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...
CANCER DISCOVERY

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Cancer Discov 2019;9:158. Published OnlineFirst December 6, 2018.

Updated version
Access the most recent version of this article at:
doi:10.1158/2159-8290.CD-NB2018-165

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