Expanding the Net to Catch More Cancer

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December 16, 2019 By Liz Highleyman

What will it take to make pancancer therapies available for a wider group of people with cancer? According to Piro Lito, MD, PhD, of Memorial Sloan Kettering Cancer Center, a recipient of a Damon Runyon Cancer Research Foundation Clinical Investigator Award, two advances that would make a difference are discovering targets found in more cancers and more efficient genetic testing.

One promising target for site-agnostic therapy is KRAS, one of the most commonly altered genes in people with cancer. This gene makes a protein that is part of a signaling pathway that regulates cell growth. Gene mutations produce abnormal proteins that allow cancer cells to grow out of control.

“KRAS is a cancer-causing protein that is activated in nearly a third of cancer patients,” Lito says.

“Once activated, KRAS drives uncontrolled cell proliferation leading to tumor formation,” he explains. “There are several different mutated forms and their prevalence varies between cancer types. For example, KRAS G12C is the most frequent KRAS mutation in lung cancer (about 13% of patients), whereas KRAS G12D is most frequent in pancreatic cancer (over 95% of patients).”

Scientists have been trying to target KRAS for more than three decades without success—some have even declared it undruggable. But this is changing.

“KRAS is a small globular protein and doesn’t have the typical anchoring points used to design inhibitors targeting other common cancer drivers,” Lito says. “Recent work has led to the discovery of drugs that specifically inhibit KRAS G12C. These inhibitors are now in Phase I clinical trials, and early findings show that they are well tolerated and have potentially promising activity in lung cancer patients. These drugs do not target the normal, or unmutated, form of KRAS, so they are predicted to have low toxicity in patients.”

Researchers recently reported results from the first human clinical trial of the experimental KRAS G12C inhibitor AMG 510. Among 23 treated participants with advanced non-small-cell lung cancer (NSCLC) harboring this mutation, 11 experienced tumor shrinkage, 11 more had stable disease

and only one had disease progression. However, the treatment did not meet this high bar for colorectal cancer patients, among whom just one of 12 had partial remission and 10 had stable disease.

A second investigational drug targeting the same KRAS mutation, MRTX849, performed similarly. In another early study, three of six study participants with metastatic NSCLC but just one of four with advanced colorectal cancer saw partial tumor shrinkage. All of those without tumor regression had stable disease.

Researchers recently reported that a so-called pan-KRAS inhibitor, which blocks a switch that turns KRAS from an inactive to an active, cancer-causing state—and therefore works against multiple KRAS mutations—has entered its first clinical trial after promising laboratory and animal studies.

To take advantage of these new therapies, people must first learn whether their cancer harbors targetable mutations.

“Molecular testing of the cancer tissue is an essential part of treatment,” Lito says. “It can help identify driver alterations that are susceptible to targeted therapies and immunotherapy.”

And testing once is not enough.

“The genetic landscape of a patient’s tumor changes with time, particularly during treatment,” he continues. “As such, molecular testing ought to be repeated—for example, when a tumor progresses. This can help us understand if new actionable alterations have occurred.”

Fortunately, new blood testing technology known as liquid biopsy will make this easier.

“Advances in liquid biopsy now enable tracking of many genetic alterations during treatment,” Lito says. “In other words, common mutations, such as KRAS G12C, can even be detected in the bloodstream. This noninvasive approach requires only a simple blood draw and can be informative in monitoring response to therapy and early disease progression. However, if liquid biopsies are negative, this doesn’t necessarily mean disease is not present and more traditional testing is still required.”
