the early 2000s. “I wanted to hijack the cell’s own quality-control machinery that normally turns over proteins to degrade disease-causing rogue proteins that we want eliminated,” he explains.

To do this, his lab developed dumbbell-shaped PROTACs: One end of the molecule binds to a target protein and the other binds to an E3 ubiquitin ligase. The ligase tags the target protein with ubiquitin, signaling to the cell’s proteasomes that the protein should be destroyed.

“We’re dragging proteins to these E3 ligases that normally wouldn’t be recognized by them, saying ‘I want this one tagged because I know this one is causing a problem,’” Crews says, adding that, unlike an inhibitor that must stay bound to a protein to work, a PROTAC needs only to temporarily bridge the target protein and E3 ligase. “It’s constantly recruiting these disease-causing proteins to the E3 ligase for tagging, and so there is a multiple turnover catalytic quality to this,” Crews explains. “Just a little bit of drug can get in there and wipe out all the preexisting population of this disease-causing protein.”

Thomas Kodadek, PhD, of Scripps Research Institute in Jupiter, Florida, who is not involved in Arvinas, predicts that “PROTACs are likely to make vastly improved versions of some existing [cancer] drugs. But where they could really change things fundamentally is in the future where people are trying to drug some of these so-called undruggable targets.”

To advance their work, Arvinas signed deals of upward of $400 million each with Merck and Genentech in 2015, and expanded the Genentech deal late last year. In its most recent deal, Arvinas will develop PROTACs for new protein targets identified by Pfizer that the pharmaceutical company will move through clinical trials.

Arvinas’s internally developed estrogen-receptor PROTAC for breast cancer and androgen-receptor PROTAC for prostate cancer are also progressing. In 2017, the company selected its first clinical trial candidates for each disease. Arvinas presented preclinical results at the 2017 San Antonio Breast Cancer Symposium demonstrating the ability of its PROTAC to degrade estrogen receptor and inhibit tumor growth. Similarly, they showed compelling evidence of effectiveness for the androgen-receptor PROTAC at the 2018 Genitourinary Cancers Symposium, held February 8–10 in San Francisco, CA.

John Houston, PhD, president and CEO of Arvinas, says he expects that clinical trials for the androgen-receptor PROTAC will begin before the end of this year, and for the estrogen-receptor PROTAC in 2019. “There are a number of big pharma companies that are moving into this space and looking at protein degradation, and even smaller companies that have started up behind us,” he says. “It’s quite a competitive space right now, which is exciting, but it means we’ve got to keep moving fast to stay in the lead.” —Catherine Carlson

Clinical Factors Predict Atezolizumab Response

Only a minority of patients with cancer respond to checkpoint inhibitors, yet oncologists haven’t had a reliable method to determine those most likely to benefit. To address this problem, researchers developed a model that uses six clinical factors to predict how long patients with advanced bladder cancer will survive after being treated with the PD-L1 inhibitor atezolizumab.

“We hope that the results of this study will help oncologists better counsel patients on the potential outcomes they might expect if treated with atezolizumab, and this will help patients make more informed decisions,” said Gregory Pond, PhD, an associate professor of oncology at McMaster University in Hamilton, Ontario, Canada.

At the 2018 Genitourinary Cancers Symposium, which took place February 8–10 in San Francisco, CA, Pond explained that his team’s goal was to use clinical factors that could easily be obtained from medical charts to determine which patients might receive the greatest survival benefit from the treatment.

First, they analyzed data from the IMvigor 210 trial, which included 310 patients with advanced bladder cancer who had already received platinum chemotherapy. The team initially considered 14 factors, such as stage at diagnosis, whether the patient smoked, and the time since last treatment. Then, using stepwise regression analysis, they identified the six most informative factors: a patient’s inability to perform basic tasks, such as caring for themselves; liver metastases; a high platelet count; a high neutrophil–lymphocyte ratio, indicating inflammation; high lactate dehydrogenase levels, indicating tissue damage; and presence of anemia.

Using just these six factors, the model had good predictive power. Whereas patients with zero or one factor had a median overall survival of 19.6 months, those with four or more factors had a median survival of only 2.8 months.

The investigators then tested the model in a second cohort of 95 patients with advanced bladder cancer who had also previously received platinum chemotherapy. The model’s predictive power was not significantly different in this cohort.

Although PD-L1 levels were statistically significant when added to the model, they did not improve the model’s overall ability to predict survival, said Pond. This indicated that the value of including them was not worth the cost of adding another variable to the model, so they were left out.

“PD-L1 is a dynamic biomarker that’s influenced by the tumor microenvironment, so a single evaluation...
in an archival tumor sample may not be able to provide sufficient information regarding response to immune checkpoint therapy,” said Padmanee Sharma, MD, PhD, codirector of the Parker Institute for Cancer Immunotherapy at The University of Texas MD Anderson Cancer Center in Houston, who was not involved in this study.

Sharma added that before this model changes clinical practice, researchers will want to see the findings replicated in more prospective studies.

In addition, to determine whether similar prognostic models may be useful for other PD-1/PD-L1 inhibitors, Pond said that his team plans to analyze their use in other patient cohorts. –Kristin Harper

**CAR T-cell Therapies Produce Durable Remissions**

Chimeric antigen receptor (CAR) T-cell therapies can lead to high rates of durable, complete remission in patients with B-cell precursor acute lymphoblastic leukemia (ALL), according to a pair of studies published in *The New England Journal of Medicine*.

The studies, which are some of the first to provide a longer-term assessment of the effectiveness of CAR T-cell therapies, focus on tisagenlecleucel (Kymriah, CTL019; Novartis), approved last year to treat patients up to age 25 with ALL, and 19-28z CAR T cells, under development at Memorial Sloan Kettering Cancer Center (MSKCC) in New York, NY. Both therapies target CD19, which is highly expressed on ALL cells.

A patient’s frozen T cells arrive at a manufacturing facility to be engineered to recognize cancer cells expressing a specific antigen.

whom our other therapies had failed, and, more importantly, we are seeing durable remissions in a good fraction of patients as well,” Maude says. “It showed us that this highly specialized and personalized therapy can be implemented across institutions and around the world.”

The second study relates to findings of a phase I trial in which 53 adult patients with ALL received infusions of 19-28z CAR T cells (N Engl J Med 2018;378:449–59). After 21 days, 83% of patients had achieved complete remission. At 29 months, the median event-free and overall survival were 6.1 months and 12.9 months, respectively. Patients with a low disease burden fared best, with a median overall survival of 20.1 months, compared with 12.4 months among patients with a high disease burden.

“These results put into focus what the best situation is to treat these patients, what scenarios will allow these patients to achieve optimal outcomes, and how to manage these patients in the future,” while identifying patient groups for whom more effective CAR T-cell therapies are needed, explains Renier Brentjens, MD, PhD, who co-leads the study at MSKCC.

For Hapog Kantarjian, MD, of The University of Texas MD Anderson Cancer Center in Houston, “there’s no doubt that CAR T cells are a major breakthrough in cancer therapy,” but he has concerns about their toxicity, high cost, and effectiveness in certain patients.

“These studies give us an idea of how to move in the future in terms of learning how to give the CAR T cells, giving them in minimal residual disease patients to have less toxicities and better efficacy,” he says.

Terry Fry, MD, of Children’s Hospital Colorado in Aurora, says that although the studies provide clear evidence that some patients achieve durable remissions with CAR T-cell therapy, “the relapse rates and some of the challenges with manufacturing are issues that we need to deal with.”

“It’s a fantastic therapy, it’s really been transformative in terms of leukemia treatment, but I think we have to get past the initial enthusiasm,” he says. “I think now it’s on us to manage expectations and be honest about where the therapy is at, and recognize that there are a lot of places to improve.” –Catherine Caruso

**Kite, Sangamo Partner on Gene-Edited Cell Therapies**

To create universal chimeric antigen receptor (CAR) T-cell therapies—and a range of other autologous and allogeneic T-cell and natural killer cell treatments for patients with cancer—Santa Monica, CA–based Kite, a subsidiary of Gilead Sciences, inked a deal with Sangamo Therapeutics of Richmond, CA, to gain exclusive rights to its zinc finger nuclease (ZFN) gene-editing technologies. Under the terms of the agreement, announced on February 22, Sangamo will receive an up-front payment of $150 million—and could receive $3 billion more for meeting certain milestones, as well as royalties on sales of up to 10 products.

By partnering with a gene-editing specialty firm, Kite is following in the footsteps of other major companies developing CAR T-cell therapies. For example, Novartis has allied with Intellia Therapeutics; Juno Therapeutics (now owned by Celgene) with Editas Medicine; and Pfizer with Cellectis.

However, given Kite’s relatively late start, “there are few dance partners left,” says Ronald Dudek, a consultant on CAR T-cell therapy development in Gaithersburg, MD. That means most companies with the intellectual property behind newer gene-editing technologies, such as CRISPR/Cas9 or transcription activator-like effector nucleases (TALEN), are already locked into exclusive partnerships, which could help explain why Kite is pursuing ZFNs instead.

To Sangamo’s credit, Dudek says, the company does have “bona fide chops in editing T cells with their