IPI-145 Shows Promise in CLL Patients

Results of a phase I study of Infinity Pharmaceuticals’ IPI-145, which inhibits both the δ and γ isoforms of phosphoinositide3-kinase (PI3K), suggest the drug is safe and effective in patients with advanced chronic lymphocytic leukemia (CLL).

In a trial among 155 blood cancer patients, 52 patients had relapsed refractory CLL. Evaluable patients in this group showed a 47% overall response to the drug, with 1 showing a complete response and 21 a partial response; 24 had stable disease and 1 was progressing. High-risk patients with mutations in the TP53 tumor suppressor gene, or loss of gene function caused by 17p deletions, also showed response rates of approximately 50%.

In addition, the study found that in 89% of patients, enlarged lymph nodes shrank by 50% or more. “Almost everyone is responding with reduction in adenopathy and about half are achieving true IWCLL [International Workshop on Chronic Lymphocytic Leukemia] responses,” says Ian Flinn, MD, PhD, director of the Blood Cancer Research Institute in Nashville, TN. Flinn presented the trial results at the annual meeting of the American Society for Hematology on December 9 in New Orleans, LA.

Lymph node shrinkage can lead to a temporary increase in lymphocytes, a sign of disease progression in other settings, but an expected reaction to all drugs in this setting. That’s why the IWCLL set criteria for CLL remission based on nodal responses and lymphocyte count. “Some of the patients in this study who are showing a nodal response may ultimately convert to remission as defined by the accepted criteria,” says Flinn, who observed similar delayed responses 5 years ago in early trials of the PI3K-δ inhibitor idelalisib (GS-1101; Gilead Sciences).

“IPI-145 have been exciting,” Flinn says. “There’s a great need for these new therapies for both relapsing and newly diagnosed CLL patients to move us away from current cytotoxic chemotherapy approaches.”

A phase III trial is planned to compare IPI-145 to the CD20 monoclonal antibody ofatumumab (Arzerra; Glaxo-SmithKline and Genmab) in patients with relapsed CLL who are not good candidates for aggressive chemotherapy. IPI-145 is being tested against multiple hematologic malignancies and has also shown encouraging results in low-grade lymphoma.

China Plans Large Center for PDX Models

The Chinese Academy of Sciences’ Shanghai Institute of Materia Medica (SIMM) will collaborate with oncology service provider Crown Biosciences on what is expected to be the world’s largest “mouse clinical trial center,” generating a collection of thousands of patient-derived xenograft (PDX) models that will aid cancer drug discovery and development.

The center will support both mouse and combined mouse/human studies on liver, non–small cell lung, gastric, colorectal, and other cancers prevalent in Asia. Initially, it will support about 700 PDX models developed by Crown, a leading supplier of such models to pharmaceutical and biotech firms, and about 100 PDX models created by Shanghai-based SIMM, China’s leading governmental drug discovery and development organization. The partners expect to build their resource within 5 years to about 4,000 models, notes Henry Li, PhD, vice president for translational oncology at Crown in Santa Clara, CA.
be damaged by treatment, leaving normal tissue can gets overlooked: Normal tissue can of T-cell Therapy prostate, may still prove difficult. other types of cancer, such as breast and cancers, “has become quite an industrial- Production of PDXs for some types of companies adopt the approach. Scaleability is very important, and maintaining and annotating the PDX models is a huge investment,” Li notes. Production of PDxs for some types of cancer, including colon and pancreatic cancers, “has become quite an industrialized process,” with the ability to convert patient tissue samples to PDX models at a rate of up to 100% with very good quality, he adds. However, he points out that engineering models of certain other types of cancer, such as breast and prostate, may still prove difficult. Partially funded by a Chinese central government grant, the center will support translational oncology projects both for SIMM’s drug development pipeline and for other organizations around the world.

Fine-tuning the Effects of T-cell Therapy

In all the excitement around T-cell therapies for cancer, one aspect often gets overlooked: Normal tissue can be damaged by treatment, leaving patients sicker than they were before. In a proof-of-principle study published in December in Science Translational Medicine, researchers at Memorial Sloan-Kettering Cancer Center in New York, NY, propose a solution (Sci Transl Med 2013;5:215ra172). They have engineered molecules called inhibitory chimeric antigen receptors (iCAR) that can protect normal tissue from the off-target effects of T-cell therapy. The T-cell therapies do exactly what they’re designed to do—attack tumor cells that express specific antigens on their surface. Unfortunately, there are very few antigens on cancer cells that aren’t also on the surface of normal cells, so T-cell therapies attack them, too.

To stop that attack, the Sloan-Kettering team designed the iCARs to turn off if they encounter a second antigen found on healthy cells that’s downregulated or absent on tumor cells. To do this, they combined an antigen-recognition domain with signaling domains of CTLA-4 and PD-1. In this context, the checkpoint blockades downstream of these proteins are used for their natural purpose: to ensure that the immune system doesn’t overreact to threats. Because the checkpoint blockades respond only to an antigen found on normal tissue but not on the tumor, the iCARs can be turned on again if they meet a tumor cell.

“What’s very exciting about the concept is that it’s reversible, mimicking what the normal immune system does, but we’ve twisted it to make it selectively protective for what we want to protect,” says molecular pharmacologist Michel Sadelain, MD, PhD, who led the work. “I think it’s a wonderful idea,” says Stanley Riddell, MD, an immunologist at the Fred Hutchinson Cancer Research Center in Seattle, WA, who praised the Sloan-Kettering team for experimentally evaluating what others have only talked about. “And I think this does demonstrate in principle that this could work.”

The real challenge will come when the iCARs are tested in the clinic, where T cells will need to be carefully engineered to express both a chimeric antigen receptor and an iCAR in a way that maximizes antitumor activity and minimizes off-target killing. However, current mouse models are not really rigorous enough to adequately test the iCARs, notes Riddell, who is working to improve these models. “The reason this paper is important is that it provides a new avenue to investigate,” Riddell explains. “As we proceed in identifying new receptors, we can think about how we can combine signaling modules to tune the response to be more selective against the tumor and less against normal tissues.”

pCR Proves Valid Surrogate Endpoint

New results from the randomized, phase III NeoAdjuvant Lapatinib and/or Trastuzumab Treatment Optimization (NeoALTTO) trial support the idea that pathologic complete response (pCR) is a valid surrogate endpoint for the effectiveness of long-term neoadjuvant treatment of breast cancer. The findings were presented at the 2013 San Antonio Breast Cancer Symposium in Texas on December 11.

Two years ago, NeoALTTO researchers reported that women with HER2-positive breast cancer who took the combination of lapatinib (Tykerb; GlaxoSmithKline) and trastuzumab (Herceptin; Genentech) were twice as likely to experience pCR as those who took either drug alone. However, it was unclear whether that benefit translated into event-free survival or overall survival (OS). According to Martine Piccart-Gebhart, MD, PhD, chair of the Breast International Group in Brussels, Belgium, who presented the results, after a median follow-up of about 4 years, OS was 65% higher—and event-free survival 62% higher—among women who achieved a pCR at the time of surgery compared with women who did not have a pCR. In addition, patients with hormone receptor–negative breast cancer were more likely to achieve a pCR than those with hormone receptor–positive disease. “Our new analysis shows that the improved pCR rates seen in the hormone receptor–negative/HER2-positive subgroup seem to translate into better long-term outcomes for patients,” said Piccart-Gebhart.

In addition, the trial indicates that for patients with hormone receptor–negative/HER2-positive breast cancer, “we could potentially use the neoadjuvant model to speed up approval of new agents,” said Piccart-Gebhart. “That’s encouraging because we know that adjuvant trials in breast cancer take forever. They are very time- and money-consuming, and require thousands of patients, so that would be really good news.” Jennifer Litton, MD, an associate professor in the department of breast medical oncology at The University of
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