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.

Shannon Maude, MD, PhD, and her team at Children's Hospital of Philadelphia in Pennsylvania published results from the phase II ELIANA trial of tisagenlecleucel, in which 75 patients with ALL were treated at 25 centers around the world (N Engl J Med 2018;378:439–48). The study achieved an overall remission rate of 81% by 3 months. At 6 months, event-free survival and overall survival were 73% and 90%, respectively, and they were 50% and 76%, respectively, at 12 months.

"What we learned from this study is that we are seeing very high remission rates in this population of patients for 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."

Novartis

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

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 Hagop 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

zinc finger technology." For the past decade, the company has been testing an autologous CD4+ T-cell therapy in which ZFNs are used to render CCR5, the receptor through which HIV enters immune cells, permanently dysfunctional. That therapy is now in multiple phase II trials for the treatment of HIV infection. Previously, Sangamo shepherded a ZFN-edited IL13 receptor–targeted CAR T-cell therapy into phase I trials for glioblastoma, but development never went further.

Despite that clinical head start and an expansive ZFN library, Kite and Sangamo may find themselves behind other companies like Tmunity Therapeutics of Philadelphia, PA, which began recruiting for the first clinical trial of CRISPR gene-edited therapy in the United States in February. That product uses a patient's own T cells engineered with a viral vector to express a T-cell receptor (TCR) with affinity to the NY-ESO-1 antigen, as well as CRISPR to disrupt the genes for the endogenous TCR and the PD-1 checkpoint protein. "Technically, everything is ready to go," says Tmunity cofounder Yangbing Zhao, MD, PhD, of the University of Pennsylvania in Philadelphia.

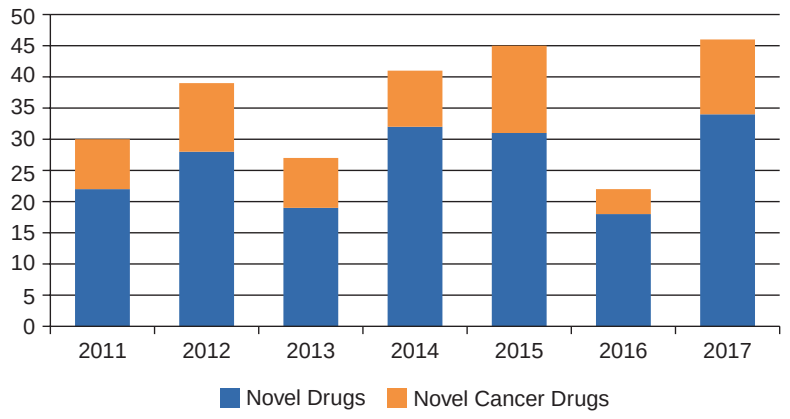
Kite and Sangamo will be looking to use ZFN technology to make similar kinds of autologous TCR-based therapies. They will also be trying to emulate what Cellectis has done with its TALEN-edited allogeneic CAR T-cell candidates, the only off-the-shelf CAR T-cell therapies clinically tested in the United States and Europe.

Cellectis's two allogeneic CAR T-cell products in phase I testing—one directed against CD123, the other against CD19—both use TALENs to inactivate the *TRAC* gene, which encodes part of the TCR, to prevent cell rejection and graft-versus-host disease. However, the anti-CD19 product additionally involves TALEN-mediated disruption of *CD52* to prevent depletion by any residual anti-CD52 alemtuzumab (Campath; Sanofi) given during the conditioning regimen prior to T-cell infusion.

"We're really just getting to the end of the first wave of the [CD19 CAR] stuff," says Waseem Qasim, MD, PhD, of University College London, UK, who is leading one of Cellectis's anti-CD19 trials. The next frontier, he says, will involve combining CAR transduction and gene editing so the construct positioning itself disrupts the TCR-encoding locus. "It's in the mix for something you could do," he says—likely making it something that Kite and Sangamo will pursue. *–Elie Dolgin* ■

BY THE NUMBERS

Novel Drugs Approved by the FDA, 2011–2017



For 2017, the FDA reported it approved 12 novel cancer drugs, a category that includes drugs with active ingredients not previously approved in the United States, and excludes new applications or combinations of existing drugs. The FDA also greenlighted the first two chimeric antigen receptor T-cell therapies for cancer—tisagenlecleucel (Kymriah; Novartis), for the treatment of B-cell precursor acute lymphoblastic leukemia, and axicabtagene ciloleucel (Yescarta; Kite) for the treatment of certain forms of large B-cell lymphoma.

For more news on cancer research, visit *Cancer Discovery* online at http://cancerdiscovery.aacrjournals.org/content/early/by/section.

NOTED

Bristol-Meyers Squibb will pay $1.85 billion to Nektar Therapeutics for rights to the experimental cancer drug NKTR-214. In the deal, Bristol will get 35% of global profits should the drug reach market, and the exclusive right to combine the drug with its PD-1 inhibitor nivolumab (Opdivo) and CTLA4 inhibitor ipilimumab (Yervoy). NKTR-214 is designed to expand cancer-fighting T cells and natural killer cells in the tumor microenvironment.

The FDA approved lutetium Lu 177 dotatate (Lutathera; Novartis, Advanced Accelerator Applications) to treat somatostatin receptor–positive gastroenteropancreatic neuroendocrine tumors. Approval was based on results of two studies: In one trial of 229 patients, those who received the drug with octreotide had longer progression-free survival than those who received octreotide alone (65.2% vs. 10.8% at 20 months, respectively; N Engl J Med 2017;376: 125–35). In another study, 16% of 360 patients treated with the drug responded.

The U.S Preventive Services Task Force recommended against ovarian cancer screening in women without symptoms who aren't at high genetic risk for the disease, concluding that screening does not save lives and may cause moderate to substantial harms. The recommendation has not changed since 2012, but now incorporates additional evidence from the UK Collaborative Trial of Ovarian Cancer Screening (JAMA 2018; 319:588–94; Lancet 2016;387:945–56).

The FDA expanded the indication for durvalumab (Imfinzi; AstraZeneca) to include treatment of inoperable stage III non–small cell lung cancer that has not progressed after chemoradiation. It's the first approved treatment for the disease to reduce the risk of progression.

The American Cancer Society (ACS) endorsed the use of electronic cigarettes (e-cigarettes) to aid in smoking cessation among smokers who won't use FDA-approved cessation products, such as nicotine gum. According to the ACS's policy statement, available at www.cancer.org, these individuals should switch to the least harmful tobacco product possible; "switching to… e-cigarettes is preferable to continuing to smoke combustible products."