kong said, than patients who have HER2 mutations.

“We want to study whether those breast cancer cells that have moderately

expressed HER2 but are not HER2 positive by the current criteria may respond to anti-HER2 treatments,” Kong said.

As tumor sequencing becomes more common, identifying patients with a HER2 mutation may become easier.

“In breast cancer there are other mutations that are becoming important,” Ma said. “Clinical sequencing includes multiple genes, so one test could screen for several potential targets, including the HER2 mutation.”

Kong said he agrees. “In the future, once more patients with HER2-mutated breast tumors are treated with neratinib, we will know which particular HER2 mutation to test for as well as whether there are other mutations that will predict sensitivity or resistance to this drug,” he said.

Ultimately, Ma said, the main goal is to be able to offer patients all the treatments that might work against their tumor.

“HER2-negative patients currently are not candidates for anti-HER2 agents,” Ma said. “This trial is proof of concept that HER2 mutations can be targeted, which could offer patients another treatment option.”

© Oxford University Press 2016.
DOI:10.1093/jnci/djw221

Tracking Tumor Resistance: The Early Promise of “Liquid” Cancer Tests

By Susan Jenks

A powerful technology that continues to evolve, researchers say, has rekindled interest in liquid biopsies as a way to disrupt tumor progression.

The technology, genetic sequencing, is allowing researchers a closer look at the genetic trail tumors leave in the blood as cancer develops. That capability, as these new “liquid” blood tests work their way into clinics, may further a deeper understanding of how tumors alter their molecular masks to defy treatment. And it may help identify changes that foreshadow early, more treatable, disease.

The tests scour the blood for DNA fragments and other genetic materials that tumors shed as they grow. Some tests measure intact circulating tumor cells; others, circulating DNA alone; and

still others look for exosomes, a grab bag of genetic debris that includes DNA, RNA, and metabolites.

Which approach, eventually, may best guide cancer treatment decisions in the future has yet to be determined—one of many unknowns that researchers face as commercial interest in liquid biopsies increases. The India-based consulting firm RNCOS estimates that the market will cross the \$1 billion mark by 2020. At least 30 companies are competing for a market foothold.

According to Richard Schilsky, M.D., senior vice president and chief medical officer of the American Society of Clinical Oncology (ASCO) in Alexandria, Va., such tests’ great promise is to monitor tumors over the long term as they change genetically to escape detection

and develop resistance. “No one is suggesting they should be used yet for early screening or as a diagnostic test. We’re not ready for that type of use,” he said.

Where liquid biopsies will probably carry initial patient benefit, Schilsky and others said, is as a backup or as a possible alternative to surgical tissue biopsies, the standard method doctors use to get information about tumors’ genetic makeup and how best to treat them. But biopsies can be painful, carry considerable cost, and may not be possible, depending on a tumor’s location or a patient’s health. So having a noninvasive and potentially cheaper way to track—and perhaps even diagnose—early cancers with a simple blood test someday has long held appeal.

“We need to know if one mutation found by liquid biopsy is representative of the tumor burden. And if you have one mutation, can you base your treatment on that one mutation?”

Prenatal Ties

Liquid biopsies began to gain traction in the cancer community about 2 years ago, although the technology is not new. Cell-free DNA technology—that is, measuring circulating DNA in the blood—grew out of prenatal testing for fetal abnormalities. Those tests, separating fetal from maternal DNA in the blood, unexpectedly detected several maternal cancers. That discovery led to liquid biopsies’ entry into the far larger cancer market today.

Among the many companies funding liquid biopsy development are industry giants such as Johnson and Johnson, Illumina, Qiagen, Foundation Medicine, and Roche. Roche won approval in June from the U.S. Food and Drug Administration for the first liquid biopsy test for patients with advanced non-small-cell lung cancer. The test picks up mutations in a mutated gene on the surface of cells, found in 10%–20% of lung cancer patients. Many of these patients often respond to the targeted drug, erlotinib (Tarceva), which tamps down the rapid cell division characteristic of all cancers.

Guardant Health, based in Redwood City, Calif., recently completed a study of its liquid biopsy assay, which measures 70 cancer-related mutations in the blood. Results of the study, the largest to date, were released at the annual ASCO meeting in Chicago this past June.

“What we intended to do is identify those mutations that can be treated,” said Philip Mack, Ph.D., director of molecular pharmacology at the University of California, Davis, Comprehensive Cancer Center. “Otherwise, there would be no impact on the clinical situation.”

Mack, a consultant for Guardant, presented the study’s findings. Overall, the genomic patterns identified by blood tests in 15,000 patients with some 50

tumor types closely matched those documented in tumor-profiling studies in the literature.

Also, in a cohort of nearly 400 patients, direct comparisons were made between circulating DNA in the bloodstream and tissue samples previously removed from the same cancer patients. If a mutation was detected in the blood it also was picked up in the tumor 94%–100% of the time. The assays also identified several treatment resistance–related mutations, which the investigators said the original tissue biopsy missed.

Fifteen percent of patients, however, had no detectable tumor DNA.

“You’re always going to miss something, but 15% is pretty good,” Mack said. What most people are concerned about is false positives, especially in early disease, when tumors shed far less DNA than their fast-growing, aggressive counterparts, he said.

Research Hurdles

But at this point, using biopsies as a diagnostic tool has several limitations. Researchers don’t yet know, for instance, which tumors shed the most DNA into the blood. Also uncertain is whether some tumors shed no detectable DNA at all.

“This is a most intriguing question,” said Sudhir Srivastava, Ph.D., M.P.H., chief of the cancer biomarker research group in the National Cancer Institute’s division of cancer prevention. The typical volume collected for routine bloodwork is 4 mL for adults. “To detect a single DNA mutation in the blood, you need 5–10 mL of blood,” he said, illustrating the technical challenges ahead, despite rapid advances in gene sequencing over the past decade.

Srivastava called for more comparison studies between tissue samples and liquid biopsies.

“We need to know if one mutation found by liquid biopsy is representative of the tumor burden,” he said. And, with tumors’ diversity, he added, “If you have one mutation, can you base your treatment on that one mutation?”

For now, Srivastava said he agrees that the most immediate use for these blood-based tests will be monitoring treatment, predicting recurrence, and tracking resistance.

But caveats remain. Sensitivity needs to improve. And “if we want to use these tests to find early mutations associated with drug resistance, it’s only useful if we can offer patients an alternative

therapy to stop exposure to harmful side effects,” ASCO’s Schilsky said.

Looking Ahead

According to Mack, investigators will meanwhile follow up on the early Guardant data to look for additional mutations that contribute to cancer’s rise. Multi-center clinical trials in patients with advanced cancers are planned, he said—to not only validate these new molecular findings but also intervene as resistance develops.

Of the three blood-based approaches to capturing cancer information, Mack said he feels measuring circulating tumor DNA remains the optimal way—and the one with the fastest turnaround time.

But even that approach, he conceded, may not be up to finding cancers anytime soon in a routine blood test in seemingly healthy people.

“Early-stage tumors are hard to detect,” Mack said. “And precancerous tumors might not show up at all with this technology.”



Sudhir Srivastava, Ph.D., M.P.H.
Photo credit:
National Cancer Institute

Whether a combination approach might work better remains to be seen. At least one company in England is exploring that possibility, believing side-by-side technologies may show more about tumor DNA content, said Leonard Lichtenfeld, M.D., deputy chief medical officer of the American Cancer Society in Atlanta. If successful, however, such tests must be refined enough to overcome concerns about detecting “something that may not turn into cancer, but lie dormant for many years,” he said.

“Our need is to identify which information we can detect has true clinical implications for the individual.”

Schilsky puts it another way: “If you have a test with infinite capacity to interpret mutations, what does that mean? The clinical community has to sort out its real value.”