Revolutionizing Hematologic Cancer Treatment: The Promise of Bispecific T-Cell Engagers

Presented by Lihua E. Budde, MD, PhD; Stacy Pak, PharmD, BCOP; and Lauren R. Seipel, DNP, NP-C, AOCNP, BMTCN

ABSTRACT

The advent of bispecific T-cell engager (TCE) therapies has marked a turning point in the management of hematologic malignancies. Several clinical trials of these agents have led to approvals from the FDA, resulting in their subsequent incorporation into standard patient care. Although ongoing efforts are being made to optimize bispecific TCE therapies, a focus on their equitable distribution is needed. At the NCCN 2023 Annual Congress: Hematologic Malignancies, panelists presented clinical trial data, 2 case studies, and updates from NCCN Guidelines to develop an evidence-based approach for the use of these immunotherapies in various clinical contexts.

“The blood cancer treatment journey is really a journey for immunotherapy development,” commented Lihua E. Budde, MD, PhD, Associate Professor, City of Hope National Medical Center, and member of the NCCN Guidelines Panel for B-Cell Lymphomas, in her discussion of the advent of bispecific T-cell engager (TCE) therapies at the NCCN 2023 Annual Congress: Hematologic Malignancies. In an additional segment of the presentation, her co-panelists Stacy Pak, PharmD, BCOP, Clinical Pharmacist Specialist in outpatient hematology, and Lauren R. Seipel, DNP, NP-C, AOCNP, BMTCN, Nurse Practitioner in hematology and hematopoietic cell transplantation, both also of City of Hope National Medical Center, introduced 2 case studies, clinical trial data, and examples from updated NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) to further rationalize and illustrate the use of these immunotherapeutic agents for hematologic malignancies.

Background: Bispecific TCEs

Dr. Budde included an FDA approval timeline in her discussion to show how the treatment landscape for bispecific TCEs has evolved in the context of hematologic malignancies. FDA approvals for these antibodies were granted for use in B-cell acute lymphoblastic leukemia (ALL) in 2014, and for follicular lymphoma (FL) and multiple myeloma in 2022. “This year, there are 4 bispecific antibodies [that have been] approved: 2 for lymphoma and 2 for multiple myeloma,” she remarked. “This list will continue to get longer and longer.”

Bispecific TCEs vary in design, she explained, with the majority being IgG-based antibodies. The novel antibody imivotamab was developed using IgM as a platform, and blinatumomab consists of 2 fused single-chain variable fragments.

“The advantages of bispecific TCEs [are that they are] immediately available, recruit endogenous immune cells, and are administered in repetitive dosing,” Dr. Budde commented.

Role in B-Cell ALL

Currently, blinatumomab is the only bispecific TCE approved for the treatment of patients with leukemia. “After 14 years of development, blinatumomab received FDA approval in 2014,” Dr. Budde stated. “[This timeline] does not include the preclinical development of this molecule.”

Full approval for use of this antibody was based on results from the phase III TOWER trial, in which patients with relapsed/refractory ALL were randomly assigned to receive blinatumomab or standard-of-care chemotherapy. With the primary endpoint of overall survival, the median duration was 7.7 and 4.0 months, respectively. The complete remission rate was 43.9% with blinatumomab and 24.6% with chemotherapy.

Compared with the CD19-directed CAR T-cell therapies tisagenlecleucel and brexucabtagene autoleucel, Dr. Budde noted that blinatumomab demonstrated a similarly “promising” complete remission rate and a favorable adverse event profile (Table 1). “However, the biggest advantage of using blinatumomab is its off-the-shelf availability,” she added.

Role in Lymphoma

“There are 3 bispecific TCEs approved for use in lymphoma,” Dr. Budde remarked. “All 3 recognize CD20 as a tumor target.”
The accelerated FDA approval of one of these IgG-based agents, mosunetuzumab, was based on findings from the GO29781 trial. The results of this study demonstrated that the majority of patients with FL who had ≥2 prior lines of therapy benefited from treatment with this antibody, with an overall response rate of 80%. "The primary endpoint was looking at the complete remission rate, which was 60%," commented Dr. Budde. "[This is] significantly higher than the historical control of 14% using a PI3K inhibitor." The median duration of response was not reached. An updated analysis further demonstrated the durability of responses, with 63% of complete responders having remained in remission at 24 months.

In addition to mosunetuzumab, the CD19-directed CAR T-cell therapies axicabtagene ciloleucel and tisagenlecleucel have been granted approval in this disease setting. Dr. Budde concluded that, based on clinical trial data, "all 3 therapeutics are good options for patients with relapsed/refractory FL."

The other 2 bispecific TCEs approved for treatment of lymphoma, epcoritamab and glofitamab, are indicated for relapsed/refractory aggressive large B-cell disease. Although these agents differ in design, according to Dr. Budde, they have been found to confer similar rates of overall response, complete remission, and grade ≥3 cytokine-release syndrome (CRS) and neurotoxicity.

Role in Multiple Myeloma
Three bispecific TCEs have been approved for the treatment of patients with multiple myeloma, with 2 having received FDA approval in August 2023. "There will likely be more bispecific TCEs approved [in this setting]," commented Dr. Budde. "Several of them are very close to the end of phase II study."

Of these IgG-based, subcutaneously administered antibodies, teclistamab and elranatamab are B-cell maturation antigen (BCMA)--directed. The third, talquetamab, is a G protein--coupled receptor family C group 5 member D (GPRC5D)--directed agent.

"The overall response [and complete remission or better] rates are quite similar across the board...[and are] encouraging for this patient population," Dr. Budde remarked. "[The 3 antibodies] have very favorable rates of CRS and very few incidences of immune effector cell-associated neurotoxicity syndrome... However, somehow the infection rate is quite high for both of the BCMA[-targeted] bispecific TCEs."

Mitigating CRS
"There are 3 main methodologies that clinicians have been using to reduce the incidences of CRS," commented Dr. Budde. Step-up dosing of bispecific TCE therapy is one of the most used; however, both premedication with steroids (Table 2) and subcutaneous dosing have also been used in the mitigation of this toxicity.

Based on 2 analyses of the GO29781 trial, the CRS incidence rate of any grade was reduced with subcutaneous versus intravenous administration of mosunetuzumab (17.8% vs 44.0%). "There was no need for additional corticosteroid or tocilizumab use when administered via..."

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<th>Table 1. CD19 Redirected T-Cell Therapy–Induced High CR Rated in ALL</th>
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<td><strong>Trial</strong></td>
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**Biggest benefit: off the shelf**

Abbreviations: ALL, acute lymphoblastic leukemia; brexu-cell, brexucabtagene; CAR, CAR T cell; CR, complete remission; CRi, incomplete hematological recovery; CRS, cytokine-release syndrome; EFS, event-free survival; HCT, hematopoietic cell transplantation; ITT, intent to treat; RFS, relapse-free survival; tisa-cell, tisagenlecleucel.
the subcutaneous route,” Dr. Budde pointed out that these immunosuppressants were administered in 11.0% and 8.0% of patients who received mosunetuzumab intravenously, respectively, with no reported administrations in those who were treated subcutaneously.

Next Steps
Although “bispecific TCEs have been tested at multiple fronts,” Dr. Budde noted that there is an ongoing effort to establish these agents as earlier-line treatment options. Questions have also arisen regarding the mechanisms of resistance to these agents, as well as the optimization of sequencing and combination of therapies.

According to Dr. Budde, an ongoing phase I/II clinical trial evaluating the safety and efficacy of combining blinatumomab with the PD-1 inhibitor pembrolizumab in patients with relapsed/refractory B-cell ALL has yielded “promising” results.5 Blinatumomab monotherapy previously achieved a complete remission rate of approximately 44%; however, when administered in combination with pembrolizumab, this rate increased to 71%.

As the discourse moved toward optimization of design, Dr. Budde stated, “There are many nuances now determining a bispecific antibody’s efficacy and toxicity.” For example, the performance of the agent may be influenced by its target of choice, affinity and avidity to that target, and CD3 activation strength.

Finally, Dr. Budde touched upon how clinicians may expand access to and availability of bispecific TCE therapies. A cross-sectional analysis found no open trials of CAR T-cell or bispecific antibody therapies in 17 states (34%); there were <3 open trials in 6 of the 10 states with a high proportion of Black residents.6 Furthermore, she pointed out that hepatitis B carriers are excluded from these trials, and Asians and Pacific Islanders are often underrepresented because of the increased prevalence of such antigen positivity in these populations.7

“At least at the current stage, these cutting-edge therapies are not getting to the majority of patients,” Dr. Budde remarked. “What I’d really like to see is an equity… that allows this treatment to be more inclusive, performed in the community, and provided to a diversified group of patients, and… where it is affordable.”

Patient Case Review
The panelists then presented case studies in the context of bispecific T-cell engagers.

Case 1: Relapsed/Refractory FL
The first patient case focused on an 82-year-old female with relapsed FL. Staging workup revealed stage IIIB disease characterized by a bulky abdominal mass, bilateral hydronephrosis, and a malignant pleural effusion. The patient underwent first-line treatment with bendamustine + rituximab, and subsequently achieved complete remission. Disease progression was reported after approximately 1 year. According to Dr. Pak, second-line therapy with rituximab + lenalidomide yielded no improvement; her workup revealed grade 1/2, TP53-mutated FL manifesting in the abdomen.

Per the NCCN Guidelines for B-Cell Lymphomas, third-line options include small-molecule inhibitors, anti-CD19 CAR T-cell therapies, and mosunetuzumab.8 Dr. Budde explained that, before the advent of mosunetuzumab, she would likely have treated the patient with a small-molecule inhibitor and chemotherapy; it would have been “difficult” to administer CAR T-cell therapy in such a case. “This is an elderly patient… [with] comorbidities, including aortic stenosis and chronic kidney disease, who also does not have a caregiver,” Dr. Budde explained. “Mosunetuzumab is quite safe, but we still need to be mindful of how she can tolerate treatment.”

A whole-exome sequencing analysis of patients who received this bispecific TCE demonstrated comparable

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Abbreviations: c, cycle; d, day; dex, dexamethasone; TCE, T-cell engager.
overall response rates between those with and without a TP53 mutation at baseline. Based on this, I feel comfortable in recommending mosunetuzumab for this patient,” Dr. Budde remarked.

The patient was premedicated with dexamethasone, acetaminophen, and diphenhydramine. According to Dr. Pak, after receiving 3 cycles of mosunetuzumab therapy, the patient demonstrated an “excellent” response on PET/CT. Thus far, ongoing treatment has been well-tolerated and is planned to conclude after 8 cycles.

**Case 2: Relapsed/Refractory Multiple Myeloma**

The second case presentation featured a 67-year-old Black female who was initially diagnosed with lambda light-chain multiple myeloma. According to Dr. Seipel, the patient underwent an “extensive” treatment course, which included palliative radiation therapy and several lines of curative therapy. After an approximate 8-month period of remission, she experienced disease progression, with ECOG performance status score of 2. She was then referred to the trial and is planned to conclude after 8 cycles.

In the phase 1 MajesTEC-1 trial, teclistamab demonstrated no dose-limiting toxicities with the subcutaneously administered recommended phase II dose. A total of 58% of patients treated at this dose level achieved a very good partial response or better. Teclistamab has since been incorporated into the NCCN Guidelines for Multiple Myeloma as a preferred regimen for those with relapsed/refractory disease who have undergone at least 4 prior therapies.

[(Compared with idecagnetabide vilceluc and cilatcabtagenate autoleucel,] the bispecific antibody definitely gives less incidence of grade ≥3 CRS and neurologic toxicities,” Dr. Budde added. “I think this is one of the main reasons to choose teclistamab for this particular patient.”

The patient was administered subcutaneous teclistamab in a step-up dosing scheme— she was premedicated with dexamethasone, diphenhydramine, and acetaminophen prior to each dose. Adverse events, such as mild injection-site erythema, generalized body aches, and low-grade CRS, were reported with step-up dosing; however, the full dose of teclistamab was well-tolerated, eliminating the need for further premedication during subsequent treatment cycles. The patient ultimately experienced complete remission, based on laboratory and imaging studies, and demonstrated an improvement in ECOG performance status score from 2 to 1.

“Around month 4, she did end up developing parainfluenza and pneumonia, both of which were treated with supportive measures,” Dr. Seipel added. “Looking at this, another consideration is that we do need to initiate infection prophylaxis for our patients.”

**Disclosures:** Dr. Budde has disclosed serving as a consultant for AbbVie, Inc., ADC Therapeutics, AstraZeneca Pharmaceuticals LP, Bristol Myers Squibb, Genentech, Inc., Kite Pharma, Nurix Therapeutics, and Roche Laboratories, Inc.; and receiving grant/research support from Amgen Inc., AstraZeneca Pharmaceuticals LP, Merck & Co., Inc., and Mustang Bio, Inc. Dr. Seipel has disclosed serving as a scientific advisor for Genentech, Inc. Dr. Pak has disclosed no relevant financial relationships.

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**References**


