Exploring Combination Approaches to Immunotherapy Treatment

BY KATIE KOSKO AND LISA MILLER


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In recent years, immunotherapy has shown its potential for treating patients with cancer. Success has been especially notable with regards to checkpoint inhibitors, including PD-1/PD-L1 and CTLA-4 single agents. As researchers continue to explore new ways that immunotherapy can improve patient outcomes, the success of these checkpoint inhibitors and other proven agents are being extended to combination approaches to treat patients for an even greater response.

Seven physicians and clinical researchers will take the stage this morning to discuss what lies ahead for combination immunotherapy in cancer research during the "Beyond Single Agents" session, which will include 4 talks and 2 oral abstract presentations. Drew M. Pardoll, MD, PhD, and F. Stephen Hodi, MD will co-chair the session.

During the session, presenters will discuss future strategies in combination immunotherapy and the factors that will influence this approach, including biomarkers and selecting the patients that will respond best to combination therapies.

Alan J. Korman, PhD, of Bristol-Myers Squibb, will discuss combining ipilimumab (Yervoy) with nivolumab (Opdivo) and how this combination can be advanced in the future, with a focus on methods to improve anti–CTLA-4 therapy. Korman said that the antibody could be made more potent by altering the Fc region or by activating the therapy at the tumor site through protease cleavage, which is currently being developed in collaboration with Cytomyx.

Erminia Massarelli, MD, PhD, MS, of City of Hope will discuss the clinical safety and efficacy of urelumab (BMS-663513), a novel anti-CD137 antibody with demonstrated antitumor potential through enhancement of T cell and natural killer cell activity. Urelumab was explored alone and in combination with the PD-1 inhibitor nivolumab (Opdivo), in patients with a variety of metastatic solid tumors and advanced non-Hodgkin lymphomas in 2 clinical trials.[1]

TABLE. ***Treatment-related adverse events across both studies of urelumab***

	Urelumab Alone	Urelumab + Nivolumab
Total number of patients	123	104
Total treatment-related AEs	65 (53%)	65 (63%)
Fatigue	18 (15%)	27 (26%)
AST increase	16 (13%)	9 (9%)
ALT increase	12 (10%)	13 (13%)
Serious treatment-related AEs	9 (7%)	10 (10%)
Treatment-related AEs leading to discontinuation	6 (5%)	7 (7%)

AE, adverse event; AST, aspartate aminotransferase; ALT, alanine aminotransferase

In the phase I monotherapy study, urelumab was given to patients with advanced solid tumors at a dose of 0.1 mg/kg or 0.3 mg/kg every 3 weeks, and to patients with advanced non-Hodgkin lymphoma at a dose of 8 mg every 3 or 6 weeks. Overall, 123 patients were given urelumab monotherapy, and 65 of these patients (53%) experienced a treatment-related adverse event (AE).

The phase I/II combination trial is still accruing patients, but as of this interim analysis, the study included a total of 104 patients, comprised of 40 patients with melanoma, 20 with non–small cell lung cancer, 22 with squamous cell carcinoma of the head and neck (SCCHN), and 22 with diffuse large B-cell lymphoma. Sixty-five of these patients (63%) experienced a treatment-related AE.

The most common treatment-related AEs experienced across both trials included fatigue (15% in the monotherapy study and 26% in the combination study), increased aspartate aminotransferase (AST; 13% and 9%, respectively), and increased alanine aminotransferase (ALT; 10% and 13%, respectively). Grade 3/4 AST and ALT increases were experienced by 3% and 2%, respectively, in the monotherapy trial, and 3% each in the combination trial **(TABLE)**.

Six patients discontinued treatment in the trial of urelumab alone, and 7 patients discontinued treatment in the combination study, both due to treatment-related AEs. No treatment-related deaths were reported in either study.

Partial remissions (PRs) were achieved by 3 patients with lymphoma in the monotherapy trial, and another 3 patients with lymphoma achieved a complete remission. In the combination study, a total of 9 out of 86 evaluable patients (10.5%) had a PR, including 8 patients with melanoma and one with SCCHN. Thirty-three out of 71 patients treated with combination therapy had a reduction in their tumor burden assessed by RECIST and iWG criteria.

The combination immunotherapy was found to increase T and natural killer cell numbers and expression of interferon-gamma (IFN-γ) in the melanoma tumors evaluated. Additionally, the combination was associated with greater stimulation of peripheral IFN-γ–induced cytokine production than with urelumab monotherapy. However, as of the interim analysis, the addition of nivolumab did not appear to add any significant clinical benefit at the doses that were investigated in this patient population.

The second study, to be presented by Jennifer Wu, PhD, Medical University of South Carolina, focused on a first-in-class antibody targeting soluble NKG2D ligand soluble MIC for cancer immunotherapy.[2]

"For a long time, my lab has been studying how tumor cells interact with the immune system and it happened to find a mechanism where tumor cells disable the immune system," Wu said in an interview.

Oncogene-induced transformation promotes the expression of MIC ligands, which bind and activate NKG2D immunoreceptors on T cells and natural killer cells, facilitating cancer cell clearance. However, advanced tumors produce a highly immunosuppressive soluble version of the MIC ligand (sMIC), which downregulates NKG2D expression on effector natural killer and T cells and immune response within the tumor microenvironment.

Wu led her research team in creating a humanized MIC-transgenic spontaneous prostate tumor mouse model in which to explore a potential antibody B10G5 therapy targeting sMIC, without blocking formation of the MIC/NKG2D complex. In preclinical proof-of-concept studies, CuraB-10 (B10G5) showed antitumor efficacy to eliminate metastasis, reduce tumor burden and increase survival when compared to placebo in these metastatic prostate cancer models. When combined with FDA-approved CTLA-4 and PD-1/PD-L1 checkpoint inhibitors, CuraB-10–mediated sMIC neutralization was found to synergize with checkpoint blockade with no observed toxicities, according to the abstract. CuraB-10 was also explored in combination with adoptive cellular therapy.

Wu said that her company CanCure, LLC, is working toward bringing this therapy into a first-in-human phase I/II trial, where it could be studied either as a monotherapy or in combination with checkpoint inhibitors, as in the proof-of-concept studies. Wu sees CuraB-10 being especially useful in cancers that are not responsive to checkpoint inhibitors alone, such as prostate cancer, as well as certain types of kidney cancer and colon cancer, and maybe even lung cancer. She added that a full combination approach may also benefit patients with melanoma.

What excites her most about clinical trials and the future of combination immunotherapy? That there are new approaches to give hope to patients who have not responded to current therapies, such as vaccines, immune checkpoint inhibitors, or T-cell therapies. Wu said that there is hope for these patients as they continue to explore the emerging science behind immunology, patient responses, and novel therapeutics. •

REFERENCES

1. Massarelli E, Segal NH, Ribrag V, et al. Clinical safety and efficacy assessment of the CD137 agonist urelumab alone and in combination with nivolumab in patients with hematologic and solid tumor malignancies. Presented at: 2016 SITC Annual Meeting; November 9-13, 2016; National Harbor, MD. Abstract 239.

2. Wu J, Zhang J, Basher F, et al. Beyond immune checkpoint: first-in-class antibody targeting soluble NKG2D ligand sMIC for cancer immunotherapy. Presented at: 2016 SITC Annual Meeting; November 9-13, 2016; National Harbor, MD. Abstract 252.

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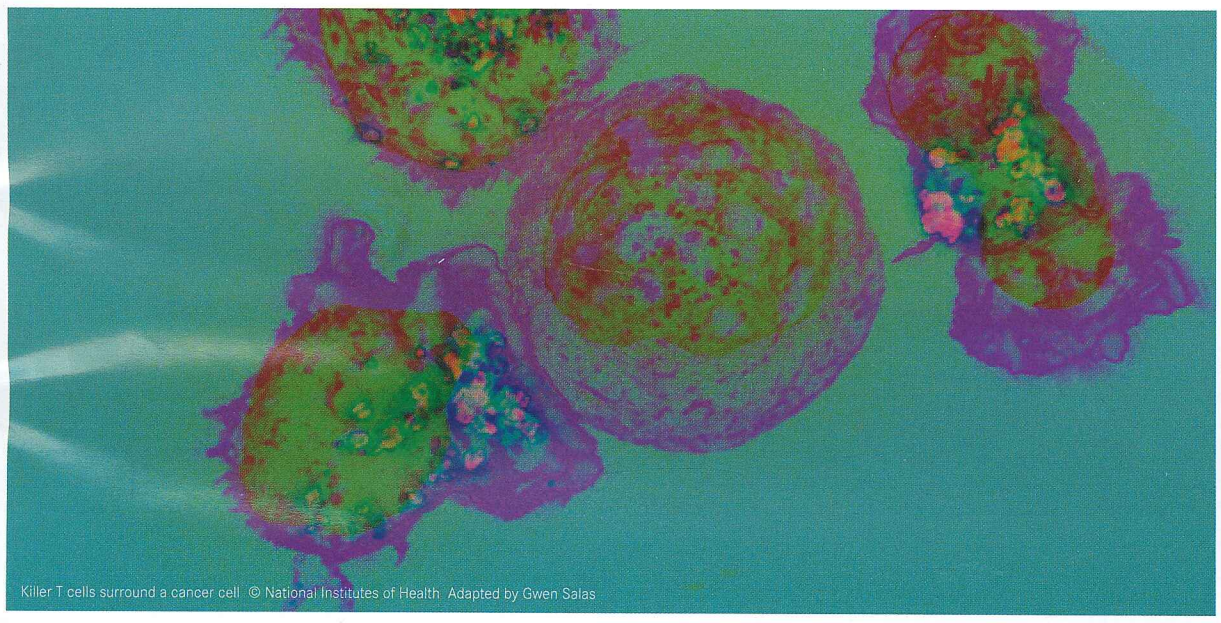
Killer T cells surround a cancer cell © National Institutes of Health Adapted by Gwen Salas

Exploring Adoptive Cellular Therapy and Bispecific Antibodies

BY PETER J. SCIAVOLINO, PHD


RIDDELL


MACKALL

Immunotherapy approaches utilizing adoptive cellular therapy (ACT) or bispecific antibodies (BsAs) as cancer therapy will be compared in the "Adoptive Cellular Therapy vs Bispecific Antibodies" session this evening. Co-chairs for this session will be Stanley R. Riddell, MD, from Fred Hutchinson Cancer Research Center, and Crystal L. Mackall, MD, from Stanford University.

Although cytotoxic T lymphocytes are important in facilitating the immune response to cancer, it is now well known that tumor cells have evolved elaborate mechanisms to manipulate the tumor microenvironment, create localized immunosuppression, and effectively evade immune detection.[1,2] One type of adoptive T-cell therapy exploits the sensitivity of T cells to be triggered upon recognition, via the T-cell receptor, of foreign antigens complexed on the cell surface with major histocompatibility complex proteins.[3,4]

ACT utilizes tumor-reactive T cells, which are identified and expanded *ex vivo* then reintroduced into the patient; the approach has been utilized, and refined, over 30 years to achieve durable responses in leukemias, melanoma, and other types of solid tumors.[4,5] This approach may, in part, help overcome local immunosuppressive effects in the tumor microenvironment by shifting cytokine secretion in favor of

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New Mechanisms in Tumor Rejection Highlighted During Presidential Session

BY TONY BERBERABE, MPH

The scientific abstracts chosen for presentation today during the Presidential Session represent some of the best abstracts submitted to the society, said Howard L. Kaufman, MD, FACS, associate director for clinical science, Rutgers Cancer Institute of New Jersey.

"The work collectively represents a sampling of the best science in the field right now," said Kaufman, president of SITC. "I think the presentations cover a range of different topics, reflecting the diverse interests across the field."

Five presentations will be highlighted during the session, which tend to be from individuals who are early in their career path, said Kaufman. "It gives the presenters a chance to showcase their work in front of a large international audience." In addition, a new feature to the session is that 2 highly regarded experts in the field will provide commentary and offer their perspectives on why these abstracts are important.


KAUFMAN

The first presentation, by Peled et al, addresses the potential influence of gut microbiota on mortality outcomes in patients who have recently received an allogeneic hematopoietic-cell transplantation (allo-HCT).[1] In cases of allo-HCT, common causes of mortality include relapse, graft-versus-host disease (GVHD), and infection. In previous studies, the researchers reported that the intestinal flora was associated with the development of GVHD, bacteremia, and reduced overall survival after allo-HCT. In the research that will be presented, the authors hypothesize that specific components of the intestinal flora are associated with relapse after transplantation.

Researchers profiled the intestinal flora of 541 patients who underwent allo-HCT, following them for 2 years post-transplantation. They determined the relationship between the abundance of microbiota species or groups of related species with relapse/progression of disease using the Cox proportional hazards model in this retrospective discovery-validation study. The

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