Many oncologists have long suspected that surgery may be redundant in some breast cancer patients who have a pathological complete response (pCR) to neoadjuvant systemic treatment. However, early attempts to avoid surgery in such patients were thwarted by high rates of locoregional recurrence, which were likely due to weakly effective agents and insufficient tools for accurately assessing treatment response. But now, armed with advances in early detection, systemic agents, and image-guided biopsy, researchers are revisiting whether surgery can be safely avoided in some breast cancer patients.

“We've come to a point where, because of all these improvements, we can consider eliminating surgery for invasive breast cancer in a select group of patients,” said Henry Kuerer, M.D., Ph.D., a professor in the Department of Breast Surgical Oncology at The University of Texas MD Anderson Cancer Center.

Dr. Kuerer is the principal investigator of a clinical trial to determine the feasibility of avoiding surgery in patients who have a pCR to systemic breast cancer treatment.

In a patient with triple-negative breast cancer, the tumor (circled) is clearly visible on mammography before neoadjuvant chemotherapy (left). After chemotherapy, mammography and image-guided needle biopsy showed no residual tumor (right). Images courtesy of Dr. Henry Kuerer.
therapy. “If this approach is proven to be safe, it could change the paradigm for the local treatment of breast cancer,” he said.

A new way of assessing response

Some HER2 (human epidermal growth factor receptor 2)–positive and triple-negative (i.e., negative for estrogen receptor, progesterone receptor, and HER2) breast cancers are particularly sensitive to systemic therapy. At least 50% of patients who have these types of tumors and receive neoadjuvant systemic therapy have a pCR, which is generally defined as the absence of invasive disease in the breast and axillary nodes.

“We’ve known for some time that patients with HER2-positive and triple-negative disease are the ones in whom systemic therapy is most likely to wipe out the cancer,” Dr. Kuerer explained. “Patients who have this kind of response are also likely to have long-term overall survival and are markedly less likely to have a recurrence.”

But these favorable outcomes leave a nagging question, Dr. Kuerer said. “If the patients don’t have any residual disease, why do they need surgery?”

The problem is that, until recently, pathological assessment of a surgical specimen was the only way to identify patients who had a pCR to systemic therapy. Physical examination of the breast and axilla to determine clinical response is notoriously inaccurate; and although breast imaging methods have improved substantially, they remain insufficiently sensitive or specific to confirm the absence of residual disease after systemic therapy.

Therefore, Dr. Kuerer and his colleagues turned to image-guided fine-needle biopsy, in which a needle is inserted through the breast into the tumor region under ultrasonography or mammography guidance and is rotated to collect a dozen or so samples from different sites. The researchers performed preoperative image-guided biopsies on 40 patients with triple-nega-

ative or HER2-positive breast cancer after neoadjuvant systemic therapy and compared the results with those from traditional examination of the patients’ surgical specimens.

“The bottom line in that study was that image-guided biopsy had an accuracy in identifying residual disease of about 98%,” Dr. Kuerer said. “And for the other 2%, there was just a tiny amount of residual disease that we felt radiation could easily eradicate.” The team published their findings last year in the Annals of Surgery.

Avoiding axillary surgery

Once they found that image-guided biopsy could accurately identify patients with a pCR in the breast, potentially sparing them from breast surgery, Dr. Kuerer and his colleagues wondered if they could go a step further.

“The question for us then became, if there’s no disease in the breast after chemotherapy, how often would we find cancer in the lymph nodes when we do the standard axillary surgery?” Dr. Kuerer said.

The idea of avoiding axillary surgery to assess lymph nodes for disease has been met with some skepticism. Axillary surgery is generally performed in tandem with surgery to remove the primary breast cancer; skip the surgery, the thinking goes, and disease in the lymph nodes could be missed.

To learn whether axillary surgery might sometimes be avoidable, Dr. Kuerer and his colleagues reviewed the records of 527 patients who received systemic therapy followed by surgery for HER2-positive or triple-negative breast cancer. None of the 116 patients whose initial ultrasonography examination revealed node-negative disease and whose breast tumors had a pCR to systemic therapy had residual disease in their lymph nodes after surgery. Of the 237 patients who did have lymph node disease at presentation and whose breast tumors had a pCR, about 90% had node-negative disease on final pathological examination.

The findings, Dr. Kuerer said, justify avoiding axillary surgery in some patients whose breast tumors have a pCR to systemic therapy. Whether the omission of surgery in both the affected breast and axilla is advisable in such patients is now being investigated in a clinical trial.

Clinical trial may pave the way

The trial (No. 2016-0046) is enrolling women 40 years or older who have a pathologically confirmed stage I or II HER2-positive or triple-negative breast tumor that is 5 cm or smaller and for whom initial ultrasonography reveals four or fewer abnormal axillary lymph nodes. The patients receive standard neoadjuvant systemic therapy as directed by their oncologists. After the neoadjuvant treatment, patients who have a pCR as assessed by image-guided biopsy forgo surgery and receive whole-breast radiation therapy; those whose biopsy shows evidence of disease undergo standard breast and nodal surgery before receiving radiation therapy.

During their neoadjuvant therapy, which typically lasts 5–6 months, patients are monitored with breast imaging, as is standard. For patients to be eligible for image-guided biopsy and a chance at skipping surgery, their breast lesion on final imaging must be 2 cm or smaller.

“We chose that size because when the abnormality shrinks down that much, we can get a really good sampling of the area with the needle biop-

[B]ecause of all these improvements, we can consider eliminating surgery for invasive breast cancer in a select group of patients.”

Dr. Henry Kuerer
sies, almost as good as with the surgery itself,” Dr. Kuerer said.

In addition, patients in whom initial ultrasonography reveals node-negative disease forgo axillary surgery. Those who have biopsy-proven disease in one to four axillary lymph nodes before systemic therapy will undergo targeted axillary dissection, in which the involved nodes are removed through very small incisions.

The trial is enrolling patients at MD Anderson and other centers, including MD Anderson’s partner institutions MD Anderson Cancer Center at Cooper in Camden, New Jersey, and Banner MD Anderson Cancer Center in Gilbert, Arizona. Thus far, seven patients have been enrolled; ultimately the trial will enroll 50. All patients will be followed up with breast imaging and physical examinations every 6 months for 5 years.

The trial may be among the first steps on a path to providing minimally invasive treatment options to more breast cancer patients.

“We’re constantly identifying new drugs and agents that are getting better and better at killing breast cancer,” Dr. Kuerer said. “So I can imagine that, very far on the horizon, surgery won’t be necessary for the vast majority of patients with breast cancers or other solid tumors.”

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For more information about clinical trials at MD Anderson, visit www.clinicaltrials.org.

IN BRIEF

Targeted Drug BLU-667 Shows Promise against Solid Tumors with RET Alterations

The kinase inhibitor BLU-667, which selectively targets the oncogenic driver RET (rearranged during transfection), is demonstrating promising clinical activity against solid tumors with RET gene alterations, according to the early results of a phase I trial.

RET alterations, which can be found in almost any cancer type, occur in most patients with medullary thyroid cancer (MTC) and are also frequently seen in patients with papillary thyroid cancer and non–small cell lung cancer (NSCLC). However, no drugs that specifically target RET are currently approved by the U.S. Food and Drug Administration.

“There is a critical unmet need for effective drugs against cancers that have the RET alteration,” said Vivek Subbiah, M.D., an assistant professor in the Department of Investigational Cancer Therapeutics at The University of Texas MD Anderson Cancer Center.

Dr. Subbiah is MD Anderson’s principal investigator of a multi-institutional clinical trial (No. 2016-1007) of BLU-667. The dose-escalation trial is currently enrolling patients who have any type of solid tumor with a RET alteration and patients who have MTC regardless of RET status. All patients must have unresectable tumors and advanced disease; patients with a targetable mutation in EGFR, ALK, or ROS1 are excluded from the trial.

Dr. Subbiah said that the trial’s early results are promising. Among 40 evaluable patients, all with RET-altered cancers, the objective (complete and partial) response rate was 45%. The overall response rates were 40% and 50% among patients with MTC and NSCLC, respectively. As of April 6, 2018, 41 of 51 enrolled patients continue to receive BLU-667.

Most adverse events were grade 1, including constipation, elevated aspartate or alanine aminotransferase levels, diarrhea, and fatigue. However, three patients experienced grade 3 adverse events: elevated alanine aminotransferase, hypertension, and tumor lysis syndrome. Tumor reductions were seen in 83% of evaluable patients treated with doses of at least 60 mg/day.

In April 2018, Dr. Subbiah, Mimi Hu, M.D., an associate professor in the Department of Endocrine Neoplasia and Hormonal Disorders, and other colleagues published their preclinical and early clinical data on BLU-667 in Cancer Discovery (doi: 10.1158/2159-8290.CD-18-0338) and presented the trial’s early results at the American Association for Cancer Research Annual Meeting (presentation No. CT043).
Increasing evidence has shown that diet, obesity, and the gut microbiome (the resident microbial community) influence colorectal cancer risk. Reducing the risk of developing recurrent or new cancers is a heightened concern for colorectal cancer survivors, but studies of diet and the microbiome have not focused on this specific population. To inform recommendations for colorectal cancer survivors, an innovative clinical trial is focusing on a diet modification—the addition of navy beans—and its effect on the gut microbiome.

“We and others have shown that poor diet, obesity, and associated inflammatory and metabolic conditions significantly contribute to disease recurrence and mortality in colorectal cancer survivors,” said Carrie Daniel-MacDougall, Ph.D., an assistant professor in the Department of Epidemiology at The University of Texas MD Anderson Cancer Center. Dr. Daniel-MacDougall is the principal investigator of a clinical trial in which beans are added to the diet of overweight or obese colorectal cancer survivors in hopes of enhancing their gut microbiomes and improving their metabolic health to lower their risk of cancer and other obesity-related conditions.

**Strong research base**

Beans were chosen for the intervention because decades of published research suggest they can reduce colorectal cancer risk. In the early 1990s, the National Cancer Institute’s Polyp Prevention Trial found that participants in the highest quartile of dry bean consumption had a reduced risk of adenoma recurrence. Laboratory investigations in ensuing years showed that beans prevented colorectal carcinogenesis in obese mice by inhibiting inflammatory mechanisms.

“Beans are high in protein and fiber. Fiber is integral to fostering a commensal, or protective, microbiome, which is important for cancer risk,” Dr. Daniel-MacDougall said. “Beans also have high levels of antioxidants and phytochemicals. They’re a natural prebiotic. And they’ve been established in cardiovascular research to improve cholesterol panels.”

**Clinical trial**

Dr. Daniel-MacDougall chose navy beans for her clinical trial because they are low in the compounds that cause...
Several types of cancer can result from gene fusions involving the NTRK1, NTRK2, or NTRK3 genes. Tumors with NTRK fusions seldom have other driver mutations, limiting the effectiveness of most targeted agents. But recent years have seen the emergence of novel agents targeting TRK (tropomyosin receptor kinase) proteins, and clinical trials of two oral TRK inhibitors are now under way at The University of Texas MD Anderson Cancer Center.

“NTRK fusion is a unique genomic alteration that can occur in almost any type of solid tumor,” said David Hong, M.D., a professor in the Department of Investigational Cancer Therapeutics. “But in general, patients with NTRK fusions tend to be younger and have gas; they do not have a strong taste or color, so they can be incorporated easily with other foods; and most people do not eat them frequently, so it will be easier to see the specific effect of adding them to the diet. The pilot phase of the Beans to Enrich the Gut Microbiome vs. Obesity’s Negative Effects Trial (BE GONE, No. 2016-0365) enrolled 20 patients with adenomatous polyps. Analysis of the results is under way.

Now the trial’s second phase has begun enrolling overweight or obese adults with a history of colorectal cancer who have completed active treatment and have normalized bowel habits. Participants cannot have undergone resections of certain portions of the colon or have dietary restrictions that would preclude consumption of beans.

The trial uses a crossover design in which each participant serves as his or her own control. During the 8-week control period, participants eat their regular diet. During the 8-week intervention period, navy beans are added to the regular diet (beginning gradually and working up to 1 cup a day). A registered dietician and the Division of Cancer Prevention and Population Sciences’ Bionutrition Research Core provide support.

During the study period, participants have blood drawn five times and provide seven stool samples. The primary outcomes to be assessed are intra- and inter-individual changes in stool 16S rRNA profiles and blood metabolites. The relationship between changes in the gut microbiome and changes in host biomarkers—including established fecal surrogates of gut inflammation and integrity, circulating adipocytokines, and a comprehensive blood lipid and metabolic panel—will also be studied. In addition, the study team will assess the effect of participants’ baseline diet and microbiome on their biological response to the bean intervention.

“People want to know: ‘What’s the one thing I can eat to improve my microbiome?’ or ‘What’s the one thing I can eat to lower my cancer risk?’” Dr. Daniel-MacDougall said. “If our research confirms an impact, it’d be easy to say, ‘Just eat more beans.’”

TRK Inhibition Shows Activity in Solid Tumors

Early results of clinical trials for adult, pediatric patients with NTRK gene fusions show promise

By Bryan Tutt

A mammary analogue secretory carcinoma of the salivary gland (arrows) that progressed during standard chemotherapy is shown before treatment (left) with the TRK inhibitor larotrectinib in a clinical trial. The patient experienced a partial response, and the tumor had shrunk considerably after two cycles of larotrectinib (right). Images courtesy of Dr. David Hong (presented at the 2016 American Association for Cancer Research Annual Meeting).
TRK Inhibition Shows Activity in Solid Tumors

[Continued from page 5]

no known cancer risk factors or other driver mutations.”

The largest subclass of tumors that tend to have these fusions is sarcomas, especially gastrointestinal stromal tumors. And although NTRK fusion is found in only a small subset of many cancers—including glioblastoma and pancreatic and lung cancers—the aberration occurs in almost all cases of certain rare cancers, such as mammary analogue secretory carcinoma and infantile fibrosarcoma. NTRK fusion is also seen in 70% of a rare subset of colorectal tumors with high levels of microsatellite instability, which is a predisposition to mutation.

Dr. Hong is MD Anderson’s principal investigator of three multi-institutional clinical trials of TRK inhibitors—two of larotrectinib and one of LOXO-195—that are currently enrolling adult and pediatric patients who have solid tumors with NTRK fusions.

Larotrectinib

A phase I trial (No. 2014-1056) of larotrectinib is enrolling adult patients who have locally advanced or metastatic solid tumors with NTRK fusions (see “Experimental Drug LOXO-101 Shrinks Tumors With NTRK Fusions,” OncoLog, July 2016). The trial’s dose-escalation phase established that a dose of 100 mg was well tolerated, and this dose is used in the trial’s ongoing expansion phase and also in a phase II trial (No. 2015-0728) of the drug. The phase II trial is enrolling patients 12 years and older who have locally advanced or metastatic solid tumors with NTRK fusions.

An early analysis of patients treated in these two trials and a non–MD Anderson phase I/II pediatric trial of larotrectinib looked at the outcomes of 55 patients with fibrosarcoma, soft tissue sarcoma, melanoma, and cancers of the thyroid, colon, lung, and other organs. At a median follow-up of 9.4 months, the total response rate was 80%: 16% of patients experienced a complete response, and 64% experienced a partial response. An additional 9% of patients had stable disease, and 11% experienced disease progression. Responses were determined according to the Response Evaluation Criteria In Solid Tumors.

Among the 55 patients studied, the only grade 3 treatment-related adverse events were elevated aspartate transaminase and alanine transaminase levels, dizziness, nausea, anemia, and decreased neutrophil count. No treatment-related adverse events led to larotrectinib dose reductions. Dr. Hong and colleagues reported the study’s results in the February 2018 issue of the New England Journal of Medicine.

“In this series of studies, larotrectinib has demonstrated rapid, potent, and durable antitumor activity in children and adults who had solid tumors with NTRK fusions.”

– Dr. David Hong

and whose disease did not respond to or progressed during treatment with larotrectinib or entrectinib, a similar experimental TRK inhibitor.

The trial is currently in its dose-escalation phase, the goals of which are to determine the maximum tolerated dose and the recommended dose for the expansion phase. The goals of the expansion phase are to determine patients’ best overall response and the incidence and severity of adverse effects.

The promise of TRK inhibition

No TRK inhibitors are currently approved by the U.S. Food and Drug Administration (FDA). However, the early results of the larotrectinib trials are so promising that the FDA granted the drug breakthrough therapy, rare pediatric disease, and orphan drug designations for the treatment of unresectable or metastatic solid tumors with NTRK fusions.

“If I were a community oncologist and had a patient who doesn’t respond to standard therapy and who has no typical risk factors—such as a young patient with papillary thyroid cancer or a lung cancer patient who’s a non-smoker—I would consider next-generation sequencing to see if there’s an NTRK fusion,” Dr. Hong said. “Efficacious drugs that target such tumors are available in clinical trials.”

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FURTHER READING


To learn more about clinical trials at MD Anderson, visit www.clinicaltrials.org and search by physician, cancer type, or treatment.
Preparing for Natural Disasters
People with cancer or other chronic illnesses should take extra precautions

No matter where you live, you could be affected by a natural disaster. Whether your region is prone to hurricanes, tornadoes, earthquakes, blizzards, or wildfires, preparing for a disaster can help keep you and your family safe. But if you are living with cancer or another chronic illness, you need to take extra precautions.

Everyone, whether chronically ill or not, should have a disaster preparedness plan. Some aspects of the plan—such as a 3-day supply of drinking water and nonperishable food—will be the same for anyone. Preparation guidelines are available from the Centers for Disease Control and Prevention (CDC) at https://bit.ly/2pOyyYY and the Department of Homeland Security at www.ready.gov/build-a-kit. However, other precautions will depend on the type of disasters that are likely to affect your region (the American Red Cross lists some of these at https://rdcrss.org/2f0qNuB). Likewise, there are some general precautions that all people with chronic illnesses should take and others that vary according to the type of illness you have and its treatment.

“People should assess their surroundings and their health and think about what challenges they might run into,” said Matthew Berkheiser, Dr.P.H., chief safety officer and associate vice president for Environmental Health and Safety at The University of Texas MD Anderson Cancer Center.

General precautions

“Anyone who takes prescription medications should have 3–5 days’ worth of their medications on hand,” Dr. Berkheiser said.

In addition, it’s a good idea to keep a list of your medications, including the doses, in your phone or wallet, as the list could be useful if you have to evacuate your home and need prescription refills before you can return.

If you have a chronic illness, you should also keep the phone number for your doctor or hospital on hand. If your doctor or hospital has an online patient portal, such as MD Anderson’s MyChart, you might want to keep the portal’s Web address and your login information with you so that you can access your records if you need to.

Individualized precautions

If you have cancer or another serious illness and are receiving outpatient treatment such as chemotherapy, radiation therapy, or another treatment requiring special equipment (such as dialysis), you should discuss disaster preparedness with your care team.

“Patients need to know how long they can go between treatments and be okay,” Dr. Berkheiser said. “That’s a conversation they need to have with their physician.”

During Hurricane Harvey, for example, some MD Anderson patients may not have come in for treatment because of flooding near their homes. In addition, Houston’s mass transit system was affected by the storm, limiting service to some areas for several days.

“Patients should understand that travel limitations may occur during a disaster,” Dr. Berkheiser said. “In case they can’t make it to the hospital where they get treated, they should find out if there’s a local doctor or hospital that can provide the same treatment.”

For example, dialysis for people with kidney failure is widely available, whereas an experimental cancer treatment in a clinical trial might be available in only one center or a few centers.

Another important travel consideration is how to evacuate your home. If you have mobility issues, you can register in advance with your state or local agency for evacuation assistance. People in the United States and parts of Canada can register for such assistance and get other disaster preparedness and emergency information by calling 211 or visiting www.211.org.

Specific disaster preparation guidelines for various chronic illnesses are available from the CDC at www.cdc.gov/disasters/chronic.html. For cancer patients in particular, the National Cancer Institute offers tips for disaster preparation at https://bit.ly/2wHR6jE. Combining this information with advice from your care team and general preparedness tips for the types of disasters that can affect your area can help you ensure that a natural disaster doesn’t cause a setback in your care.

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IN BRIEF

Premalignant Colorectal Polyps Show Immune Activation in Lynch Syndrome Patients

Colorectal polyps from patients with Lynch syndrome, a hereditary condition that increases colorectal cancer risk, display immune system activation well before cancer development, according to preclinical research from The University of Texas MD Anderson Cancer Center. This finding challenges traditional models of cancer immune activation and suggests that immunotherapy may be useful for colorectal cancer prevention in such patients.

Lynch syndrome, the most common hereditary colorectal cancer syndrome, is caused by inherited mutations in DNA mismatch repair (MMR) genes. Colorectal cancers with MMR deficiencies accumulate large numbers of mutant proteins called neoantigens, which are believed to stimulate an immune response. And such cancers can be successfully treated with immune checkpoint inhibitors. However, not much was known about immune activation in premalignant colorectal polyps in patients with Lynch syndrome.

Therefore, researchers led by Eduardo Vilar-Sanchez, M.D., Ph.D., an assistant professor in the Departments of Clinical Cancer Prevention and Gastrointestinal Medical Oncology, analyzed gene expression to characterize the immune profile in 11 premalignant polyps and three early-stage tumors from 14 patients with Lynch syndrome. As a control, the researchers analyzed 17 premalignant polyps from patients with familial adenomatous polyposis (FAP), a hereditary colorectal cancer syndrome that does not exhibit MMR deficiencies.

The resulting profiles revealed significantly higher expression of several markers for immune activation—including CD4-positive T cells, proinflammatory molecules, and checkpoint proteins such as PD-L1 and LAG3—in Lynch syndrome polyps than in FAP polyps. However, contrary to traditional models of immune activation, the immune profiles in the Lynch syndrome polyps were independent of the rate of mutations or neoantigens.

“Our findings don’t follow the standard model. The majority of premalignant lesions do not have an excessive increase in mutations or neoantigens,” Dr. Vilar-Sanchez said. “However, there is already immune activation, meaning the activation precedes the development of the mutations.”

In April 2018, Dr. Vilar-Sanchez and colleagues published the study’s report online in JAMA Oncology (doi: 10.1001/jamaoncol.2018.1482), and graduate research assistant Kyle Chang presented the findings at the American Association for Cancer Research Annual Meeting (session No. PO.PR01.02).

The researchers hope to initiate clinical studies of immunotherapy to prevent colorectal cancer in high-risk populations such as patients with Lynch syndrome.