“These data will not change the standard of care, but they provide an enormous opportunity for discovery,” she said. “We hope to uncover important information about the mechanisms and biomarkers of resistance to endocrine-based therapy with CD4/6 inhibitors.” —Janet Colwell

**Anti-CD22 CAR Therapy Leads to All Remissions**

In a first-in-human trial of an anti-CD22 chimeric antigen receptor (CAR) T-cell therapy in children and young adults with relapsed/refractory acute lymphocytic leukemia (ALL), researchers found that the immunotherapeutic approach was not only feasible and safe, but also effective, leading to remissions in most patients. Data from the trial were shared last month at the American Society of Hematology’s annual meeting in San Diego, CA.

Although anti-CD19 CAR T-cell therapy has led to complete remissions in 80% to 90% of patients with relapsed/refractory ALL, “we’re learning now that one of the limitations of this approach is loss of CD19 expression occurring in, potentially, a substantial number of patients,” said Terry Fry, MD, of the Pediatric Oncology Branch, Center for Cancer Research, at the NCI, who presented the trial’s findings at a press conference during the meeting.

Seeking an alternative target—and noting the effectiveness of the anti-CD22 monoclonal antibody ozogamicin (Pfizer), which targets CD22, an antigen widely expressed on B-cell leukemias and lymphomas—researchers launched a phase I dose-escalation study of anti-CD22 CAR T-cell therapy, enrolling 16 children and young adults with relapsed/refractory CD22-expressing ALL in the study. Eleven of the 16 patients had relapsed after previously receiving anti-CD19 CAR T cells. All of the patients had had at least one allogeneic stem cell transplant.

Researchers collected T cells from the patients and modified them to recognize and bind to CD22. Patients then received an infusion of their own modified cells at one of three “doses”—3 × 10^6 transduced CAR T cells/kg, 1 × 10^7 cells/kg, or 3 × 10^7 cells/kg—and were evaluated for a response and adverse effects after 28 days, on average. Only one of the six patients treated at the lowest dose achieved remission, but eight of the 10 participants who received a higher dose experienced remission with no evidence of residual disease. Six of the nine patients who achieved remission subsequently relapsed; the other three remain in remission, with one remission continuing for more than a year, Fry reported.

Most of the patients who relapsed experienced decreases in CD22 expression, with only one patient experiencing CD22 loss. Fry observed that the opposite seems to occur following anti-CD19 CAR T-cell therapy, with antigen loss, not reduced expression, more likely.

The primary adverse effect of anti-CD22 CAR T-cell therapy was cytokine release syndrome, reported Nirali Shah, MD, also from the NCI’s Pediatric Oncology Branch, who shared the findings with meeting attendees. However, Shah said that all cases, which involved fever and low blood pressure, were mild. One patient died of sepsis, but not until after the cytokine release syndrome ended.

Although researchers continue to enroll patients in the trial, they are already asking new questions about how best to use the therapy, Fry commented. For example, he and his team are wondering whether physicians should wait for disease relapse following anti-CD19 CAR T-cell therapy before starting with anti-CD22 CAR T-cell therapy, or whether remissions would last longer if the therapies were given simultaneously—issues they plan to investigate.—Suzanne Rose

**Rucaparib Approved for Ovarian Cancer**

The FDA greenlighted Boulder, CO-based Clovis Oncology’s rucaparib (Rubraca) to treat women with advanced ovarian cancer who have already received at least two chemotherapies and have a somatic or germline *BRCA1* or *BRCA2* mutation as identified by an approved companion diagnostic test. Up to 20% of high-grade serous ovarian cancers have a deleterious *BRCA* gene mutation.

To detect the *BRCA* alterations—and thus determine which patients are eligible to receive rucaparib—the agency also gave a nod to the FoundationFocus CDx-BRCA test on December 19. Marketed by Foundation Medicine of Cambridge, MA, the test is the first next-generation sequencing-based companion diagnostic to receive FDA approval.

Rucaparib belongs to a class of anticancer agents called PARP inhibitors, which induce synthetic lethality in cancer cells with defective homologous repair, such as those harboring deleterious *BRCA* mutations.

Approval of the drug and the companion diagnostic was based on data from two multicenter, single-arm trials evaluating their efficacy and safety. Studies of efficacy involved 106 women with *BRCA*-mutated advanced ovarian cancer who had already been treated with at least two chemotherapy regimens. At trial enrollment, *BRCA* status was determined with either local germline test results or a Foundation Medicine clinical trial assay. Mutation status was later verified by the FoundationFocus CDxBRCA test in 96% of the patients for whom a tumor sample was available.

Among all 106 patients, the objective response rate to rucaparib was 54%, with a median duration of response of 9.2 months. Among patients sensitive to platinum-containing regimens, the response rate was 66%. For patients with platinum-resistant and platinum-refractory disease, the response rates were 25% and 0%, respectively. There was no significant difference in response rates between patients with a *BRCA1* mutation and those with a *BRCA2* mutation.

The safety of rucaparib was assessed in a trial involving 377 patients. The most common side effects were nausea, fatigue, vomiting, anemia, abdominal pain, constipation, decreased appetite, diarrhea, thrombocytopenia, and dyspnea. Two cases of acute myeloid leukemia were reported.

Another PARP inhibitor, olaparib (Lynparza; AstraZeneca), was approved in 2014 to treat women with germline *BRCA*-mutated advanced ovarian cancer who had received at least three prior chemotherapies. In the trial that led to its approval, 34% of 137 such patients responded to olaparib. Head-to-head comparisons of PARP inhibitors have not been done, but the efficacy of olaparib and rucaparib...
seems comparable based on published data.

In addition, although the toxicities of PARP inhibitors are generally similar, “there will be some innate and unique side effects among the different PARP inhibitors,” says Ursula Matulonis, MD, of Dana-Farber Cancer Institute in Boston, MA. For example, she notes that rucaparib is more likely to cause liver enzyme abnormalities as well as grade 3 anemia, potentially complicating prescribing decisions and making personalized treatment plans and follow-up essential for patients taking the drugs.

Because many patients don’t benefit from PARP inhibitors, or may not benefit for very long, physicians want to test the drugs in combination with other therapies, such as antiangiogenic agents or PI3K inhibitors. “Can we make the cancer cell more homologous repair–deficient?” asks Matulonis. Also, “after there’s evidence of benefit for PARP inhibitors, or may not benefit from prior endocrine therapy with mTOR inhibitors due to the psychiatric effects of mTOR inhibition. However, the drug was also associated with dose-limiting side effects in a significant number of patients, investigators said during the 2016 San Antonio Breast Cancer Symposium in Texas, December 6–10.

In the phase III trial, 432 postmenopausal women who had received a prior aromatase inhibitor and the mTOR inhibitors everolimus (Afinitor; Novartis) or ridaforolimus (Ariad) were assigned to receive buparlisib plus fulvestrant or fulvestrant alone. Almost 70% had received two or more lines of endocrine therapy and 90% experienced disease progression while, or after, taking an mTOR inhibitor. In the buparlisib group, patients had longer progression-free survival (PFS) compared with the control group (3.9 vs. 1.8 months) and a higher 6-month PFS rate (31% vs. 20%).

Among those who took buparlisib, median PFS was higher in patients whose tumors had mutant, not wild-type, PIK3CA (4.7% vs. 2.8%), and in patients with nonvisceral disease versus those with metastasis to the liver or lung (4.2 vs. 3.1 months). “Some patients who did not benefit from prior endocrine therapy with mTOR inhibition did benefit from taking buparlisib,” said study co-author Ruth O’Regan, MD, of the University of Wisconsin-Madison, who presented the findings during a press briefing. “It suggests that buparlisib may be useful in many cancers that become resistant to mTOR inhibitors.”

However, concerns remain about toxicities associated with buparlisib, including increased liver enzymes. Also troubling, the drug was associated with severe anxiety and depression, and several patients attempted suicide during the trial, said O’Regan.

These serious adverse events led to medication interruptions or dose reductions in a higher percentage of patients taking buparlisib plus fulvestrant compared with fulvestrant alone, researchers reported.

“We need to be cautious about [using drugs that cross] the blood–brain barrier due to the psychiatric effects of inhibiting PI3K in the brain,” said Carlos Arteaga, MD, of Vanderbilt-Ingram Cancer Center in Nashville, TN, who commented on the study. He added that future research should focus on developing isoform-specific PI3K inhibitors that act on the mutated form of the protein while sparing the wild-type version that is essential for normal body function.

Several studies are currently testing next-generation PI3K inhibitors that specifically target the alpha isoform encoded by the PIK3CA gene in patients with advanced disease. They include the SOLAR-1 trial of fulvestrant combined with alpelisib (Novartis) and the SANDPIPER study of fulvestrant plus taselisib (Genentech). Researchers are also investigating the effectiveness of combining PI3K inhibitors and CDK4/6 inhibitors, said O’Regan.

“Our findings provide a nice view into the biology of PI3K inhibition,” she said. “We now need to focus on developing new PI3K inhibitors with comparable activity and a better safety profile.” –Janet Colwell

**BLU-285, DCC-2618 Show Activity against GIST**

Mutations in **KIT** and **PDGFRα** are genetic drivers in more than 85% of gastrointestinal stromal tumors (GIST). Tyrosine kinase inhibitors (TKI), such as imatinib (Gleevec; Novartis), may