Published OnlineFirst December 12, 2018; DOI: 10.1158/2159-8290.CD-NB2018-169

in New York, NY, who was also not connected to the trial, was impressed by the results. She points out that AMG 420 had a lower rate of cytokine release syndrome than BCMA-targeting CAR T cells, potentially making it more suitable for older patients. However, she has concerns about the relatively high infection rate, which may result from needing to administer AMG 420 via continuous infusion. Lentzsch is involved in an ongoing phase I trial of AMG 701 (Amgen), a BiTE with a similar mechanism as AMG 420, but a longer half-life that allows it to be given weekly.

"BCMA probably does represent the best target we have in myeloma," Lonial says, adding that all three BCMA-targeting approaches being developed—BiTEs, CAR T cells, and antibody–drug conjugates—are likely to become valuable therapies. "I don't think only one of them is going to win—I suspect we're going to have, hopefully, more than one way to get at BCMA." *–Catherine Caruso* ■

Augmenting CAR T Cells with PD-1 Blockade

Patients with B-cell malignancies who experience poor initial responses to chimeric antigen receptor (CAR) T-cell therapy may benefit from the addition of immune checkpoint blockade, according to several reports presented during the 2018 American Society of Hematology (ASH) Annual Meeting in San Diego, CA, in December.

The findings suggest that this sequential approach "may improve the function and persistence of CAR T cells," said Shannon Maude, MD, PhD, of the Children's Hospital of Philadelphia, PA, who led one of the studies.

Lack of CAR T-cell durability is thought to be mediated in part by a patient's immune system reacting, through checkpoint pathway activity, against their own reengineered T cells, leading to the loss of function or physical deletion of these cells. Anti–PD-1 therapies such as pembrolizumab (Keytruda; Merck) and nivolumab (Opdivo; Bristol-Myers Squibb) may therefore prove especially useful in this situation.

However, "it's definitely not a home run," said Peter Riedell, MD, of the University of Chicago, IL, who was not involved in these trials. "In a subset of patients, [the strategy] has been effective in reengaging these cells to attack the target," he said, "but there are multiple mechanisms that lead to failure of CAR T cells, and if it's not a consequence of T-cell exhaustion, then giving a checkpoint inhibitor may not be the answer."

Maude's study included 14 children and adolescents with relapsed/refractory B-cell malignancies: One had lymphocytic lymphoma, the rest acute lymphoblastic leukemia. These patients had responded transiently or not at all to the CD19-targeted therapy tisagenlecleucel (Kymriah; Novartis) or its next-generation humanized counterpart, CTL119 (Novartis), and received pembrolizumab or nivolumab within 2 to 7 weeks of CAR T-cell infusion.

Checkpoint inhibition helped seven patients reestablish their initial response to tisagenlecleucel. In three patients, B-cell counts, which had recovered early after dropping on tisagenlecleucel alone, plummeted again—a sign of renewed CAR T-cell function—with the addition of PD-1 blockade; all three remain in complete remission. Meanwhile, of four patients whose disease had spread beyond the bone marrow, there were two complete and two partial responses. However, no responses occurred among another four patients who hadn't benefited from CAR T-cell therapy to begin with.

Two other studies, both from the University of Pennsylvania in Philadelphia, evaluated adding anti–PD-1 therapy to CAR T-cell therapy, but in adults with relapsed/refractory non-Hodgkin lymphoma (NHL) or multiple myeloma, respectively. The NHL trial, led by Stephen Schuster, MD, reported comparable results with those of Maude's study among patients treated with pembrolizumab, following tisagenlecleucel or CTL119, to reverse T-cell exhaustion: Three of 11 patients responded to combination therapy, and one experienced stable disease.

However, checkpoint inhibition may not work in tandem with CAR T-cell therapy for all hematologic malignancies. In the myeloma trial presented by Adam Cohen, MD, among five patients treated with pembrolizumab-containing drug regimens after their disease progressed on BCMA-directed CAR T-cell therapy, only one showed signs of CAR T-cell reexpansion—and even then, the response was transient. "It suggests something different about the biology of myeloma that's ultimately leading to resistance and relapse," Cohen said. Yet, "that doesn't mean we should totally abandon" this sequential strategy in myeloma without larger studies, he added.

Schuster, Riedell, and Joseph McGuirk, DO, of the University of Kansas Cancer Center in Kansas City, are testing the safety and efficacy of routinely administering pembrolizumab, within weeks of tisagenlecleucel, for patients with diffuse large B-cell lymphoma (DLBCL)—instead of waiting until they relapse on or are unresponsive to CAR T-cell therapy. Other groups are evaluating the near-concomitant administration of PD-L1 inhibitors and additional CD19-targeted CAR T-cell therapies for DLBCL: For example, encouraging early results were reported at ASH for the combinations of axicabtagene ciloleucel (Yescarta; Gilead) with atezolizumab (Tecentriq; Genentech), and of JCAR014 (Juno Therapeutics) with durvalumab (Imfinzi; AstraZeneca). *–Elie Dolgin* ■

T-DM1 Reduces HER2+ Breast Cancer Recurrence

Historically, patients with early-stage HER2-positive breast cancer and residual invasive disease—after neoadjuvant chemotherapy alongside HER2-targeted agents, chiefly trastuzumab (Herceptin; Genentech)—have faced a higher likelihood of invasive recurrence following surgery than patients with no remaining invasive disease. Investigators have been searching for a more effective treatment option for these patients than additional trastuzumab therapy, the current standard of care.

According to recent findings from the phase III KATHERINE trial, patients in this high-risk population who receive the antibody–drug conjugate ado-trastuzumab emtansine (T-DM1/Kadcyla; Genentech) instead of additional trastuzumab are half as likely to develop recurrence.

"Both the magnitude and the consistent degree of benefit across all subgroups of patients in the study

Published OnlineFirst December 12, 2018; DOI: 10.1158/2159-8290.CD-NB2018-169

©SABCS/Scott Morgan 2018

Given its greater effectiveness at preventing recurrence of some breast cancers after neoadjuvant therapy, T-DM1 will likely replace standard trastuzumab treatment for certain women, according to Charles Geyer Jr., MD.

were remarkable and pleasantly surprising," said Charles Geyer Jr., MD, of Virginia Commonwealth University Massey Cancer Center in Richmond, lead author of the study, which was presented during the 2018 San Antonio Breast Cancer Symposium in Texas in December, and concurrently published (N Engl J Med 2018 Dec 5 [Epub ahead of print]).

KATHERINE enrolled a total of 1,486 patients who had received neoadjuvant treatment that included a taxane with trastuzumab and were found to have residual disease at the time of surgery. They were randomly assigned to receive 14 cycles of either T-DM1 or trastuzumab. T-DM1 reduced the risk of recurrence or death by 50%; at 3 years, 88.3% of patients in this group were free of invasive disease, compared with 77% in the trastuzumab arm. The superiority of T-DM1 was consistent regardless of patient characteristics, including menopausal and hormone receptor status, the amount of residual disease at surgery, and lymph node involvement.

Side effects were more frequent with T-DM1, chiefly peripheral sensory neuropathy, reduced platelet counts, and elevation of liver enzymes. However, most adverse events in both arms of the trial were mild, said Geyer, and most toxicities in the T-DM1 arm were resolved with dose reductions.

"From the available data, it appears that the benefits of T-DM1 will far outweigh its toxicity" in this patient population, said Nancy Davidson, MD, of the Fred Hutchinson Cancer Research Center in Seattle, WA, who was not involved in the trial.

Both Geyer and Davidson believe that these findings are likely to change the way oncologists practice—even though the FDA hasn't yet approved T-DM1 for this indication. "Since T-DM1 is already an FDA-approved agent for advanced breast cancer and oncologists are versed in its use, I expect they will now recommend T-DM1 to women with residual HER2-positive disease in the post-neoadjuvant setting," said Davidson.

Meanwhile, KATHERINE is scheduled to continue into the spring of 2023, said Geyer, which will provide a more complete picture of T-DM1's effects on survival over time. As well, ongoing trials are now investigating T-DM1's potential use as a neoadjuvant treatment. *–Kristin Harper* ■

GSK to Buy Tesaro, Developer of Niraparib

GlaxoSmithKline (GSK) announced plans in December to buy Waltham, MA–based biotech Tesaro, maker of the once-daily oral PARP inhibitor niraparib (Zejula), in a deal valued at $5.1 billion.

The acquisition will bring GSK into an increasingly crowded field of PARP-targeting drugs—one that has seen sluggish sales and slower-than-expected use among oncologists, because maintenance therapy is still relatively new in ovarian cancer. Yet company executives are confident that they can turn niraparib into a commercial success, both as a monotherapy and in combination with other agents for treating not only gynecologic cancers, but also other tumor types.

"Our strong belief is that PARP inhibitors are important medicines that have been underappreciated in terms of the impact they can have on cancer patients," says GSK president and chief scientific officer Hal Barron, MD.

Four PARP inhibitors are currently available for patients with advanced breast and gynecologic cancers. The market leader, olaparib (Lynparza; AstraZeneca), earned FDA approval in December 2014 as maintenance therapy for ovarian cancer; approvals for fallopian tube, peritoneal, and breast cancers soon followed. Then came rucaparib (Rubraca; Clovis Oncology) and niraparib—approved in December 2016 and in March 2017, respectively—for recurrent ovarian, fallopian tube, and peritoneal cancers, also as maintenance therapy.

In October, talazoparib (Talzenna; Pfizer) joined the formulary with an approval for germline *BRCA*-mutant, HER2-negative advanced breast cancer. Meanwhile, international pivotal phase III trials for AbbVie's veliparib and, in China, BeiGene's pamiparib in ovarian cancer are ongoing.

Many of these PARP inhibitors are also being evaluated in other tumor types, including cancers of the stomach, colon, bladder, and brain. Trials are ongoing with niraparib, for example, in patients with prostate cancer, non–small cell lung cancer, Ewing sarcoma, breast cancer, and for the management of certain ovarian cancers.

In general, says Premal Thaker, MD, of Washington University School of Medicine in St. Louis, MO, the approved PARP inhibitors all work about equally well in patients with ovarian cancer. The main differences boil down to side effects and dosing regimens. Niraparib seems to cause higher rates of thrombocytopenia and neutropenia than other agents—"but then it also has the convenience of once-a-day dosing, which does make it more useable and patient-friendly," she says. By contrast, both olaparib and rucaparib must be taken twice a day.

Initially, PARP inhibitors were approved only for women whose platinum chemotherapy–sensitive disease featured germline *BRCA1/2* mutations or homologous recombination deficiency—defects that increase genetic instability and make tumors intrinsically sensitive to the drugs. Niraparib was then greenlighted without requiring the use of a molecular biomarker, followed soon after by a similar expanded indication for olaparib.

Both olaparib and niraparib are now in phase III trials as first-line maintenance therapy for ovarian cancer. Preliminary data with olaparib suggest that this treatment strategy can delay the progression of germline *BRCA*-mutant disease.

Phase II combination trials in ovarian cancer, pairing niraparib with the angiogenesis blocker bevacizumab (Avastin; Genentech) or the PD-1 inhibitor pembrolizumab (Keytruda; Merck), are also ongoing. As well, by acquiring Tesaro, GSK will gain the biotech's portfolio of early-phase immune checkpoint inhibitors, including a PD-1 inhibitor called

AACR American Association for Cancer Research

CANCER DISCOVERY

T-DM1 Reduces HER2+ Breast Cancer Recurrence

Cancer Discov 2019;9:158-159. Published OnlineFirst December 12, 2018.