"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 antibody–drug conjugate inotuzumab 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"—3×10^5 transduced CAR T cells/kg, 1×10^6 cells/kg, or 3×10^6 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