

# Understanding Lymphoma: Bispecific Antibodies

## What are Bispecific Antibodies?

### MECHANISM OF ACTION—HOW DO THEY WORK?

Bispecific antibodies (bsAbs) are a new class of immunotherapy drugs designed to recognize two different targets expressed on the cell surface, called antigens. Like other monoclonal antibodies (such as rituximab, a monoclonal antibody that targets the CD20 protein present on the surface of B cells), bsAbs can be administered intravenously (IV) or subcutaneously (SC, 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 are most commonly 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 (cancer) 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 prevents 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 depends on their mechanism of action. Natural antibodies (produced by the body's immune system) 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 that 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 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 (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 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. In lymphoma, epcoritamab (Epkinly) and glofitamab (Columvi) are FDA-approved to treat relapsed or refractory 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). These drugs have thus emerged as a new class of immunotherapy with potential to treat aggressive lymphoma as second- or third-line agents. In particular, 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 "Treatments Under Investigation in Lymphoma" below for a list of clinical trials involving bsAbs and lymphoma.

## SIDE EFFECTS OF BSABS

Safety concerns for T-cell-engaging bsAbs include cytokine release syndrome (CRS) 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 they usually follow CRS. Additional toxicities described for bsAbs include fever, injection-site reactions (such as swelling, rash, or pain), 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](http://www.clinicaltrials.gov).

**Table 1. Phase 2 or 3 Clinical Trials of BsAbs in Lymphoma.**

Agent (Commercial name)	Targets	Condition
HX009	CD47/PD-1	r/r Lymphoma
Odronebamab (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)
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
Blinatumomab (Blincyto)	CD19/CD3	NHL

ALCL, anaplastic large cell lymphoma; bsAbs, bispecific antibodies; CLL/SLL, chronic lymphocytic leukemia; CTCL, cutaneous T-cell lymphoma; DLBCL, diffuse large 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; 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 (treatments widely used by health care 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 (eg., 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 decisions?

## 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 who 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 ([lymphoma.org/publications](http://lymphoma.org/publications)) and the *Clinical Trials Search Request Form* ([lymphoma.org](http://lymphoma.org)), talk to their physician, or contact the LRF Helpline for an individualized clinical trial search by calling **(800) 500-9976** or emailing [helpline@lymphoma.org](mailto:helpline@lymphoma.org).

Patients and their caregivers are encouraged to keep copies of all medical records. This includes test results as well as information on the types, amounts, and duration of all treatments received. Medical records are important for keeping track of any side effects resulting from treatment or potential disease recurrences.

## LRF FOCUS ON LYMPHOMA 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. It provides convenient and comprehensive lymphoma management 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

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## LYMPHOMA CARE PLAN AND PATIENT EDUCATION PROGRAMS

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'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](http://lymphoma.org/publications). LRF also offers a variety of educational activities, including live meetings and webinars, for individuals looking to learn directly from lymphoma experts. To view our schedule of upcoming programs, please visit [lymphoma.org/programs](http://lymphoma.org/programs).

### LRF Helpline

The LRF 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. LRF 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](http://lymphoma.org), or contact the LRF Helpline at **(800) 500-9976** or [helpline@lymphoma.org](mailto:helpline@lymphoma.org).

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

Supported through grants from:    

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