LYMPHOMA RESEARCH • FOUNDATION

Understanding Lymphoma and Bispecific Antibodies

What are Bispecific Antibodies?

Bispecific antibodies (bsAbs) are an innovative class of immunotherapy drugs designed to recognize two different targets expressed on the cell surface, called *antigens*. Like standard monoclonal antibodies (such as rituximab, a monoclonal antibody that targets B cells), bsAbs can be administered intravenously (IV) or *subcutaneously* (SC) i.e., underneath the skin. Once in the bloodstream, bsAbs travel throughout the body and attach themselves to the cell(s) that express their specific antigens. These drugs and are most classified according to their mechanism of action (how a drug works in the body to produce its effect):

- **Cell-bridging bsAbs** recognize one antigen from the disease 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 cancer, cell-bridging bsAbs work by linking a malignant cell to a cancer-fighting T or NK cell.
- **Antigen crosslinking bsAbs** recognize two antigens in the same cell. In cancer, antigen crosslinking bsAbs can work by either blocking signals for the cancer cell to survive, which prevent the cancer cells from growing or by activating the body's own immune cells (boosting the body's immune response to cancer).

HOW ARE THEY DIFFERENT FROM OTHER ANTIBODIES?

The main difference between standard antibodies and bsAbs relies on their mechanism of action. Natural antibodies and monoclonal antibodies used in therapy interact with a single antigen in the cell that is being targeted. For instance, rituximab (Rituxan) targets one antigen, CD20, in lymphoma B-cells. In contrast, bsAbs are designed to interact with two distinct antigens, which can be from the same cell (for antigen crosslinking bsAbs) or from two different cells (for cell-bridging bsAbs). By targeting more than one antigen, bsAbs can be less susceptible to drug resistance compared to standard monoclonal antibodies, especially in complicated diseases that are caused by multiple factors, like cancer. 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 to produce a therapeutic effect.

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 CD19 on malignant B-cells and engage cancer-fighting T cells (by binding to CD3). Blinatumomab (Blincyto) and teclistamab (Tecvayli) are FDA-approved to treat a different blood cancer such as B-cell precursor acute lymphoblastic leukemia and multiple myeloma respectively.

APPROVED BISPECIFIC ANTIBODIES IN LYMPHOMA

- Mosunetuzumab (Lunsumio)

  A bsAbs targeting CD20/CD3 treatment for adult patients with relapsed/refractory (R/R) lymphoma after two or more lines of systemic therapy.

  - Follicular Lymphoma

Clinical trials with T cell-engaging bsAbs like mosunetuzumab (BTCT4465A), glofitamab (RO7082859), epcoritamab (Gen3013) and 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). These drugs have thus emerged as a new class of immunotherapy with potential to treat aggressive lymphoma as second- or third-line agents. BsAbs may be valuable therapeutic alternatives for patients with relapsed/refractory lymphomas who have not responded to or are not eligible for stem cell transplant or chimeric antigen receptor (CAR) T cell therapy. Please see section "Treatments Under Investigation in Lymphoma" below for a list of clinical trials involving bsAbs and lymphoma.

SIDE EFFECTS OF BISPECIFIC ANTIBODIES

Safety concerns for T-cell engaging bsAbs include cytokine release syndrome (CSR) and neurological effects (including immune effector cell-associated neurotoxicity syndrome, 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 may also occur because of the immune response in the brain after receiving the bsAbs, and usually follow CRS. Additional toxicities described for bsAbs include fever, injection-site reactions, and low blood cell counts.

TREATMENTS UNDER INVESTIGATION IN LYMPHOMA

Several bsAbs are in development for patients with lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). The majority of bsAbs in clinical trials for lymphoma are cell-bridging and work by directing T cells (CD3) to cancer cells (CD19). A small number of registered clinical trials for this indication are testing antigen crosslinking and therapies directing NK cells to cancer cells. Please refer to the Table below to find the latest information on clinical trials involving bsAbs and lymphoma. For a complete list of all bsAbs in clinical trials for lymphoma, please visit www.clinicaltrials.gov.

AGENT (COMMERCIAL NAME)	TARGETS	CONDITION
HX009	CD47/PD-1	R/R Lymphoma
Odronextamab (REGN1979)	CD20/CD3	R/R B cell NHL
HLX301	TIGIT/PD-1	Lymphoma
AZD7789	PD-1/TIM-3	R/R Classical HL
IBI318	PD-1/PD-L1	R/R Extranodal NK/T Cell Lymphoma (nasal type)
Mosunetuzumab (BTCT4465A)	CD20/CD3	NHL, R/R NHL, DLBCL, CLL
CD30 biAb-AATC	CD30/CD3	HL, CD30-positive DLBCL, CD30-positive ALCL, CD30-positive CTCL
NVG-111	ROR1/CD3	CLL/SLL, MCL
GB261	CD20/CD3	B cell NHL, CLL
Glofitamab (RO7082859)	CD20/CD3	HGBCL, DLBCL, refractory DLBCL, NHL, transformed B cell NHL, PMLBCL and MCL
Blinatumomab (Blincyto)	CD19/CD3	NHL
Epcoritamab (Gen3013)	CD20/CD3	DLBCL, FL, NHL, HGBCL, MZL, PMLBCL, CLL/SLL, MCL

ALCL, anaplastic large cell lymphoma; bsAbs, bispecific antibodies; CLL/SLL, chronic lymphocytic leukemia; CTCL, cutaneous T cell lymphoma; DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; HGBCL, high grade B cell lymphoma; HL, Hodgkin lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; NK, natural killer; PD-1, programmed death protein 1; PD-L1, programmed death-ligand 1; PMLBCL, primary mediastinal large B cell lymphoma; ROR1, tyrosine-protein kinase transmembrane receptor; SLL, small lymphocytic lymphoma; 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 viable therapeutic option for my type of lymphoma?
- What are the benefits of bsAbs compared to conventional therapies?
- How can I enroll in a clinical trial?
- What is the goal of my treatment?
- What are the risks, possible sides effects *including CRS*, 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?
- Are there any patient assistance programs available?
- 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 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 LRF's website at www.lymphoma.org, talk to their physician, or contact the LRF Helpline for an individualized clinical trial search by calling 800-500-9976, completing LRF's online clinical trials request form, or emailing helpline@lymphoma.org.

LRF HELPLINE AND LYMPHOMA SUPPORT NETWORK

A lymphoma diagnosis often triggers a range of feelings and concerns. In addition, cancer treatment can cause physical discomfort. The LRF Helpline staff members are available to answer your general questions about a lymphoma diagnosis 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. A part of the Helpline is LRF's one-to-one peer support programs, Lymphoma Support Network. This program connects patients and caregivers with volunteers who have experience with lymphomas, similar treatments, or challenges, for mutual emotional support and encouragement. You may find this useful whether you or a loved one is newly diagnosed, in treatment, or in remission.

MOBILE APP

Focus on Lymphoma is the first app to provide patients and their caregivers 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 this resource, visit our website at lymphoma.org/mobileapp, or contact the LRF Helpline at 800-500-9976 or 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. LRF offers a Lymphoma Care Plan as a resource for patients and their caregivers. LRF'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 https://lymphoma.org/wp-content/uploads/2020/09/LRF-Care-Plan-Form_091620-1.pdf.

Resources

LRF offers a wide range of free resources that address treatment options, the latest research advances, and ways to cope with all aspects of lymphoma and CLL/SLL including our award-winning mobile app. LRF also provides many educational activities, including our in-person meetings, webinars for people with lymphoma, as well as patient guides and e-Updates that provide the latest disease-specific news and treatment options. To learn more about any of these resources, visit our website at www.lymphoma.org, or contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org.

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