Understanding Lymphoma and Chronic Lymphocytic Leukemia (CLL)

Bispecific Antibodies

Lymphoma Research Foundation

Bispecific antibodies (bsAbs) are a new class of immunotherapy drugs (drugs that use the body's immune system to fight cancer) designed to recognize two different targets expressed on the cell surface, called *antigens*.

Introduction

What are Bispecific Antibodies?

Mechanism of Action- how do they work?

Bispecific antibodies (bsAbs) are a new class of immunotherapy drugs (drugs that use the body's immune system to fight cancer) designed to recognize two different targets expressed on the cell surface, called *antigens*. These drugs can be administered *intravenously* (infused directly into a vein) or subcutaneously (underneath the skin). Once in the bloodstream, bsAbs travel throughout the body and attach themselves to the cell(s) that have their specific antigens. According to their mechanism of action (how a drug produces an effect in the body), these drugs can be classified into cell-bridging bsAbs (the most commonly used) and antigen crosslinking bsAbs. Cell-bridging bsAbs bind to one antigen from the cancer cell (e.g. CD20 or CD19 in B-cell lymphomas) and one antigen from a healthy immune cell (e.g. CD3 in T cells or CD16 in natural killer [NK] cells). In contrast, antigen crosslinking bsAbs bind to two antigens in the same cell.

How are they different from other antibodies?

The main difference between standard antibodies and bsAbs depends on their mechanism of action. Natural antibodies (produced by the body's immune system) and monoclonal antibodies (proteins made in the laboratory that bind to cancer cells and help the immune system destroy them) used in therapy interact with a single antigen in the cell that is being targeted. For instance, rituximab (Rituxan) targets one antigen (called CD20) in lymphoma B-cells. In contrast, bsAbs interact with two distinct antigens, linking a cancer cell to a cancer-fighting T or NK cell and causing an immune response directed against the cancer. In addition, by targeting more than one antigen, bsAbs have a lower risk of drug resistance (cancer does not respond to treatment) compared to standard monoclonal antibodies. BsAbs vary in their size and structure, and this can affect how the drug is given and for how long it will remain in the body. In general, smaller bsAbs are eliminated more rapidly from the body and require continuous dosing (taking the drug without stopping) to produce a therapeutic effect (response to the treatment).

Bispecific Antibodies and Lymphoma

In blood cancer, most bsAbs in clinical development work by linking cancer cells to healthy immune cells that fight cancer. The majority combine regions that bind to CD20 on malignant (cancer) B-cells and engage cancer-fighting T cells (by binding to CD3). Epcoritamab (Epkinly) and glofitamab (Columvi) are FDA-approved to treat relapsed or refractory diffuse large B cell lymphoma (DLBCL), and mosunetuzumab (Lunsumio) is approved to treat relapsed or refractory follicular lymphoma. Clinical trials with T cell-engaging bsAbs odronextamab (REGN1979) have shown promising results in patients with *aggressive* (fast-growing), *relapsed* (disease comes back after treatment) or *refractory* (disease does not respond to initial treatment) B cell non-Hodgkin lymphoma (NHL). Other examples of bsAbs are blinatumomab (Blincyto; binds to CD19 in the cancer cell) and teclistamab (Tecvayli; binds to BCMA [B-cell maturation antigen]). Both drugs are FDA-approved to treat a different blood cancer such as B-cell precursor acute lymphoblastic leukemia and multiple myeloma, respectively. These drugs have emerged as a new class of immunotherapy with potential to treat aggressive lymphoma as second-line (treatment given when initial treatment [first-line] does not work or stops working) or third-line agents (given when the second-line option does not work or stops working) In particular, bsAbs may be valuable therapeutic alternatives for patients with DLBCL who have not responded to or are not eligible for stem cell transplant or chimeric antigen receptor (CAR) T-cell therapy (a special type of immunotherapy that uses the patient's immune cells to fight cancer). Please see section "Treatments Under Investigation in Lymphoma" below for a list of clinical trials involving bsAbs and lymphoma.

For more information on bsAbs, please view the *Understanding Lymphoma and CLL Guide* on the Foundation's website (visit lymphoma.org/publications).

Side Effects of bsAbs

Safety concerns for T-cell engaging bsAbs include cytokine release syndrome (CRS; caused by a large, and rapid release of inflammatory chemicals called cytokines into the blood) and neurological effects (including a type of neurological damage caused by immune cells called *immune effector cell-associated neurotoxicity syndrome*, or ICANS). When the bsAbs attack the cancer cells, the body's immune cells are activated and release inflammatory chemicals called cytokines. While cytokines are a natural part of the body's inflammatory response, a sudden release of a large quantity of cytokines can lead to CRS. This condition can be very serious and requires medical treatment. Neurological effects (including headache, confusion, tremors or dizziness) may also occur as a result of the immune response in the brain after receiving the bsAbs, and usually follow CRS. Other toxicities described for bsAbs include fever, injection-site reactions (such as swelling, rash or pain), low blood cell counts, and increased risk for infections.

Treatments Under Investigation in Lymphoma

Several cell-bridging bsAbs are in development for patients with lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). While many trials include bsAbs that engage T-cells (similar to the currently approved bsAbs), a small number of registered clinical trials are directed at a different immune cell called NK cells. Please refer to the **Table 1** below to find some examples of the latest information on clinical trials involving cell bridging bsAbs and lymphoma. For a complete list of all bsAbs in clinical trials for lymphoma, please visit **www.clinicaltrials.gov**.

Table 1: Phase 2 or 3 clinical trials of bsAbs in lymphoma

Agent (Commercial name)	Targets	Condition
Odronextamab (REGN1979)	CD20/CD3	r/r B cell NHL
HLX301	TIGIT/PD-1	Lymphoma
AZD7789	PD-1/TIM-3	r/r Classical HL
CD30 biAb-AATC	CD30/CD3	HL, CD30-positive DLBCL, CD30-positive ALCL, CD30-positive CTCL
GB261	CD20/CD3	B cell NHL, CLL

ALCL, anaplastic large cell lymphoma; bsAbs, bispecific antibodies; CLL, chronic lymphocytic leukemia; CTCL, cutaneous T cell lymphoma; DLBCL, diffuse large B cell lymphoma; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; PD-1, programmed death protein 1; TIGIT, T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif; TIM-3, T cell immunoglobulin and mucin domain-containing protein 3; r/r, relapsed/refractory.

Questions to Ask Your Doctor

- Are bsAbs a valid therapeutic option for my type of lymphoma?
- What are the benefits of bsAbs compared to conventional therapies (treatments widely used by healthcare professionals and accepted by medical experts)?
- How can I enroll in a clinical trial?
- What is the goal of my treatment?
- What are the risks, possible side effects, and benefits of the treatment I will receive?
- What side effects should I expect? Which of these should prompt me to seek medical attention?
- What should I do to take care of myself before and during treatment?
- How long will each treatment session last?
- How long will the entire treatment process last?
- What are the chances that the treatment will be successful?
- How will the treatment affect my normal activities (e.g., work, school, childcare, driving, sexual activity, exercise)?
- Will I be able to work during treatment?
- How often will I need a checkup?
- How much will the treatment cost? Will my insurance cover it?
- Will a particular therapy impact potential future treatment decision?

Clinical Trials

Clinical trials are not a "last resort" for patients. Every drug available today had to be tested in clinical trials before it was approved for general use, and all new and emerging treatments for lymphoma and CLL/SLL must be tested this way before patients can use them in the future. Clinical trials pose both benefits and risks for participants. Participating in a clinical trial can widen treatment options and provide access to new treatments that are not otherwise available to all patients. However, new treatments may or may not be as effective and safe as standard therapies. Patients who are randomized to the control group (a group of patients that do not receive the treatment under investigation) will receive the standard therapy that they would have received if they had not enrolled in the trial. All patients enrolled in a clinical trial are carefully monitored throughout the study.

Clinical trials are crucial in identifying effective drugs and determining optimal doses for patients with lymphoma. Patients interested in participating in a clinical trial should view the Understanding Clinical Trials fact sheet on the Foundation's website at www.lymphoma.org, talk to their physician, or contact the Foundation's Helpline for an individualized clinical trial search by calling **800-500-9976**, completing the Foundation's online clinical trials request form, or emailing **helpline@lymphoma.org**.

Lymphoma Care Plan

Keeping your information in one location can help you feel more organized and in control. This also makes it easier to find information pertaining to your care and saves valuable time. The Foundation's Lymphoma Care Plan document organizes information on your health care team, treatment regimen, and follow-up care. You can also keep track of health screenings and any symptoms you experience to discuss with your health care provider during future appointments. The Lymphoma Care Plan document can be accessed by visiting **lymphoma.org/publications**.

Patient Education Programs

The Foundation also offers a variety of educational activities, including live meetings and webinars for individuals looking to learn directly from lymphoma experts. These programs provide the lymphoma community with important information about the diagnosis and treatment of lymphoma, as well as information about clinical trials, research advances and how to manage/cope with the disease. These programs are designed to meet the needs of a lymphoma patient from the point of diagnosis through long-term survivorship. To view our schedule of upcoming programs, please visit **lymphoma.org/programs**.

Helpline

The Foundation's Helpline staff are available to answer your general questions about lymphoma and treatment information, as well as provide individual support and referrals to you and your loved ones. Callers may request the services of a language interpreter. The Foundation also offers a one-to-one peer support program called the Lymphoma Support Network and clinical trials information through our Clinical Trials Information Service. For more information about any of these resources, visit our website at **lymphoma.org**, or contact the Helpline at **(800) 500-9976** or **helpline@lymphoma.org**.

Para información en Español, por favor visite **lymphoma.org/es**. (For Information in Spanish please visit **lymphoma.org/es**).

Focus on Lymphoma Mobile App

Focus on Lymphoma is the first app to provide patients and their care partners with tailored content based on lymphoma subtype, and actionable tools to better manage diagnosis and treatment. Comprehensive lymphoma management, conveniently in one secure and easy-to-navigate app, no matter where you are on the care continuum. Get the right information, first, with resources from the entire Lymphoma Research Foundation content library, use unique tracking and reminder tools, and connect with a community of specialists and patients. To learn more about this resource, visit our website at **lymphoma.org/mobileapp**, or contact the Foundation's Helpline at **(800) 500-9976** or **helpline@lymphoma.org**.

Lymphoma Research Foundation

Research. Community. Cure.

Helpline
(800) 500-9976
helpline@lymphoma.org

lymphoma.org
lymphoma@lymphoma.org

Stay Connected

The Lymphoma Research Foundation appreciates the expertise and review of our Editorial Committee:

Leo I. Gordon, MD, FACP
Co-Chair
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Kristie A. Blum, MD
Co-Chair
Emory University School of Medicine

Jennifer E. Amengual, MD
Columbia University

Carla Casulo, MD
University of Rochester Medical Center

Alex Herrera, MD
City of Hope

Shana Jacobs, MD
Children's National Hospital

Patrick Connor Johnson, MD
Massachusetts General Hospital

Manali Kamdar, MD
University of Colorado

Ryan C. Lynch, MD
University of Washington

Peter Martin, MD
Weill Cornell Medicine

Neha Mehta-Shah, MD, MSCI
Washington University School of Medicine in St. Louis

M. Lia Palomba, MD
Memorial Sloan Kettering Cancer Center

Pierluigi Porcu, MD
Thomas Jefferson University

Sarah Rutherford, MD
Weill Cornell Medicine

Supported through grants from:

Genentech, A Member of the Roche Group | Biogen | AstraZeneca | REGENERON | MERCK

Understanding Lymphoma and Chronic Lymphocytic Leukemia (CLL) is published by the Lymphoma Research Foundation for the purpose of informing and educating readers. Facts and statistics were obtained using published information, including data from the Surveillance, Epidemiology, and End Results (SEER) Program. Because each person's body and response to treatment is different, no individual should self-diagnose or embark upon any course of medical treatment without first consulting with his or her physician. The medical reviewer, the medical reviewer's institution, and the Foundation are not responsible for the medical care or treatment of any individual.

Last updated May 2024