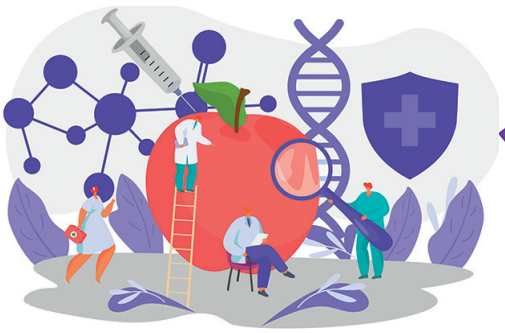
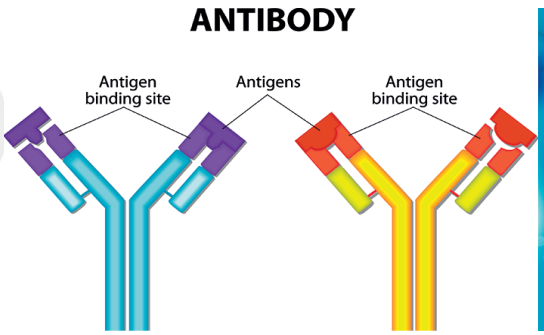
HNHCP
Haematology Nurses & Healthcare Professionals Group





Haematology Nurses and Healthcare Professionals (HNHCP)

Bispecific Antibody Immunotherapy (BsAbs):

A Resource for Healthcare Professionals

Dear Colleague

It is with great pleasure that we present the "Haematology Nurses and Healthcare Professionals (HNHCP) – Bispecific Antibody Immunotherapy (BsAbs): a resource for healthcare professionals.

As in many other disciplines, developments in haematology follow each other in rapid succession. Multiple therapeutic approaches are used in treatment of cancer, including surgery, chemotherapy, radiotherapy, targeted treatments, hematopoietic stem cell transplantation and immunotherapy. To ensure the safety and sustainability of bispecific antibody immunotherapy, it is crucial to address the physical and psychological aspects of the patient's experience. Effective communication and comprehensive management are highly valued by patients and their caregivers. All these developments mean that the content of nurses 'work has changed significantly, with increasing demands on theoretical knowledge and insight and on the ability to apply them in daily work.

Nurses and healthcare professionals will find useful information in this brochure, which will increase knowledge about Bispecific Antibody Immunotherapy, their administration and the recognition and treatment of associated toxicities. A faculty consisting of specialist nurses working in the field of haematology/oncology, haematologists, and patient advocates have collaborated to develop this program dedicated to increasing knowledge about Bispecific Antibody Immunotherapy. This program features topics relevant to the multidisciplinary team approach to caring for patients receiving Bispecific Antibody Immunotherapy and their relatives. Nurses, other allied healthcare professionals and patient organisations play an important role in this process and the group is excited to share with you the most current information and up-to-date recommendations for addressing the unique long-term management of patients' needs.

The Bispecific Antibody Immunotherapy: a resource for healthcare professionals learning program was made possible by an educational grant from Pfizer and Roche. On behalf of the Haematology Nurses and Healthcare Professionals Group and the faculty who worked on this initiative, we hope that the Bispecific Antibody Immunotherapy learning program will be of value to you in your care of patients undergoing Bispecific Antibody Immunotherapy

Sincerely,

Erik Aerts

President

Haematology Nurses and Healthcare Professionals Group

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Bispecific Antibody Immunotherapy learning program: A Resource for Healthcare Professionals is also available online at

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Contents

Summary Points:

- Bispecific antibodies (BsAbs) are engineered antibodies targeting two different antigens or two different epitopes on the same antigen
- BsAbs are used in diagnosis and therapy, including the treatment of solid tumors and hematologic malignancies
- BsAbs are off-the-shelf immunotherapy products with a reliable manufacturing process that is generally shorter than that for CAR T-cell treatment
- Like other immunotherapies, the major drawback of BsAb treatment is on-target/off-tumor side effects

Module I: Introduction to Bispecific Antibody Immunotherapy

A. Introduction

B. Historical development

C. Applications of bispecific antibodies in treating cancer

D. Comparison of bispecific antigens with other immunotherapies used in cancer treatment

E. General disadvantages of bispecific antigens

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Introduction

Therapeutic antibodies have become a key component in the array of anti-cancer treatment. The effectiveness of monoclonal antibodies, for example, is related to their specificity and mechanisms of action. They provide notable improvements in therapeutic efficacy, especially in patients with disease that is refractory to other forms of treatment.

As the name implies, a monoclonal antibody usually recognizes a single target. However, this mechanism of action may not be effective given the complexity of tumor pathogenesis, clonal evolution and the involvement of multiple mediators in signaling pathways that mediate tumor growth and/or recurrence (Goebeler 2024). The modular structure of monoclonal antibodies together with advances in protein engineering technologies has provided a basis for selecting antibody structures and protein modifications with desirable functional characteristics and binding specificities leading to the development of bispecific or multispecific antibody agents (Goebeler 2024).

Bispecific antibodies (BsAbs) are antibodies with binding sites directed at two different antigens or two different epitopes on the same antigen. BsAbs are capable of mediating therapeutic effects beyond those of natural monospecific antibodies by recruiting immune effector cells to cancer cells or by targeting different signaling pathways with a single molecule. Their uniqueness stems from their ability to exert multiple mechanisms of action simultaneously (Klein 2024).

In sum, a typical antibody (of the immunoglobulin G or IgG class) is a Y-shaped protein with two binding sites recognizing the same target. This type of antibody can attach to and neutralize a single antigen. The term „monoclonal" signifies that only one species of antibody is present. BsAbs are engineered monoclonal antibodies targeting two different antigens simultaneously; that is, each tip of the Y is designed to attach to a different antigen. BsAbs can, for example, target and attach to CD3 receptor sites on T cells and CD20 receptor sites on B cells in parallel, thus linking tumor-cell destroying CD3-positive T-lymphocytes to CD20-positive B-cell lymphoma cells.

Historical development

The original concept of BsAbs was first proposed by Alfred Nisonoff in the 1960s. Nisonoff combined 2 different antigen binding sites in one molecule and obtained a $F(ab')_2$ molecule with dual specificity. Years later, hybridoma technology was invented, which solved the problem of producing pure monoclonal antibodies and opened a new era of monoclonal antibody therapy. Further developments in the field followed but the real breakthrough came in 1996 when knobs-into-holes technology was invented. Here, a smaller amino acid is replaced with a larger amino acid (T336Y) in the CH3 region of an antibody chain to form a "knobs" structure, and in parallel substituting a larger amino acid in the other chain with a smaller amino acid to form a "holes" structure (Y407T) (Ma 2021). Subsequent progress in antibody engineering and antibody biology allowed the continued evolution of constructing BsAbs in the laboratory and their use in cancer immunotherapy.

Due to their specificity and mechanisms of action, monoclonal antibodies are a key component of anti-cancer treatment. Monoclonal antibodies, which are also laboratory-produced, have several mechanisms of action including "flagging" cancer cells to trigger an immune response, which subsequently destroys the cancer cells, preventing the growth of cancer cells, or these agents block immune system inhibitors so that the immune system can function properly to kill cancer cells. However, monoclonal antibodies can only target one antigen. Therefore, due to their ability to target two antigens, the clinical therapeutic effects of BsAbs are superior to those of monoclonal antibodies, especially due to their ability to link immune-effector cells to tumor cells.

Catumaxomab was the first BsAb to receive regulatory approval in 2009 as a treatment for malignant ascites. This agent was subsequently removed from the market in 2013, for a variety of reasons. In 2014, blinatumomab was approved for the treatment of relapsed/refractory (r/r) acute B-cell lymphoblastic leukemia (B-ALL) and in 2017, Emicizumab, which acts as a Factor VIII mimetic by linking factor IX and X, for the treatment of hemophilia A, was approved (Surowka 2014).

Due to the interest in these molecules and advances in technologies required to produce them, over 100 BsAbs have reached clinical trials with a high rate of drug approvals since 2021. From 2021 to 2023, 11 novel BsAbs were approved by health authorities in the US, Europe, Japan and/or China. Of these 11 agents, 9 were approved for the treatment of cancer of which 7 were approved for the treatment of hematologic malignancies (**Table 1**).

Generally speaking, advancements and expansion of therapeutic options have improved prognosis and overall survival for many patients with hematologic malignancies, especially in those patients who experience disease recurrence and relapse after treatment. However, the availability of more options may make it difficult for both healthcare professionals and patients to navigate through and subsequently select treatment choices.

Progress in antibody engineering and better understanding of antibody biology enabled the generation of BsAbs.

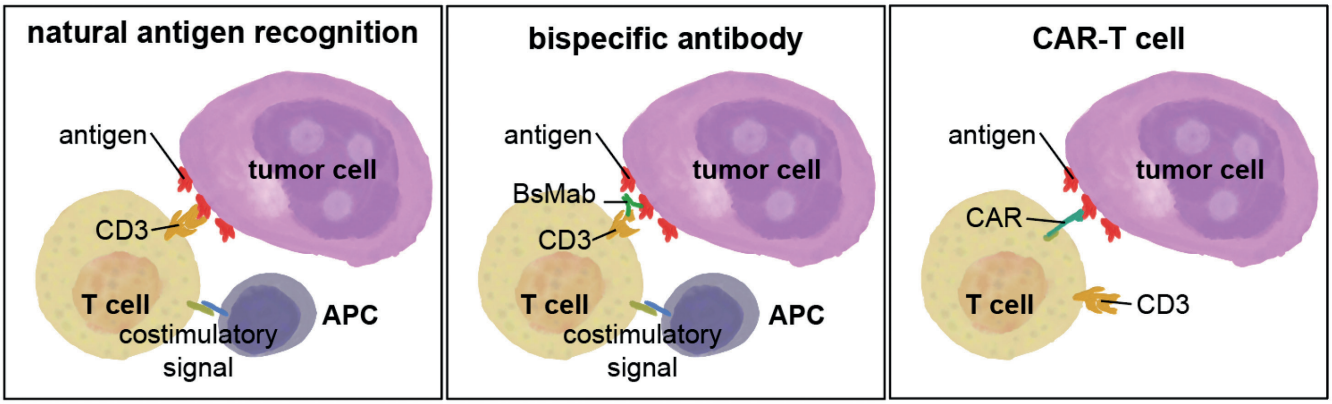

Figure 1: Comparison of T-cell mediated tumor killing. In natural antigen recognition, a cytotoxic T cell will recognize a tumor cell expressing an antigen with its CD3 receptor specific for the antigen. Another cell of the immune system, an antigen presenting cell (APC), must co-stimulate the T-cell by activating a co-stimulatory receptor on the T-cell, e.g., CD28, and typically another T-cell has to generate a co-stimulatory signal (for instance CD28 or 4-1BB. The key component of this system is the specificity of the CD3 receptor to the tumor-antigen. In the absence of such a specific CD3 receptor, tumor cell recognition can be enabled artificially with a bispecific antibody (BsAb), binding any CD3 on T-cells with one of its binding sites and linking it to the tumor antigen bound on the other binding site of the antibody. However, a co-stimulatory signal by another cell (e.g., APC) is still required for full T-cell activation. CAR T cells have a chimeric antigen receptor (CAR). This receptor is transfected into the genome of the CAR T cell and artificially designed. It will recognize the tumor antigen and bypass the natural CD3 receptor of the T-cell altogether. Additionally, the CAR contains a costimulatory domain, removing the requirement of a co-stimulatory signal by another cell and enabling self-activation of the T cell upon antigen recognition.

Unlike other anti-cancer therapies, the application of BsAbs is diverse and the potential combination of targets is flexible.

Applications of bispecific antibodies in treating cancer

In addition to anti-cancer treatment, BiAbs are being employed to treat diseases such as hemophilia A, diabetes, and ophthalmological diseases.

In terms of anti-cancer therapy, the main strategy is to use BsAbs to precisely target and reactivate immune cells, help regulate the activation of immune cells, fine-tune the fate and function of immune cells, improve the tolerance of immune cells, and promote a return to immune homeostasis [see Modules 2 and 3].

According to an article published in early 2024, more than 300 clinical trials of more than 200 different bispecific molecules of which 75% were applied to treating solid tumors and 25% to treating hematologic malignancies, are currently underway (Klein 2024). A significant number of BsAbs are in later stage (2 and 3) clinical trials.

Comparison of bispecific antigens with other immunotherapies used in cancer treatment

Chimeric antigen receptor T-cell therapy (CAR-T) is produced by extracting lymphocytes from the patient's peripheral blood by a process called leukapheresis. The T-cells in the extracted lymphocytes are expanded and transfected with the chimeric antigen receptor (CAR) using gene technology. The transfected T cells, now CAR T cells, are expanded in vitro and shipped back to the patient for infusion. This process can take several weeks and is patient-specific; that is, CAR T-cell therapy is always manufactured for a specific patient and cannot be infused into another patient.

The modified and reinfused CAR T cells can recognize all cells expressing the target antigen (on-target effect), regardless if these cells are cancer cells (on-target on-tumor) or physiological cells (on-target off-tumor). For example, anti-CD19 CAR T cells will recognize cancer cells expressing CD19 [such as precursor B-cell acute lymphocytic leukemia (ALL) or diffuse large B-cell lymphoma (DLBCL)

cells] but also most physiological B-cells, since most of them express CD19.

In contrast to CAR T-cell therapy, BsAbs can be produced in advance and are not manufactured for a specific patient, but rather in bulk. Also, BsAbs are not living cells and can be stored for longer periods of time, thus they are available off-the-shelf. Further, bispecific T-cell engagers (BiTEs, the category of BsAbs most used to treat hematologic malignancies) do not require administration of a conditioning regimen prior to administration. A major difference between BsAb and CAR T-cell therapy is the co-stimulatory activity of CAR T cells that BsAbs are currently lacking. Two signals are required to engage T cells – antigen recognition and a co-stimulatory signal. Both signals are engineered in the CAR of CAR T cells, whereas BsAbs can only enable antigen recognition by linking the target antigen to the CD3 receptor of T cells while relying on the microenvironment for co-stimulatory activation (Figure 1). As a consequence, BsAbs have lower anti-tumor activity than CAR T cells but also have a lower risk of treatment-related adverse events, such as cytokine release syndrome (CRS) (Subklewe 2021; Moon 2022) and have a lower risk of antigen loss on the tumor cell (Cho 2022).

BsAbs differ from monoclonal antibodies in that they simultaneously bind to two antigens. Binding or blocking multiple targets can be beneficial to stop disease, as most conditions have complicated multifaceted effects throughout the body. The ability to target two or more antigens simultaneously may decrease the risk of drug resistance and tumor progression compared to a monoclonal antibody, which targets one antigen. By comparison with monoclonal antibodies, BsAbs offer advantages in terms of superior cytotoxic effects (Schmid 2019).

Table 1. Approved Bispecific Antibodies and Bispecific Antibodies currently under Regulatory Review for Treatment of Hematologic Malignancies

Trade name (proprietary name)	Targets	Mechanism of Action	Indication
Approved			
Blincyto (blinatumomab)	CD19 x CD3ε	T cell engager	B-cell ALL
Lunsumio (mosunetuzumab)	CD20 x CD3ε	T cell engager	Relapsed/refractory follicular lymphoma
Columvi (glofitamab)	CD20 x CD3ε	T cell engager	Relapsed/refractory DLBCL
Epkinly (trade name in US) Tepkinly (trade name in Europe) (epcoritamab)	CD20 x CD3ε	T cell engager	Relapsed/refractory DLBCL
Tecvayli (teclistamab)	BCMA x CD3ε	T cell engager	Relapsed/refractory MM
Elrexfio (elranatamab)	BCMA x CD3ε	T cell engager	Relapsed/refractory MM
Talvey (talquetamab)	GPRC5D x CD3ε	T cell engager	Relapsed/refractory MM
Under regulatory review			
n.a. (linvoseltamab)	BCMA x CD3ε	T cell engager	Relapsed/refractory MM
n.a. (odronextamab)	CD20 x CD3ε	T cell engager	Relapsed/refractory DLBCL

ALL, acute lymphoblastic leukemia; BCMA, B-cell maturation antigen; BsAbs, bispecific antibodies; CD, cluster of differentiation; DLBCL, diffuse large B cell lymphoma; MM, multiple myeloma
Adapted from: Surowka 2024

BsAbs may present an alternative treatment for older patients with cancer because they have relatively low rates of high grade (≥ grade 3) CRS and immune effector cell-associated neurotoxicity syndrome (ICANS) due to a lack of co-stimulatory activity. Further, their availability as an off-the-shelf treatment makes them useful and convenient in community oncology settings (Gurumurthi 2023) and more readily available for those patients who cannot afford to delay the start of treatment. BsAbs do not require lymphodepleting chemotherapy (as CAR T cell-therapy currently does), and they can be dose-adjusted to fit individual patient requirements.

Which treatment is more cost effective is a topic currently being debated; both treatments are associated with high financial toxicity (Subklewe 2021). BiTEs compare favorably to CAR T cells when production costs, logistics, treatment, days of hospitalization and short- and long-term adverse events are considered (Subklewe 2021). Data on the long-term response to BiTEs and CAR T-cell therapy is needed to estimate the cost-effectiveness of these novel treatments (Subklewe 2021).

General disadvantages of bispecific antigens

Similar with monoclonal antibodies, the major concern of BsAb treatment is still the 'on-target off-tumor' side effect. This term signifies the linking of effector T cells with physiological cells expressing the tumor antigen (e.g., CD19 on physiological B cells). This side effect can lead to significant CRS and may require the administration of initial treatment in an in-patient setting or rarely in an intensive care unit (Gurumurthi 2023) [see Module 4]. However, after the first treatment cycle most cells expressing the target antigen are eliminated, significantly lowering the risk of CRS in subsequent cycles and allowing management in an out-patient setting. Close monitoring of the patient during treatment is essential to recognize and prevent more serious reactions. Alternatively, patients should be treated and managed in cell therapy centers for the first 1 or 2 cycles, followed by transition to out-patient oncology clinics to continue treatment [see Module 4].

There is to date little evidence on the long-term effects, such as immunogenicity risk, of BsAbs or the development of anti-drug antibodies that may cross-react with a related product (Bogdanowicz 2024), although the risk of these adverse effects is considered to be very low with current fully humanized antibody technology.

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Summary Points

- Through innate (also known as non-specific, natural or native) and adaptive (also known as acquired) immunity, the immune system recognizes and eliminates a variety of pathogens
- Cytokines, small proteins involved in cell-to-cell communication, can overproduce in an immune system response to infection or immunotherapy causing systemic symptoms
- T-cells can be activated by BsAbs to destroy infected or cancer cells
- Bispecific antibody (BsAb) immunotherapy is designed to simultaneously recognize two different targets expressed on the cell surface: CD3 on the surface of T-cells, and other antigens expressed on the surface of malignant cells
- T-cell engaging bispecific antibodies (or BiTES) are the most common type of BsAb now in use as a treatment for hematologic malignancies

Module II: Mechanism of Action of Bispecific Antibodies

Overview of Immune System

The main task of the immune system is to defend the body against pathogens. Through immune surveillance, all targets that are identified as non-self are attacked and eliminated. Targets include not only cells infected with pathogens such as viruses, bacteria, parasites, or harmless environmental substances, but also transformed (e.g., malignant) cells that acquire antigenicity and thus immunogenicity through the expression of neo-antigens, which can be recognized as foreign by the immune system (Sharpe 2015). All substances that are recognized as being non-self by the immune system act as a trigger for the immune response.

There are two main components of the immune system for recognizing and eliminating pathogens:

1. Innate immunity, also known as nonspecific, natural, or native immunity, which includes more primitive elements of the immune system such as macrophages, natural killer (NK) cells and antigen-presenting cells (APCs), and
2. Adaptive immunity or acquired immunity, encompassing T and B-cells (**Figure 1**)

The interaction of the immune system with cancer development is complex. Although the immune system can prevent or slow cancer growth, cancer cells can escape detection and destruction. For example:

- Undergo genetic changes that make cancer cells less visible to the immune system
- Possess proteins on their surfaces that turn off immune cells
- Transform normal cells around the tumor so they interfere with how the immune system responds to the cancer cells.

For purposes of this introduction, a review of the roles of T and B-cells in the immune system as these roles relate to the use of bispecific antibody immunotherapy will be briefly presented here.

Innate immunity

The innate immune system is activated immediately or within hours of detection of an intruding pathogen or patterns in cells not recognized as "normal". The innate immune response is an antigen-independent or non-specific defense mechanism. It was long hypothesized that innate immunity does not have a memory to recognize the same pathogen should a second exposure occur. Recently, however, scientists have proposed that innate immune responses include adaptive characteristics comparable to immunologic memory.

The main function of innate immunity is to attract immune cells to sites of infection and inflammation by producing cytokines. Cytokines are small proteins involved in cell-to-cell communication. The immune system uses a variety of different cytokines to signal cell growth, activation and function (**Box 1**). They differ not only in terms of the cell type that produces them (i.e., macrophages, masT-cells, or neutrophils), but also in the cell type that can recognize them, and the effects they induce.

Box 1. Categories of Cytokines

- Colony-stimulating factors (CSF): essential for cell development and differentiation
- Interferons: inhibit viral replication and modulate the immune response; necessary for immune-cell activation. Type I interferon mediates antiviral immune responses, type II interferon is important for antibacterial responses
- Interleukins: provide context-specific instructions, with activating or inhibitory responses
- Chemokines: produced in specific locations in the body or at a site of infection to attract immune cells. Different chemokines will recruit different immune cells to the site of infection
- Tumor necrosis factor (TNF): family of cytokines, stimulates immune-cell proliferation and activation; critical for activating inflammatory responses

Cytokines function in 3 ways:

- **Cell activation:** Cytokines direct cells to a site of infection or cell irregularity and can heighten or lessen the processes associated with inflammation.
- **Cell differentiation:** Cytokines can direct immature cells to develop into a specific type of cell. For example, direct an immature cell to mature into a white blood cell capable of fighting infection.
- **Cell proliferation:** Cytokines can direct cell replication. For example, stimulate white blood cells to reproduce.

Furthermore,

- **Pro-inflammatory cytokines** trigger or heighten inflammation by relaying messages that coordinate the immune response to fend off attackers.
- **Anti-inflammatory cytokines** stop or lessen inflammation by relaying messages that prevent an excessive immune response that can lead to tissue damage.

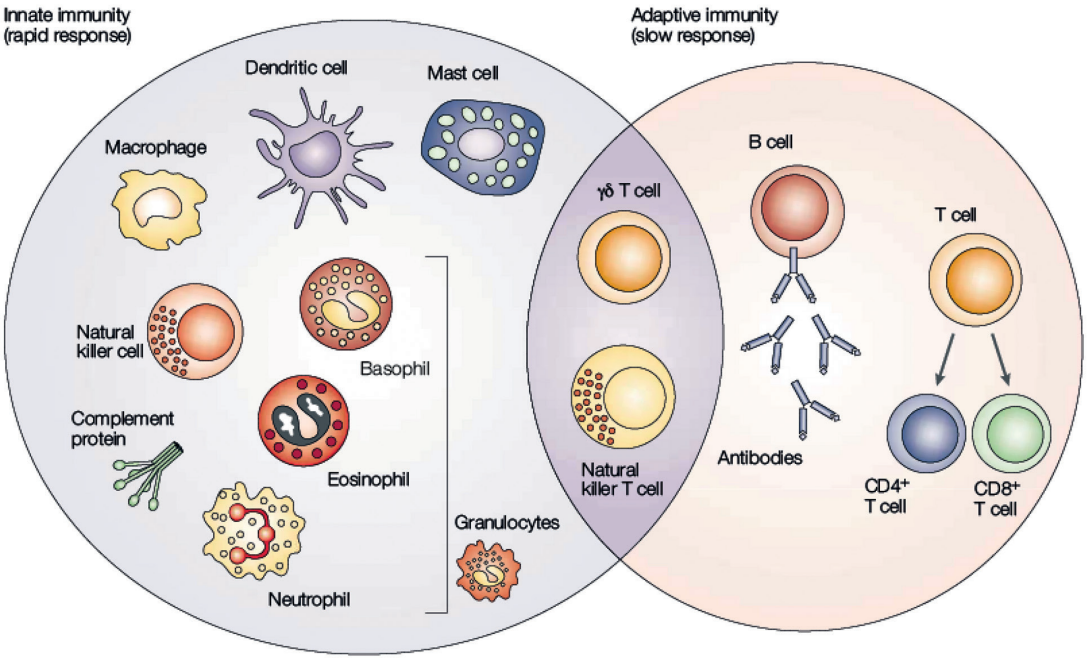

Figure 1. Overview of the cell types of the innate and adaptive immune system. All cells of the immune system are derived from a multipotent stem cell in the bone marrow. The innate immune system consists of a diverse set of cells as well as numerous soluble factors and proteins. The adaptive system consists of antibodies, B-cells and CD4+ and CD8+ cells, which enable a highly-specific response against a particular target. Source: Sharpe 2015; Dranoff 2004

Immune cells that release cytokines include:

- Macrophages
- Dendritic cells
- T and B lymphocytes
- Monocytes
- Neutrophils
- Basophils
- Eosinophils
- Mast-cells

Cytokine release syndrome (CRS) occurs with an overproduction of cytokines in response to an infection, or to immunotherapy treatment [see Module 4].

Adaptive immunity

The adaptive immune system includes T-cells and B-cells. Unlike the cells of the innate immune system, T and B-cells can identify specific features of pathogens and/or cancer cells. For example, DNA provides instructions for cell growth, survival and reproduction. A change in DNA can cause cells to divide more quickly and, in some cases, lead to malignancy. DNA can also affect cell protein production. T and B-cells can recognize subtle differences in cell function and structure and subsequently identify the cell as harmful or abnormal.

Several steps need to happen before T-cells become activated:

1. An antigen-presenting cell (APC), a cell of the innate immune system, locates an intruder and processes antigens of the intruder to a protein called major histocompatibility complex (MHC). T-cells can not recognize antigens of an intruder unless they are attached to MHC.
2. With its T-cell receptor (CD3), a T cell binds to the MHC, of which there are two types. MHC-I and MHC-II. Both are recognized by CD3; however, an additional co-receptor is required for binding. On cytotoxic T-cells, CD8 binds specifically to MHC-I while on helper T-cells CD4 binds to MHC-II. Although virtually all cells express MHC-I, only APC will express MHC-II.

3. An additional co-stimulatory signal by a bystander cell or the APC itself is required to fully activate the T cell. Typically, the CD28-receptor on T-cells is activated by CD80 or CD86 on APCs, but also the 4-IBB (CD137) receptor on T-cells can be activated to enable co-stimulation. An activated cytotoxic T cell kills infected cells or cancer cells. An activated helper T cell sends signals to other immune cells to initiate their activation to fight the intruder.

Mechanism of Action of Bispecific Antibody Immunotherapy

The field of recombinant BsAbs targeted for diagnostic and therapeutic purposes has been transformed by continually developing engineering technologies leading to a variety of BsAbs with varying size, half-life, valency, flexibility and permeability (Hosseini 2021). Recombinant DNA technology is now the most used technique for producing BsAbs.

Bispecific antibodies represent an innovative class of immunotherapy drugs designed to simultaneously recognize two different targets expressed on the cell surface. These targets are known as antigens. With this action, BsAbs can cause multiple physiological or anti-tumor responses, which may be independent or connected. Hence, the synergistic features of BsAbs may produce more significant treatment effects than those produced by monoclonal antibodies.

Most BsAbs used in cancer immunotherapy have a mechanism of action that involves T cell-driven natural or endogenous immunity, or by providing synthetic immunity through BsAb-driven engagement, activation and recruitment of immune cells (Klein 2024). The most relevant of these types for hematology oncology is effector cell engagers, including T-cell engagers. Factors that may influence tumor cell killing capabilities of BsAbs are antigen-binding affinity, molecular size, flexibility, mobility, localization of the epitope on the cell surface, BsAb format, ease of immunological synapse formation, balance between co-stimulatory and co-inhibitory molecules influencing T-cell activation, and the residual or concomitant presence of other competing therapeutic antibodies that could result in steric hindrance (Falchi 2023).

Mechanism of action of BsAbs with T-cell-engaging activity

BsAbs are divided into three categories according to their targets: 1) antibodies targeting two different tumor antigens (not currently in clinical use); 2) antibodies targeting one tumor antigen and one immune-related molecule (bispecific T-cell engagers, the most common design used for malignancies); 3) antibodies targeting two immune-related molecules (currently not in clinical use with the exception of lymphoma- and myeloma-directed therapy where the tumor antigen happens to be an immune-related molecule). T-cell-engaging BsAbs, or BiTES, belong to the second category because one BiTE molecule usually targets one CD3 molecule on the T cell and one tumor antigen simultaneously (Tian 2021). This dual binding causes the redirection and activation of T-cells to kill cancer cells resulting in the release of granzymes and perforins as well as pro-inflammatory cytokines, which then leads to HLA-independent T-cell mediated destruction of tumor cells and activation of other immune cells (Rodriquez-Otero 2024). In sum, the T-cell-engager brings the patient's immune cells (i.e., T-cells) to target the cancer cells in an efficient manner. These molecules are the most developed BsAbs for clinical use, especially as treatment for hematological malignancies, due to their ability to induce tumor-specific immune cell activation.

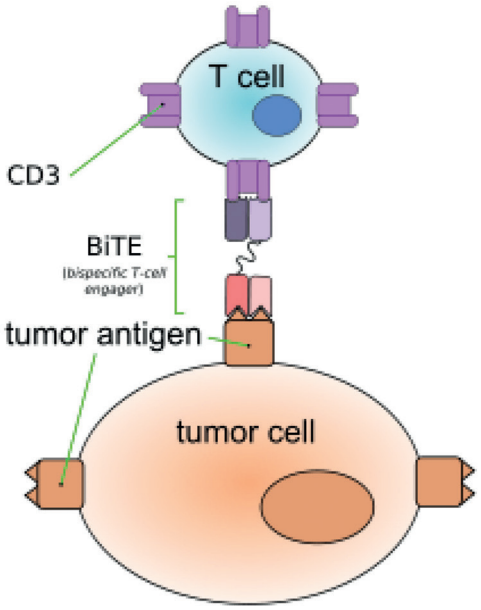

Figure 2. A BiTE linking a T-cell to a tumor cell. A primary requirement for successful therapy with BiTE therapy is the identification of appropriate tumor-associated antigens that are expressed on target cells but not expressed on normal cells to avoid on-target/off-tumor toxicity.

T-cell engagement, as described above, relies on the activation of the immune system and cannot be achieved by the combination of two conventional monoclonal antibodies. Therefore, in the treatment of cancer, the main mechanism of action – and most effective – is T cell engagement, and the largest number of approved BsAbs as well as those in current clinical trials are in this category (Surowka 2024).

Table 1. Targets of Bispecific Antibody Immunotherapy Activity		
Target	**Definition**	**BsAb / Indication**
CD3	T-cell receptor on the surface of T-cells and some NKT-cells	T-cell binding part of most T-cell engagers
CD19	A protein found on the surface of B-cells through all stages of the B-cell development process. It is also expressed by some plasma cells. CD19 plays two major roles: it acts as an adaptor protein to recruit cytoplasmic signaling proteins to the cell membrane, and it works within the CD19/CD21 complex to decrease the threshold for B cell receptor signaling pathways. Because it is found on all B-cells, it is a biomarker for B lymphocyte development. Also expressed on vascular cells of the brain and possibly responsible for severe ICANS (Parker 2020)	Blinatumomab B-cell ALL
CD20	A marker of B cell malignancies (i.e., B-cell lymphomas, B-cell chronic lymphocytic leukemia). Expressed by mature B-cells in all stages of development and on malignant B-cells. Targeting of malignant lymphoma cells and eradication of mature B-cells results in a significant but manageable immunosuppression due to a decrease in antibody levels, which may recover after years.	Mosunetuzumab, glofitamab, epcoritamab Relapsed/refractory follicular lymphoma, relapsed/refractory DLBCL
BCMA	A member of the tumor necrosis factor receptor (TNFR) superfamily. Expressed preferentially by mature B lymphocytes, with minimal expression in hematopoietic stem cells or nonhematopoietic tissue. Essential for the survival of long-lived bone marrow plasma cells. Overexpression and activation of BCMA are associated with progression of MM.	Teclistamab, elranatamab Relapsed/refractory MM
GPRC5D	G protein-coupled receptor, class C, group 5, member D is expressed on plasma cells with a cell phenotype and has little to no expression in normal B-cells, T-cells, or natural killer cells. Its specific function has not yet been determined.	Talquetamab Relapsed/refractory MM

Formats of BsAbs

Advances made in the technologies used to develop BsAbs is reflected in the growing number of BsAbs formats. Currently, there are 6 formats:

> T-cell engagers (TCE); factor VIII mimetic, dual signaling inhibition; bispecific receptor tyrosine kinase inhibitor; bispecific check point inhibitor; dual ligand inhibitor; half-life extended ligand inhibitor (Surowka 2024).

Bispecific T-cell engagers (BiTE), which consist of two binding sites simultaneously for a selective tumor antigen and CD3 molecule expressed on host T-cells, has emerged as the most promising form of BsAb immunotherapy (Wei 2022). Due to the unique characteristics of the hematologic system, malignant T-cells constantly interact with immune cells, making it easier for BiTE to exert anti-tumor activity.

A diverse selection of BiTEs has been developed and the specific targets in hematology oncology are mainly CD19, CD20, and B-cell maturation antigen (BCMA). The ideal target antigens should conform to the conditions expressed on malignant T-cells to avoid on-target/off-cancer toxicity and reduce the possibility of antigen-loss variants (**Table 1**) [see Module 5].

Targets of bispecific antibody immunotherapy

BsAbs offer an advantage over monoclonal antibodies in terms of selectivity and specificity in that they can be designed to target tumor-associated antigens on the surface of tumor cells while reducing damage to normal cells. This allows for more targeted and effective treatment with fewer side effects (Sun 2023). To further diminish adverse effects on normal cells, BsAbs targets tumor-specific antigens, which are only expressed on tumor cells, which further avoids toxicity to normal cells. Hence, BsAbs are designed with higher selectivity to redirect T-cells to TSA-expressing tumor cells.

Every cell in the body expresses several antigens, and more than 250 of them have historically been grouped numerically by cluster of differentiation (CD). The expression of antigens on tumor cells plays an important

role not only in the selection of BsAb treatment but also guides the development of new BsAb molecules.

Summary:

T-cell-redirecting strategies are a highly promising therapeutic modality for the treatment of hematological malignancies. When used to treat these malignancies, bispecific antibody immunotherapy works by linking cancer cells to healthy immune cells that attack and destroy malignant cells. Most of these molecules combine regions that bind to CD19 or CD20 on malignant B-cells and engage cancer-fighting T-cells (by binding to CD3).

Bispecific antibody immunotherapy provides a treatment that overcomes the limitations of the immune system that has failed to recognize and eliminate cancer cells.

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Notes

Summary Points

- The effectiveness of bispecific antibody immunotherapy (BsAb) in the treatment of hematologic malignancies is closely associated with the target for which they were developed, i.e., CD19, CD20, BCMA and GPRC5D.
- Blinatumomab, one of the first BsAbs to receive regulatory approval, targets malignant and benign B cells via the CD19 cell surface antigen and has shown efficacy in treating relapsed/refractory B-cell acute leukemia.
- Blinatumomab is currently the only approved BsAb for use in pediatric B-cell acute leukemia and has shown promising efficacy results in comparison to standard chemotherapy.
- Molecules used in treating multiple myeloma target either GPRC5D or BCMA antigens, both of which are found on plasma cells in some forms of multiple myeloma.
- While cytokine release syndrome is frequently reported as a treatment-emergent adverse effect of BsAbs therapy, cases, in most instances, are grade 1 or 2.
- Off-the-shelf availability and good tolerability of BsAbs may make this form of anti-cancer treatment a suitable option for older patients with cancer.

Target Selection in Bispecific Antibody Immunotherapy

The effectiveness of bispecific antibodies (BsAbs) is closely linked to the target for which they were developed. CD19 and CD20 are relatively stable cell-surface antigens found on B cells and these targets have therefore been used for most BsAbs currently approved and in development for B-cell lymphomas/leukemia. BCMA (B-cell maturation antigen) is a protein found on most multiple myeloma cells, but not usually found on healthy cells except plasma cells. Similarly, GPRC5D (G protein-coupled receptor, class C, Group 5, member D) is expressed on plasma cells. BsAbs targeted to these antigens are currently used to treat relapsed/refractory multiple myeloma (**Table 1**).

Table 1. T-cell-engager Bispecific Antibodies (BiTEs) currently approved for Treatment of Hematologic Malignancies

BsAb	Target	Indication
Blinatumomab	CD19 / CD3	B-cell ALL
Epcoritamab	CD20 /CD3	r/r DLBCL
Mosunetuzumab	CD20 / CD3	FL
Glofitamab	CD20 /CD3	r/r DLBCL
Teclistamab	BCMA/ CD3	r/r MM
Elranatamab	BCMA / CD3	r/r MM
Talquetamab	GPRC5D / CD3	r/r MM

ALL, acute lymphoblastic leukemia; BCMA, B-cell maturation antigen; DLBCL, diffuse large B-cell lymphoma; GPRC5D, G protein-coupled receptor, class C, Group 5, member D; MM, multiple myeloma; r/r, relapsed/refractory

Bispecific Antibody Immunotherapy currently used to Treat Hematologic Malignancies

B-cell precursor acute lymphoblastic leukemia (ALL)

Blinatumomab targets malignant and benign B cells via the CD19 cell surface antigen while simultaneously engaging the patient's own T-cells through the CD3 antigen. The molecule activates T-cells, resulting in the formation of a synapse between the T cell and malignant B cell. In a prospective study, the combination of dasatinib a tyrosine kinase inhibitor (TKI) and blinatumomab was safe and resulted in a 4-year overall survival (OS) of 78% for Ph+ B-cell precursor ALL (Chiaretti 2022; Foà 2020). In this study, half of the patients received allogeneic stem cell transplantation. Results indicate that blinatumomab plus a TKI might obviate the need for transplantation in most patients. Similarly good results are being shown with a chemotherapy-free regimen for newly diagnosed Ph (+) ALL when ponatinib and blinatumomab are used during induction (Short 2022).

A recently published review advocates using BsAbs in combination as front-line treatment of ALL, as this is the setting in which the chance of cure is greatest. It is the opinion of the authors, that incorporation of blinatumomab into front-line treatment regimens might allow for reduction of the intensity and duration of intensive chemotherapy and for the design of dose-dense regimens delivered over shorter periods of time (for example, less than 1 year) (Short 2023). Blinatumomab is approved by the European Medicines Agency (EMA) and Federal Drug Administration (FDA) for the treatment of r/r B-cell precursor Ph (-) ALL in adults and children older than 1 year. In June 2024, blinatumomab was approved by the FDA for use in frontline consolidation in patients with CD19-positive Ph (-) B-cell precursor ALL (FDA 2024). Of note, further development of **blinatumomab** has been hampered by a somewhat intricate administration procedure that involves continuous infusion over several weeks due to the agent's short half-life and significant neurological toxicities [see Module 4].

B-cell Lymphomas

BsAbs immunotherapies, primarily those targeting CD20, a marker known to be on B cells, and CD3 show promise in the treatment of patients with B-cell non-Hodgkin lymphoma (B-NHL) and will likely become an important addition to currently available therapeutic agents for this hematologic malignancy (Falchi 2023a). T-cell-engaging BsAbs are in continual development for the treatment of B-NHL, which is the most common non-Hodgkin lymphoma type. **Blinatumomab** was the first BsAb used in patients with r/r B-NHL, showing good response rates with durable benefit (Goebeler 2016). In heavily pre-treated patients with diffuse large B-cell lymphoma (DLBCL), blinatumomab showed high efficacy with an overall response rate of 43% and approximately 20% complete responses (CR), of which only a small number were durable (Viardot 2016; Viardot 2020).

Blinatumomab has been investigated in clinical trials in mantel-cell lymphoma. In a phase 2 study, a small group of patients with high-risk DLBCL received blinatumomab consolidation as a single continuous infusion. One cycle of blinatumomab consolidation provided a CR of 87.5% in patients who had had a partial response (PR) to front-line therapy. Adverse events that did occur were low grade (Katz 2022).

In later phase 1 and 2 studies, **mosunetuzumab** was evaluated as single-agent BsAb. In patients who had received 3 prior therapies, the overall response rate (ORR) was 35% and CR was 19% in patients with aggressive NHL, whereas in those with indolent NHL, ORR was 66% and CR was 48% (Budde 2022). In an analysis of 90 patients with r/r follicular lymphoma (FL), ORR at extended follow-up of 18.3 months was 80% and CR was 60% (Matasar 2022). These data lead to the approval of **mosunetuzumab** for patients with r/r FL after ≥ 2 prior lines of therapy by EMA and the FDA.

In patients with r/r large B-cell lymphoma (DLBCL) treated with **epcoritamab**, phase 2 trial results indicated that 39% of patients previously heavily treated had a CR at median follow-up of 12.6 months, with similar response rates in 52 patients previously treated with CAR T-cell therapy and median duration of response of 12 months. At 12 months, 80% of CRs were maintained and 67% of patients were alive. Cytokine release syndrome (CRS) of any grade was observed in 49.7% and grade ≥ 3 in 2.5% (Thieblemont 2023). A phase 3 trial of epcoritamab vs physician's choice in patients with r/r DLBCL ineligible for curative therapy is underway (Falchi 2023a). **Epcoritamab** is also being investigated in a phase 3 trial evaluating epcoritamab in combination with standard therapy, R-CHOP, in newly diagnosed DLBCL, and in a trial evaluating epcoritamab in combination with other cytotoxic agents in patients with r/r FL (Genmab 2023). **Epcoritamab** is approved for treatment of r/r DLBCL after 2 or more lines of therapy by both EMA and the FDA and received conditional approval in August 2024 by EMA for the treatment of adults with r/r FL after two or more lines of systemic therapy.

Safety data for the approval of **glofitamab** come from a phase 1 / 2 trial in patients with r/r DLBCL after ≥ 2 lines of prior treatment. An analysis of 155 patients indicated that CRS was the most common adverse event (63% of patients) and adverse events of grade ≥ 3 of any type occurred in 62%. Efficacy data showed that at 12 months, 39% had a CR with a median time of 42 days to CR. The 12-month PFS was 37% (Dickinson 2022). **Glofitamab** is approved for use in patients with DLBCL by both EMA and the FDA. 78% of CR were ongoing at 12 months and 50% of patients were alive. (Dickinson 2022). In that study, 63% of patients experienced CRS, which was grade ≥ 3 in 4%.

Glofitamab is administered for a fixed duration of maximum 8.3 months. **Glofitamab** is approved for use in patients with r/r DLBCL after 2 or more systemic lines of therapy by both EMA and the FDA.

A phase 3 trial of **glofitamab** in combination with GemOx chemotherapy vs R-GemOx in patients with r/r DLBCL not otherwise specified treated with at least one line of systemic treatment, showed significant OS and CR improvement, 25.5 months vs 12.9 months and 58.5% vs 25.3%, respectively, with a safety profile consistent with the known risks of the individual study drugs (Abramson 2024).

Glofitamab is also being investigated in a phase 3 trial evaluating glofitamab in combination with other cytotoxic agents, P-R-CHP, in newly diagnosed DLBCL (Clinical trial NCT06047080).

Glofitamab has also been evaluated in a phase 2 study in patients with previously untreated DLBCL and a high burden of disease. In combination with R-CHOP, interim CR rate was 46.7% and CR at end of treatment was 80% and ORR was 93.3%. BsAb-related adverse events were neutropenia (grade 3-4, 45.8%) and CRS (grade 1-2, 20.8%; grade 3-4, 0) (Falchi 2023b). In patients with r/r DLBCL who had disease progression after treatment with CAR T-cell therapy and for which there is no established standard therapeutic procedure, monotherapy with glofitamab provided an ORR of 67% and 4 patients achieved a CR after 12 cycles of treatment. Because circulating CAR T-cells were found in peripheral blood in several patients, the authors suggest that glofitamab may enhance residual CAR T-cell activity (Rentsch 2022).

BsAb treatment in older patients

For older patients, BsAbs may represent a treatment option that is better tolerated in comparison to standard chemotherapy or to CAR T-cell therapy because of off-the-shelf availability. In a small trial of 54 elderly/unfit patients with mostly high-risk DLBCL or high-grade B-cell lymphoma (HGBCL), **mosunetuzumab** provided an ORR of 56% and a CR of 43%. Common (> 10%) treatment-emergent adverse events were rash (31%), CRS (26%), and fatigue (26%). Further, about 65% of those who achieved a CR remained in a CR beyond 12 months with a median duration of response of 35 months. **Mosunetuzumab** is now being investigated in combination with other frontline therapies and in the consolidative setting in this population (Olszewski 2022). However, community use of BsAbs in older patients may be limited due to reported incidences of grade 2 CRS events, which may necessitate hospitalization in 15% for **epcoritamab** in patients with LBCL, 17% for **mosunetuzumab** in patients with FL, 12% for **glofitamab**, and 19% for **odronextamab**[1] in patients with DLBCL (Thieblemont 2022; Dickinson 2022; Abramson 2021; Bannerji 2022). Encouragingly, CRS often occurred in these studies in cycle 1 during step-up dosing soon after infusion and was observed to have a short duration lasting from 1 to 3 days and rarely required intensive care unit admissions. A solution might be to treat older patients in designated cell therapy centers for the first 1 or 2 cycles of treatment (Gurumurthia 2023).

The case for using BsAbs as an alternative to CAR T-cell therapy in r/r lymphoma is compelling, given less frequent toxicity and the capacity to manufacture to scale as off-the-shelf product thus providing rapid access (Gurumurthi 2023).

Multiple myeloma

Multiple myeloma (MM) is the second most common hematologic malignancy of adults in the Western world. While newer treatments have improved survival and provided a better quality of life, patients with adverse cytogenetics or high-risk disease have less favorable outcomes. The development of BsAbs represents a game-changer in MM, although their potential is limited by the immunosuppressive tumor microenvironment, which may limit efficacy. However, by using the patient's immune system to destroy the malignant plasma cells, BsAbs offer a promising treatment to overcome immunosuppression for patients with r/r MM (Lancman 2021).

Teclistamab was the first BsAb to receive FDA and EMA approval for the treatment of r/r MM. It re-directs T-cells through two cellular targets (BCMA and CD3) to activate T-cells and subsequent lysis of BCMA-expressing myeloma cells (Moreau 2022). Approvals were based on the results of the phase 1 / 2 MajesTEC-1 study. After a median follow-up of 14 months, the ORR was 63% and 39% of patients achieved a CR or better. The median duration of response was 18 months (Usmani 2021). Thus, the MajesTEC-1 study indicated that treatment with teclistamab resulted in deep and durable responses (Moreau 2022). The most frequent adverse events were CRS (72% of study participants), infections (76%, of which 45% were grade 3 to 4 events), and neurological events (14.5%): almost all the events were grade 1 or 2 and mostly occurred during the step-up and cycle 1 dosing (95% of cases) (Moreau 2022). Teclistamab is currently being evaluated in several monotherapy and combination studies in various lines of therapy. Teclistamab is approved for the treatment of r/r MM in patients who have received at least four prior lines of therapy (Janssen Biotech 2024).

Elranatamab is a bispecific BCMA-directed cell engaging antibody that binds BCMA on plasma cells, plasma blasts, and MM cells and CD3 on T-cells leading to cytolysis of the BCMA-expressing cells. It received approval from the FDA and EMA in 2023 following publication of the MagnetisMM-3 study, which showed an ORR of 61%, with a median duration of response not reached and a median progression-free survival of 17.2 months in patients with r/r MM. Adverse events reported in the study were hematological toxicity (> 80%), CRS (58%), and infection (67%) (Lesokhin 2023).

Talquetamab is a subcutaneous GPRC5D / CD3 BsAb approved by the EMA and FDA in 2023 for the treatment of r/r MM in patients who have received at least four prior lines of therapy (Janssen Biotech 2024). Accelerated approval was based on the results of the MonumenTAL-1 phase 1 / 2 study, which showed an ORR of 74% and 73% with a 0.4 mg/kg and 0.8 mg/kg dose, respectively. Median progression-free survival was 7.5 months with the 0.4 mg/kg dose and 11.9 months with the higher 0.8 mg/kg dose. Serious adverse events were observed in 47% with few patients discontinuing therapy due to events. Hematological toxicity was common as were other non-hematologic events such as CRS (76%) dysgeusia (47%), infection (61%) nail disorders (50%) musculoskeletal pain (43%) and skin disorders (41%) (Chiari 2022).

[1] As of June 2024, odronextamab is under regulatory review for approval by EMA and the FDA for use in treating r/r FL and in r/r DLBCL. /

Bispecific Antibody Immunotherapy in Pediatrics

Blinatumomab is currently the only approved BiTE for use in pediatrics. Clinical trials have shown that blinatumomab could effectively treat r/r B-cell precursor ALL with a better overall survival and CR than salvage chemotherapy (Kantarjian 2017). A phase 1 / 2 trial of 70 children with r/r B-cell precursor ALL CR within the first 2 cycles was achieved by 39% of the participants, of which 52% were minimal residual disease negative (Stackelberg 2016). A phase 3 trial in children with first relapses of B-cell precursor ALL, and patients treated with blinatumomab had significantly better 2-year disease-free survival compared with patients randomized to chemotherapy. More recently, an international study found that 59% of children with multiply r/r disease achieved a CR within two cycles of blinatumomab and 65% proceeded to allogeneic transplant with a trend toward improved OS in this cohort through the follow-up period of 18 months (Locatelli 2020). By substituting one cycle of blinatumomab for a third cycle of consolidative chemotherapy in children with high-risk, first-relapse B-cell precursor ALL, event-free survival was significantly improved in a European study (Locatelli 2021). Used in maintenance therapy, blinatumomab shows promise in reducing chemotherapy and shortening treatment time. Combination treatment with tyrosine kinase inhibitors or immune check point inhibitors is currently being evaluated in clinical trials (Zhao 2019).

While **blinatumomab** exhibits a favorable overall toxicity profile, it still presents distinct and potentially significant adverse effects. As in adults, CRS and neurotoxicities occur in children requiring strict observation during infusion. The short half-life of blinatumomab necessitates long infusion times, which may be challenging for pediatric patients (Wei 2022). Alternative means of more convenient and patient-friendly administration, such as subcutaneous or extended half-life intravenous infusions, could be considered an unmet need for children receiving blinatumomab (Lyons 2024).

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Notes

Summary Points

- Prior to initiation of bispecific (BsAb) T-cell engaging immunotherapy, patients should be screened for active infection, proper organ (i.e., cardiac) and bone marrow function, and comorbidities.
- Due to the associated significant toxicity profile of BsAb immunotherapy, it is highly advisable to provide patients and their caregivers with appropriate and sufficient information on side effects, how to recognize them, and when to seek assistance from a healthcare professional.
- Step-up dosing is rather unique to BsAb immunotherapy; the rationale for using step-up dosing is that these molecules are T-cell engagers, which means the T cells are engaged and subsequently activate other immune cells. In response, B cells release cytokines leading to sometimes severe adverse effects.
- Cytokine release syndrome (CRS) most often occurs with BsAb immunotherapy during step-up dosing and can be severe if not treated early and appropriately
- Neurotoxicity associated with T-cell engagers is infrequent and can develop concurrently with, or shortly after CRS, or alone and is characterized by headache, confusion, and seizures.

Module IV: Administration and Side Effects of Bispecific T-cell Engaging Immunotherapy

A. Introduction

B. Patient Preparation

- i. Patient selection
- ii. Patient and caregiver education

C. Techniques for encouraging and supporting Shared Decision-making

D. Administration Procedures

- i. Premedication

E. Adverse Events

- i. Cytokine release syndrome (CRS)
  - a. Prophylaxis
  - b. Grading
  - c. Management
  - d. Dose modifications and retreatment
- ii. Neurotoxicity
  - a. Clinical manifestations
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  - c. Management
- iii. Infections
  - a. Prophylaxis
  - b. Management

F. Evaluation and Management of Other Common Side Effects of T-cell Engager Bispecific Immunotherapy

G. Influence of Bispecific Antibody Immunotherapy on Health-related Quality of Life

References

Introduction

Bispecific antibodies currently in use as monotherapy for patients with heavily pretreated hematologic malignancies have demonstrated remarkable response rates. Currently, all of these molecules (blinatumomab, teclistamab, elranatamab, talquetamab, mosunetuzumab, glofitamab, and epcoritamab) are classified as T-cell engagers or BiTEs. The administration of these molecules is performed in steps to reduce the risk and severity of cytokine release syndrome (CRS), the most common – and dangerous – adverse event associated with BiTEs due to their activation of T cells. More positively, the toxicity profiles of BiTEs seem to be associated with a lower incidence and severity of key toxicities such as CRS and neurotoxicity than CAR T-cell therapy, which means they could be administered to a wider patient population in a broader range of treatment settings (Crombie 2024). The development of BsAbs with targets different from those already identified (i.e., CD3, CD19, CD20, BCMA and GPRC5D) may change the type and scope of side effects experienced by patients.

This Module will address not only the safe administration of BiTEs, but also the prophylaxis, early recognition and management of common BiTE-related immune activation toxicities and their implications for healthcare professionals as well as patients and caregivers.

Patient Preparation

Patient selection

Performance of a comprehensive physical assessment and the performance of routine baseline laboratory testing are advisable prior to inhiation of BsAb immunotherapy. Patients should be screened for active infection, proper organ (i.e., cardiac) and bone marrow function, and comorbidities (Ludwig 2023). It may be necessary to defer treatment if active infection is present or to conduct a more thorough cardiac examination and possibly change treatment setting to accommodate emergency interventions if cardiac comorbidities are identified. Screening for nutritional risk can provide the implementation of appropriate multidisciplinary measures before nutritional issues become severe with the potential to delay or possibly prevent treatment.

Older patients

Because there is no typical older patient with cancer, chronologic age and biologic (or functional) age can differ widely in individual patients, adding a layer of complexity to treatment decision-making. Chronologic age can be influenced by the aging process, physiologic reserve and comorbidities as well as by social environment and health behavior.

Because of the interplay of various conditions in the older patient (i.e., comorbidities, polypharmacy, cognitive impairment, depressed mood and fall risk to name a few) all older patients should be evaluated by geriatric screening and/or assessment to identify deficits in their health and functional status including their nutritional status prior to commencing treatment with BsAbs. Nutritional deficits in this population have been associated with a higher risk of mortality (Aaldriks 2013; Zhang 2021; Zhang 2019) and a major risk factor for poor treatment responses (Murry 1998).

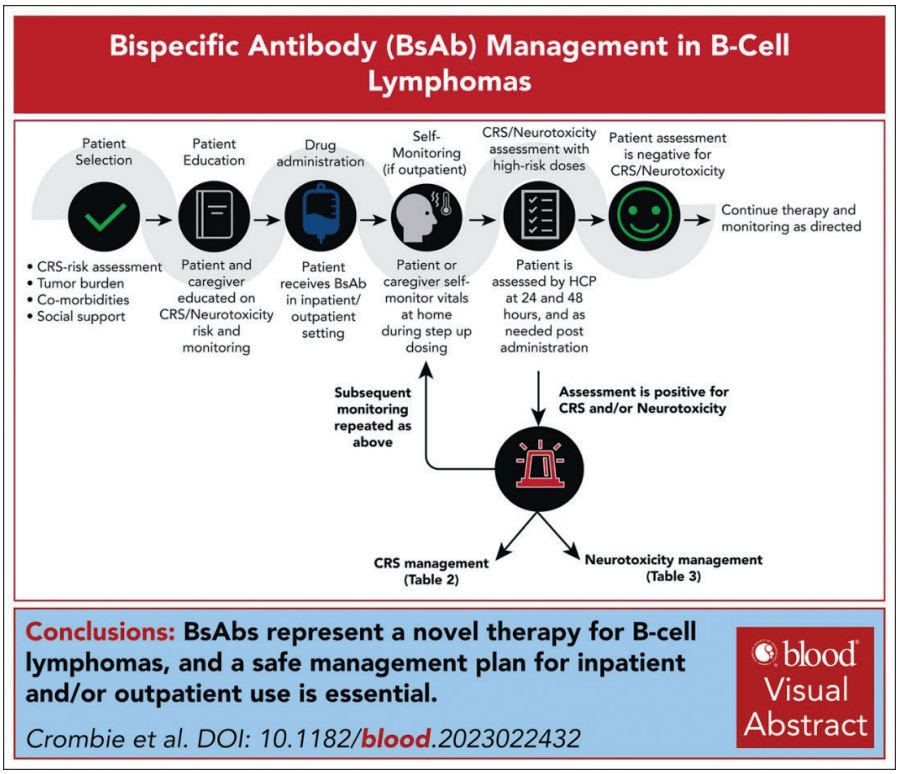

Figure 1. Sample flow diagram of the management of patients int-ended to receive BsAb immunotherapy.
Source: Crombie 2024

Table 1. Education Topics to Address with Patient/Caregiver

Topic	Educational content
Information on BsAb treatment	Dose, scheduling, route of administration, treatment duration, pre-medications, goal of treatment
Treatment toxicities (general)	What they are, when they occur, signs and symptoms, measures for self-monitoring and frequency. Possibility of hospitalization to manage treatment toxicities.
CRS symptoms to monitor for	Temperature ≥ 38° C Pulse: > 110 bpm or > 20 bpm from baseline (at rest); irregular heartbeat BP: increase in systolic BP of > 10 mmHg and/or < 90 mmHg
Neurotoxicity symptoms to monitor for	Confusion; difficulty with speech or concentration, difficulty staying awake; abnormal actions; headache, feeling anxious; seizures
Increased risk of infection	Monitor temperature: In the home setting 3 times per day for the first 48 hours after each step-up dose administered in the ambulatory clinic setting
General considerations	Instructions to notify HCP of any changes in general state (i.e., headache, dizziness, body aches, nausea/vomiting). Caution not to drive or use heavy machines for approximately 48 hours after step-up doses or in the presence of neurologic changes
Emergency contacts	When to contact healthcare professionals, who to contact, when to seek assistance at a designated emergency department and what information to provide when there. HCP to provide emergency contact information

BP, blood pressure; BsAb, bispecific antibody immunotherapy; CRS, cytokine release syndrome; HCP, healthcare professional
Sources: Rivera 2020

Patient/caregiver education

Another important step before the actual administration of BsAb immunotherapy is the provision of patient/caregiver information (**Figure 1**). Due to the associated significant toxicity profile of BsAb immunotherapy, it is highly advisable to provide patients and their caregivers with appropriate and sufficient information to be able to provide informed consent. A healthcare professional with knowledge of BsAb immunotherapy should deliver information on the risks and benefits of this treatment in language easily understood by patients/caregivers and be available to follow-up with patients should further questions arise.

Patient education, which includes verbal and written information on side effects, self-monitoring, management of events, and information on who to contact should an emergency situation arise is essential for prompt symptom recognition, reporting, and management (**Table 1**) (Crombie 2024; Taylor 2019). Follow-up to assess patient understanding of educational materials and to assess any changes in the home setting should take place at regular intervals.

Patients and caregivers should be taught to recognize substantial changes in vital signs and clinical symptoms of hypoxia or hypotension. It is helpful if patients/caregivers are given baseline vital sign data to be used as a comparison if needed.

It is suggested that patients carry a card in their wallet, which states that they have received BsAb treatment, the potential side effects, and relevant contact information of the treating facility (Crombie 2024).

Techniques for encouraging and supporting Shared Decision-making

Shared decision-making is an important aspect of patient-centered healthcare. Shared decision-making may be especially important for patients with relapsed or refractory hematologic malignancies as there is often no uniform standard of care, making treatment selection complex. Also, with relapse, the challenges experienced during the initial diagnosis often resurface and may become exacerbated (Hulin 2017). In this setting, there may be more opportunity for healthcare professionals and patients to tailor treatment decisions based on clinical factors and patient pReferences , values and goals (Kane 2014). Features of shared decision-making include a) educating the patient about treatment options and inviting patient participation in decision-making, b) assessing the patient's decisional role pReferences , c) discussing each treatment option, and d) supporting the patient's exploration of treatment options before making a treatment decision (Elwyn 2012; Legare 2013).

According to literature review, there are three critical but modifiable barriers in communication and treatment decision-making in the hematologic malignancy setting.

1. Clinicians often underestimate the information needs of patients with hematologic malignancies as well as the desired types of information
2. Clinicians perceptions of treatment values and goals often do not align with those of the patient
3. Clinicians and patients report conflicting perceptions of roles in treatment decision-making, with patients often preferring a shared or active role, which is a view not often shared by the clinician (Covvey 2019).

Unfortunately, relatively few clinical studies have investigated treatment pReferences and how these pReferences are shaped by long-term experiences of cancer survivorship. One small qualitative study investigated and identified through patient interview, four characteristics of treatment identified by patients as having high priority and four as having lower priority (**Box 1**).

Another study performed a review to identify barriers to treatment decision-making as reported in the literature in hematologic malignancies. These were: clinician misperceptions of patient values and treatment goals; discordant perceptions of patient role preference during treatment decision-making; clinician language style (LeBlanc 2019). Of interest, from the results of a Cochrane systematic review on using decision aids (i.e., pamphlets, videos or web-based educational tools on treatments, treatment options, etc.) to support patient decision-making (not specifically addressing a population of cancer patients), the use of decision aids makes patients feel more knowledgeable, better informed, and clearer about what matters most to them. Furthermore, when provided with these types of aids, they probably have more accurate expectations of benefits and harms, and probably participate more in decision-making. The use of decision aids may help patients to achieve decisions that are consistent with their values and patients are more likely to enter into discussions with their physician about treatment plans (Legare 2017).

In addition to decision aids as described above to support shared decision-making, some authors advocate using communication tools to assess patient treatment goals and values regarding outcomes (e.g., efficacy, safety, quality of life), gather information about the patient's preferred level of involvement in the decision-making process, and assessment of information gaps to ensure patient understanding (Bylund 2023). Although only previously evaluated in the setting of patients with solid tumors, one tool to support shared decision-making is the 9-item Shared Decision Making Questionnaire (SDM-Q-9) (Wu 2019). Involving caregivers with opportunities for information exchange outside of the medical encounter (Hubbard 2010) and involvement of a broader range of members of the multidisciplinary team as well as attention to cultural diversity may all help to support shared decision-making (Kane 2014).

Nurses working in oncology play a crucial role in helping patients navigate and understanding the key decisions they may be facing. Their broad base of knowledge and experience related to the medical side of difficult decisions about symptom management and disease treatment that may affect life expectancy and quality of life and their close relationship with patients and families provides insights into patient pReferences and values and enables nurses to play a crucial role in shared decision making – even if they do not recognize their influencing role (**Table 2**) (Olling 2021).

Box 1. List of treatment characteristics of high or lower priority as identified by patients with relapsed/refractory malignant myeloma

Higher priority	
Life expectancy	The amount that a treatment prolongs life (or not)
Physical side effects	Does not increase common side effects such as fatigue
Cognitive side effects	Does not contribute to memory or concentration problems
Financial impact	How the costs of treatment are covered (e.g., by government, insurance)
Lower priority	
Mode of administration	How treatment is given (i.e., orally at home or IV at hospital/clinic
Treatment intervals	Allows for "down-time" or "off-treatment" breaks during treatment periods
Psychological/emotional side effects	Treatment side effects are predictable so that you can make plans
Sleep and mood side effects	Does not increase sleep disturbances and mood swings

Source: Parsons 2019

Table 2. Nursing Roles in Shared Decision Making	
Role	**Activities**
Care-team member	Resolve conflicts within the multidisciplinary team and support the shared decision-making process while remaining objective about the best option. Close contact with patients allows direct participation in shared decision making.
Decision coach	Frequent patient contact allows nurses to provide nondirective support. Assessment of patient's decisional needs to tailor decision support activities based on needs, monitor and facilitate progress in implementation of decisions; support patients in clarification of values and desired goals of outcomes
Patient advocate	Nurses use their oncology knowledge and experience to help patients integrate complex cancer-care information with personal pReferences including those related to quality of life; nurses advocate for the patient's pReferences as members of the multidisciplinary team
Ongoing liaison	Nurses act as intermediary to present patient's perspective to other members of the team; in this role, they bridge the gap between healthcare professionals and patients/families. Nurses perform on-going assessment of potential decisional conflicts and/or feelings of decision regret
Adapted from: Olling 2021	

Dosing and Administration Schedules for T-cell Engager Bispecific Immunotherapies

Step-up dosing is rather unique to BsAb immunotherapy. The rationale for using step-up dosing is that these agents are T-cell engagers, which means the T-cells are engaged to kill the target. In a reaction to the "attack", B cells release cytokines. If an overactivation of immune cells occurs, the result can lead to CRS and/or immune effector cell-associated neurotoxicity syndrome (ICANS). Starting with low doses can help to "prime" the immune system or debulk the disease and lessen the risk of CRS (Lim 2024). The treatment schedule for blinatumomab uses a single step-up dosing (about 1/3 of the full dose), the other BsAbs use double step-up dosing or triple step-up dosing (weekly or biweekly dosing) (**Table 3**). The first step-up dose generally ranges from 1/300 to 1/3 of the full dose and the second step-up dose is between 1/60 and ½ of the full dose. The step-up dose schedule usually considers the resolution of any adverse events that have occurred before administering a second dose (Lim 2024).

The effect of the "priming" dose may be lost if drug administration is interrupted or delayed due to the presence of infection or the presence of adverse events that need to be resolved before continuation of treatment. Restarting the dose after interruption or delay should be evaluated on an individual basis and some pharmacokinetic data (Elmeliegy 2024). If a treatment interruption longer than approximately 6 weeks occurs once the full dose has been reached, it may be necessary to repeat the priming and escalation doses.

Administration of most BsAbs using subcutaneous (SC) injection offers several advantages over intravenous (IV) administration. Subcutaneous dosing can improve patient convenience and compliance over IV infusion but most importantly, slower absorption with SC dosing could reduce the risk of CRS and other adverse events and increase dose intensity (Ball 2023).

Lastly, in addition to differences in the route of administration, duration of administration differs between BsAbs. For example, mosunetuzumab and glofitamab have fixed schedule regimens, whereas teclistamab and talquetamab are administered until disease progression or toxicity is detected.

> Healthcare professionals involved in the administration of T-cell engager BsAbs immunotherapy are advised to consult the manufacturer's prescribing information for molecule-specific instructions on dosing schedules and on treatment-related toxicities and their management. The internet addresses for the manufacturers of the molecules described in this Module are provided in the References section.

Administration Procedures

Most manufacturers recommend that these molecules be administered by a qualified healthcare professional (HCP) with appropriate medical support to manage severe reactions such as CRS and ICANS.

Premedication

Premedication, including the use of prophylactic corticosteroids, should be administered according to the prescribing label for each BsAb (Crombie 2024). Generally,

Table 3. Dosing Schedules for T-cell Engager BsAb Immunotherapies approved to Treat Hematologic Malignancies

BsAb	Route	Step-up dosing	Weekly/subsequent dosing	Notes
Blinatumomab (Blincyto®) B-cell ALL with MRD	IV		**Induction: Days 1-28,** 28 mcg/day continuous IV using infusion pump **Consolidation: Days 1-28**, 28 mcg/day	Hospitalization recommended for first 9 days of first cycle and first 2 days of second cycle. Supervision by HCP or hospitalization recommended for subsequent cycle starts and re-start
Blinatumomab (Blincyto®) B-cell ALL, r/r	IV	**Induction Cycle 1:** Days 1-7, 9 mcg/day Days 8-28, 28 mcg/day **Induction Cycle 2:** Days 1-28, 28 mcg/day	**Consolidation Cycles 3-5:** Days 1-28, 28 mcg/day **Continued therapy Cycles 6-9:** Days 1-28, 28 mcg/day	Hospitalization recommended for the first 9 days of first cycle and the first 2 days of second cycle. For all subsequent cycle starts and reinitiation (i.e., treatment interrupted for 4 or more hours), supervision by HCP or hospitalization recommended
Mosunetuzumab (Lunsumio®) r/r follicular lymphoma	IV	**Cycle 1** Day 1, 1 mg; Day 8, 2 mg; Day 15, 60 mg **Cycle 2** Day 1, 60 mg	**Cycles 3+** Day 1, 30 mg	
Glofitamab (Columvi®) r/r DLBCL, DLBCL, follicular lymphoma	IV	**Cycle 1** Day 1, Obinutuzumab 1000 mg; Day 8, 2.5 mg; Day 15, 10 mg **Cycle 2** Day 1, 30 mg	**Cycles 2-12** Day 1, 30 mg	Administer in a setting with immediate access to medical support to manage CRS. Specific dosing instructions should be followed for restarting glofitamab.
Epcoritamab (Epkinly®) (Tepkinly®) r/r DLBCL, high-grade B-cell lymphoma	SQ	**Cycle 1** Day 1, 0.16 mg; Day 8, 0.8 mg	**Cycle 1** Day 15, 48 mg; Day 22, 48 mg **Cycles 2 & 3** Days 1, 8, 15, 22, 48 mg **Cycles 4-9** Days 1 & 15, 48 mg **Cycle 10+** Day 1, 48 mg	Hospitalization for 24 hours after administration of Cycle 1, Hospitalization with Day 15 dose of 48 mg (full dose)
Teclistamab (Tecvayli®) r/r MM	SQ	Day 1, 0.06 mg/kg Day 4, 0.3 mg/kg	Day 7, 1.5 mg/kg Then: weekly until disease progression	Hospital admission strongly advised during step-up dosing for CRS monitoring
Talquetamab (Talvey) r/r MM Weekly	SQ	Day 1, 0.01 mg/kg Day 4, 0.06 mg/kg	Day 7, 0.4 mg/kg Then: weekly until disease progression	Hospital admission strongly advised during step-up dosing for CRS monitoring
Talquetamab (Talvey®) r/r MM Biweekly	SQ	Day 1, 0.01 mg/kg Day 4, 0.06 mg/kg Day 7, 0.4 mg/kg	Day 10, 0.8 mg/kg every 2 weeks until disease progression	Hospital admission strongly advised during step-up dosing for CRS monitoring
Elranatamab (Elrexfio®) r/r MM	SQ	Day 1, 12 mg Day 4, 32 mg	Day 8: 76 mg through week 24 Week 25: 76 mg biweekly	Hospitalization for 48 hours after administration of the first step-up dose, and for 24 hours after administration of the second step-up dose.

ALL, lymphoblastic leukemia; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; HCP, healthcare professional; IV, intravenous infusion; MM, multiple myeloma; MRD, minimal residual disease; r/r, relapsed/refractory; SQ, subcutaneous injection; Sources: Amgen (blinatumomab); Genentech (mosunetuzumab); Genentech (glofitamab); Genmab (epcoritamab); Janssen (talquetamab); Janssen (teclistamab); Pfizer (elranatamab)

a combination of acetaminophen (an antipyretic and analgesic), diphenhydramine (an antihistamine), and corticosteroid are recommended. Dexamethasone is preferred as it is associated with a trend toward lower incidence of CRS than with other corticosteroids.

Adverse Events

The adverse effects of T-cell engager BsAbs immunotherapy stem from the pharmacological effect of these agents, which is based on mounting an immunological attack towards tumor-associated antigens that causes both T-cell proliferation and tumor cell lysis (Geraud 2024). As is true for all anticancer agents that target tumor associated antigen, toxicities are either an expected "on-target" effect related to tumor associated antigen, or an unexpected "off-target" effect that is unrelated to tumor associated antigen. The safety profile of "on-target" adverse effects varies depending on the type and extent of effect that the tumor-associated antigen has on healthy tissue.

Cytokine release syndrome (CRS) is the first occurring and most common systemic reaction to T-cell engagers. Other main adverse events reported with T-cell engagers are neurological adverse events such as immune effector cell-associated neurotoxicity syndrome (ICANS), infections, tumor flare reactions and cytopenias (Geraud 2024). Adverse events associated with T-cell engagers are highly related to the treatment dose intensity. The adverse event profile of T-cell engagers is relatively constant and predictable, and events generally occur during step-up dosage or just after administration (Geraud 2024). However, the onset and severity of known adverse events can be affected by certain patient-, disease- and treatment-related risk factors (**Table 4**).

Cytokine release syndrome

Although CRS is also a common side effect of CAR-T cell therapy and other immune effector therapies, the timing of onset, quality, and severity in its occurrence with T-cell engaging therapies is different (Crombie 2024). Furthermore, CRS is a major challenge to the further development of T-cell engaging BsAbs.

Signs and symptoms of CRS are very similar to those of an infusion-related reaction; infusion-related reaction symptoms correspond to allergic symptoms with hypersensitive reaction, whereas CRS symptoms correlate with febrile reaction due to inflammatory immune response induced by the activity of the therapy. The infusion related reaction often precedes CRS. For purposes of this text, these two events will be described together as CRS.

The appearance of fever, which may be an isolated sign, can be complicated by severe reactions if CRS is not identified and treated early. Signs and symptoms of a severe reaction include hypotension, tachypnea, hypoxemia, organ dysfunction. Because the signs and symptoms of CRS may overlap with those of infections or other disorders, a detailed medical history, physical examination and laboratory tests should be performed in all patients with suspected CRS.

Table 4. Risk Factors for Specific Adverse Events occurring with T-cell Engager BsAb Immunotherapy

	CRS	ICANS	Infections
Patient-specific	Co-morbidities; infections	CRS; younger age; pre-existing neurological conditions	Age; comorbidities; previous frequent episodes of infections; CRS; lymphopenia (B-cell and T-cell deficiency); neutropenia;
Disease-related	Tumor burden	Tumor burden	Refractory, poorly controlled disease
Treatment-related	Higher dose of BsAbs		High-dose and long duration of glucocorticosteroids; TNF- α inhibition; bacterial and granulomatous infections; previous CD38 monoclonal antibody administration; virus reactivation
Comments	CRS occurs early after BsAb administration	Often preceded by CRS	Biological age more important than chronological age; history of previous infections is a sensitive parameter for infection risk; BCMA-targeting therapies cause more pronounced B-cell depletion and normal plasma cell depletion; CRS more associated with bacterial than viral or fungal infections

BCMA, B-cell maturation antigen; BsAbs, bispecific antibodies; CRS, cytokine release syndrome;
ICANS, immune effector cell-associated neurotoxicity syndrome
Adapted from: Ludwig 2023

Table 5. American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading for Cytokine Release Syndrome

Signs/ Symptoms	Grade 1	Grade 2	Grade 3	Grade 4
Fever[1]	Temperature ≥ 38.0°C	Temperature ≥ 38.0°C	Temperature ≥ 38.0°C	Temperature ≥ 38.0°C
		WITH		
Hypotension	None	IV fluids if needed but not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin). The addition of a second agent, apart from vasopressin, is a strong indication of hemodynamic instability after the first intervention
		AND/OR[2]		
Hypoxia	None	Requiring low-flow O_2 via nasal cannula[3] or blow-by	Requiring O_2 via high-flow nasal cannula, facemask, non-rebreather mask or Venturi mask	Requiring O_2 via positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)

BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CRS, cytokine release syndrome; IV, intravenous.
[1] Fever is defined as temperature ≥ 38.0°C not attributable to any other cause. If fever is no longer present due to antipyretics or tocilizumab or corticosteroids, fever is no longer required to grade CRS severity; CRS grading is driven by hypotension and/or hypoxia instead. [2] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS. [3] Low-flow nasal cannula is defined as oxygen delivered at ≤ 6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 L/minute
Adapted from: Lee, 2019

CRS generally occurs within 24 hours of intravenous infusion of BsAbs and after at least 24 hours with subcutaneous administration (Usmani 2021). However, the incidence, timing and onset of CRS varies by disease subtype, BsAb product, route of administration (intravenous vs subcutaneous), and dosing schedule (Crombie 2024).

In the MajesTEC-1 study, which provided data for the approval of teclistamab, 50% of cases of CRS were grade 1 and 21% were grade 2 and 33% of patients had > 1 CRS event. CRS occurred during the step-up schedule and tocilizumab was found to reduce the risk of subsequent CRS in patients receiving it for their first CRS event. These authors also recommend assessing the patient prior to BsAb administration for fever and/or signs of infection (Martin 2023). Most studies report the occurrence of BsAb-associated CRS events in cycle 1 during step-up dosing soon after infusion, from within a few hours to the next day, lasting from 1 to 3 days and rarely requiring intensive care unit admission (Gurumurthi 2023).

Prophylaxis

Pre-medication with steroids and step-up dosing at the time of treatment initiation can be used to mitigate CRS risk and reduce severity and duration. Steroids as pre-medication and following each step-up dose are often used to further reduce the risk of CRS. More recently, the use of CD3 antibodies with reduced CD3 affinity to uncouple T-cell killing from cytokine secretion has been investigated (Klein 2024).

Grading

The American Society for Transplantation and Cellular Therapy has developed a schema for the grading of CRS **(Table 5)**.

Management

Supportive care should be initiated in patients who develop CRS, including prompt administration of IL-6 receptor-blocking antibodies (i.e. tocilizumab) or steroids.

Table 6. Management of Cytokine Release Syndrome by Grade	
Grade 1	Home: acetaminophen if recurrent fever and clinically stable; oral hydration Home or outpatient setting: Refractory/recurrent fever consider dexamethasone 10 mg once. Remain at home if clinically stable and no other symptoms of concern; evaluation in a healthcare facility if not. Consider administration of dexamethasone and in-person evaluation for patients with multiple disease risk factors or comorbidities; consider daily dexamethasone with persistent symptoms Consider anti-cytokine therapy (e.g. tocilizumab) if protracted fever (> 48 hours despite medications); early tocilizumab after administration of dexamethasone should be considered for patients with multiple medical risk factors
Grade 2	Evaluate all patients in person. Inpatient management recommended for most cases of grade 2 CRS unless outpatient facility has qualified personnel and no hypoxia Acetaminophen as needed, up to 3-4 times/day Dexamethasone 10 mg every 12 hours Administer IV fluids/supplemental oxygen as appropriate Administer tocilizumab if symptoms persist despite IV fluids and dexamethasone or if clinically unstable
Grade 3	Immediate hospital admission for hemodynamic monitoring, IV fluids, oxygen therapy and vasopressor administration Administration of acetaminophen IV as needed, dexamethasone IV until resolution to ≤ grade 1, followed by dexamethasone taper Evaluate for sepsis and consider empiric antibiotics Administer tocilizumab and consider alternative agent if persistent grade 3 despite maximal dosing If CRS not responsive to management measures, then ICU admission
Grade 4	Admission to ICU for hemodynamic monitoring, IV fluids, oxygen therapy and vasopressors Acetaminophen IV and dexamethasone IV until resolution to ≤ grade 1, followed by dexamethasone taper Administer tocilizumab and if repeated doses of tocilizumab have been used, consider alternative agent if persistent grade 4 CRS despite maximal dosing of first agent
ICU, intensive care unit. Patients treated with antipyretics or corticosteroids may not experience fever as a presenting symptom of CRS. Tocilizumab should not be administered more than twice per CRS event (at least 8 hours apart), or 3 times within a 6-week period. Adapted from: Crombie 2024	

Temporary dose reduction or interruption can be used if BsAbs with short half-lives are being administered via continuous intravenous infusion (van de Donk 2023). Other supportive care interventions include antipyretics (acetaminophen), intravenous fluid administration and oxygen supplementation (**Table 6**). Typically, patients recover quickly following supportive care measures, but more severe CRS (grades 3 – 4) might require intensive monitoring and support in an intensive care unit and should be considered life-threatening.

Dose modification and retreatment

Dose modifications, dose interruptions, or delay of next dose possibly requiring repeating the step-up dosing schedule for repriming may be necessary after an episode of CRS. As these measures will differ between BsAbs, it is advisable to refer to the prescribing information for individual BsAbs for detailed instructions. Also, the necessity and appropriateness of retreating a patient with a BsAb after an episode of high-grade toxicity, such as CRS, should be determined as based on the manufacturers' instructions (Crombie 2024).

Neurotoxicity

Neurotoxicity associated with T-cell engagers is infrequent and can develop concurrently with, or shortly after CRS, although it can occur alone (van de Donk 2023). When it does occur, it does so as immune effector cell-associated neurotoxicity syndrome (ICANS), which is characterized predominantly by headaches and dizziness, and/or delirium, dysphagia, tremor, lethargy, and difficulty concentrating. ICANS occurs less commonly and is generally of lower severity with BsAbs than with CAR T-cell therapy with reported incidences of 1% - 8% across clinical studies (Crombie 2024). Step-up dosing and premedication can reduce the risk of ICANS. Because neurotoxicity occurs rarely with BsAbs, routine neurologic testing for patients who are asymptomatic with normal neurological examination at baseline is not necessarily required.

Blinatumomab is associated with a high frequency of neurotoxicity (all grades, 47% – 53%; ≥ grade 3, 7% – 13%), which, in most cases, resolves completely (Klein 2024).

Clinical manifestations

Symptoms or signs of ICANS can be progressive. Early symptoms can include:

- Tremor
- Dysphagia
- Mild difficult with expressive speech (i.e. naming objects)
- Impaired attention
- Apraxia
- Mild lethargy
- Headache
- Visual changes
- Generalized weakness (Lee 2019; Gust 2018)

The most prevalent symptom of ICANS is transient cognitive impairment (Gust 2020). While tremor and headache may occur, they are considered nonspecific symptoms, whereas expressive aphasia is a specific symptom and may progress to global aphasia, which is characterized by expressive and receptive difficulty whereby patients appear wide awake but are mute and unable to follow commands (Lee 2019).

ICANS grading

Using consensus, ASTCT developed an ICANS grading scheme in which various signs and symptoms of neurotoxicity are considered to establish the severity of ICANS and the final ICANS grade is determined by the most severe event among the different domains (**Tables 7 and 8**).

Table 8. ICE Scoring System for Neurotoxicity

Orientation to year, month, city, hospital	4 points
Naming 3 objects	3 points
Following simple commands	1 point
Writing standard sentence	1 point
Attention to count backward from 100 by 10	1 point

ICE, immune effector cell encephalopathy

Table 7. ASTCT ICANS Consensus Grading

Neurotoxicity domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score[1]	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness[2]	Awakens spontaneously	Awakens to voice	Awakens only to touch stimulation	Patient is unarousable OR requires vigorous/repetitive touch stimulation to arouse. Stupor/coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly OR non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 min); or repetitive clinical OR electrical seizures without return to baseline in between
Motor findings[3]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuro imaging	Diffuse cerebral edema on neuro imaging; decerebrate/decorticate posturing; OR cranial nerve VI palsy; OR papilledema; OR Cushing's triad

ICE, Immune Effector Cell-Associated Encephalopathy score; ICP, intracranial pressure; N/A, not applicable
ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, increased ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is grade 3 ICANS
[1] A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable; [2] Depressed level of consciousness should be attributable to no other cause (i.e., sedation medications); [3] Tremors and myoclonus associated with immune effector cell therapies may be graded according to other tools but do not influence ICANS grading; [4] Intracranial hemorrhage with/without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading
Adapted from: Lee 2019

Table 9. Management of Neurotoxicity by Severity Grade	
ICANS grading	**Management**
Grade 1: ICE 7-9 points	Consider observation or close monitoring in outpatient setting; consider dexamethasone
Grade 2: ICE 3-6 points	Hospital admission for monitoring; dexamethasone
Grade 3: ICE 0-3 points	Monitor in ICU setting; neurology consult; dexamethasone; administer antiepileptic medications for seizure management if needed; consider adding anakinra if symptoms persist beyond 24 h and continue until resolution
Grade 4: ICE = 0	Monitor in ICU setting; neurology consult; dexamethasone; administration of antiepileptics for seizure management if needed; consider adding anakinra if symptoms persist beyond 24 h, continue until resolution
Adapted from: Crombie 2024	

Management

Management of neurotoxicity should be multidisciplinary, involving neurology specialists if appropriate and is based on the severity of the neurotoxicity (**Table 9**).

Infections

As previously described, T-cell engaging bispecific treatment should be withheld in the presence of active infection as concurrent infection and immune cell stimulation may heighten the risk and severity of immune toxicity (Crombie 2024). Furthermore, patients treated with T-cell engaging bispecific should generally be considered immune-compromised as they previously received several lines of cytotoxic and/or lymphodepleting treatments and are commonly exposed to corticosteroids (Geraud 2024). The risk of bacterial, viral, and opportunistic infections is increased with T-cell engagers, although there is marked heterogeneity in the frequency of infections between clinical studies (van de Donk 2023).

Prophylaxis

Screening at baseline for Hepatitis B and C virus (HBV and HCV), HIV, cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infections as well as other screening and diagnostic evaluations for the presence of infection should be performed. Patients should receive vaccinations against influenza, pneumococcal disease, herpes zoster and COVID-19 are recommended (Geraud 2024). Patients should receive prophylaxis against varicella zoster virus with acyclovir or valaciclovir and prophylaxis against pneumocystis carinii pneumonia/pneumocystis jirovecii pneumonia (PCP/PJP) during therapy and for several months thereafter (Ludwig 2023).

Table 10. Manifestations and Management of Possible Side Effects of T-cell Engager Bispecific Immunotherapy		
Side effect	**Manifestations**	**Management**
Tumor flare reaction	Rarely occurs; characterized by short-term volumetric increase in lymphoma lesions accompanied by erythema, pain, fever; can cause local compression or organ dysfunction; occurs most frequently after first does, may occur together with CRS	Irradiation of a high-risk site (i.e., airway, mediastinum) if significant concern for vital organ compromise; typically responds to corticosteroid therapy
Tumor lysis syndrome	Rarely occurs; higher risk in patients with high tumor burden or impaired renal function	Prophylaxis with hypouricemic agents and hydration
Cytopenias	Cytokines, which are produced by the bone marrow microenvironment, impair hematopoiesis causing cytopenias	Follow infection prophylaxis management strategies; administration of growth factors and thrombopoietic agents after treatment completion; withhold therapy if necessary after weighing pros and risks
Keratotoxicity of GPRC5D targeting BsAbs	An off-target effect of talquetamab causing loss of taste, difficulties swallowing, skin rash, nail toxicities, non-infectious fever, anorexia	Use emollient creams for rash; saliva replacement sprays and rinses; skipping a dose may be effective in mitigating this side effect
Sources: Ludwig 2023; van de Donk 2023; Crombie 2024		

Management

Close monitoring for symptoms of infection is important. Supportive care to prevent infections includes growth factor support in patients who are neutropenic, and intravenous immunoglobulin supplementation in patients with hypogammaglobulinemia (van de Donk 2023). Management of infection will depend on the manifestation and the infectious agent. For unknown bacterial species, diagnostic measures should be intensified, including blood and sputum cultures.

Patients and caregivers should be provided with written instructions on the signs and symptoms of infection, preventative measures, home-care interventions, and when and whom to contact should symptoms become severe.

Evaluation and Management of Other Common Side Effects of T-cell Engager Bispecific Immunotherapy

(see **Table 10**)

Influence of Bispecific Antibody Immunotherapy on Health-related Quality of Life

Generally speaking, health-related quality of life (HRQoL) deteriorates with each subsequent relapse and line of therapy (Engelhardt 2021). With this in mind, treatment goals for patients with relapsed/refractory hematologic malignancies should strive to not only manage disease and treatment-related symptoms, but also maintain or potentially improve QoL in addition to extending survival.

Little research to date has reported on the evaluation of quality of life in patients receiving BsAb therapies. There may be many reasons for this, most notably that these therapies have only recently been used more widespread in clinical practice, and research is focused on treatment-related issues to substantiate efficacy and safety of the molecules, rather than on patient-related issues such as data on physical, mental and social functioning and symptomatic burden; that is, data that provides insight into the impact of treatment and disease on well-being. Patient-reported outcomes (PROs) were established within healthcare for over a decade and are central to the delivery of person-centered care. A PRO is "any report of the status of a patient's health condition that comes directly from the patient without interpretation of the patient's response by a clinician or anyone else" (FDA 2009).

Here is a brief overview of the few available studies that reported findings from PROs provided by patients treated with BsAbs for malignant hematologic diseases. Overall, results are encouraging.

Patients participating in the MajesTEC-1 study completed a global health status to assess their health-related quality of life. Overall HRQoL was improved with BsAb treatment as shown by higher scores on the global health status questionnaire and reduced pain. No overall changes in physical functioning and fatigue were reported by patients (Popat 2022). In a study of the impact of elranatamab on QoL in patients with r/r MM, improvements in PROs occurred early, with marked reductions in pain and disease symptoms and notable improvements in patients' outlook for their future health (Mohty 2023).

Patients enrolled in EPCORE NHL-1 who received epcoritamab completed assessments at baseline, on day 1 of cycles 3, 5, 7 and 9 and at the end of treatment. In this group of heavily pretreated r/r DLBCL, treatment with epcoritamab provided consistent and clinically meaningful improvements in lymphoma symptoms and health-related QoL including a positive impact on daily activities (Phillips 2024).

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Notes

Summary Points

- Beyond bispecific antibodies, tri- and multi-specific agents are in current development with a promising outlook that includes improving efficacy, and reducing side effects and tumor resistance
- Considering tumor-related and immune system-related factors, moving the use of bispecific antibody immunotherapy to first-line treatment in combination with other anti-cancer therapies may be advantageous in some hematologic malignancies
- Advances in selecting the most appropriate target are likely to gain importance in future bispecific antibody immunotherapy development
- Further evaluation of risk factors associated with cytokine release syndrome and optimization of prophylactic and management measures are important for the continued safe use of bispecific antibodies
- As more information on the use of bispecific antibody immunotherapy and the management of side effects becomes available, the incorporation of these agents as standard of care, also in the community setting, will become possible

Module V: New Developments in Bispecific Antibody Immunotherapy in Hematologic Malignancies

Introduction: What's in the pipeline?

Bispecific antibody (BsAb) immunotherapy represents a "game-changer" in the treatment of cancer, specifically in the treatment of hematologic B-cell malignancies. New, novel agents that aim to enhance efficacy and reduce toxicity by targeting alternative antigens, or those that target multiple antigens (e.g., trispecific antibodies), and agents that engage the activity of several immune cells are being evaluated (Braun 2024). Still, there are obstacles to overcome such as dosing and treatment resistance before these agents enhance clinical outcomes.

New in the pipeline are trispecific antibodies. With these molecules, at least one of the three specifities is intended to bind T or natural killer (NK) cells and at least one targeting a tumor-associated antigen (Braun 2024). Although no trispecific antibodies as anti-cancer treatment in hematologic malignancies have been approved at this time, the pipeline is long, and many are now being evaluated in clinical trials.

Another area under current investigation and development is immune cell engagers (ICE), which are molecules able to redirect immune effector cells against cancer cells to trigger efficient tumor cell killing by acting as a bridge between immune cells and target cells. The substitution of the CD3 binding domain with a CD16 domain allows the recruitment of NK cells. The addition of a third binding domain provides ICE with new binding capabilities, including increased specificity for tumors or enhanced immune-cell activation.

Bispecific antibody immunotherapy as first-line treatment and in combination with other cytotoxic treatments

While most BsAbs are currently approved for relapsed/refractory disease, the lower tumor burden and a tumor microenvironment more conducive to anti-cancer therapy in patients with early-stage disease may be advantageous to achieving a more favorable response with BsAbs at an earlier disease stage (Omer 2023). Based on this background, CD20 x CD3 molecules are being evaluated in patients newly diagnosed with DLBCL in combination with cyclophosphamide-hydroxydaunorubicin-oncovin-prednisone (CHOP), rituximab-CHOP, or polatuzumab-R-CHP with the aim of improving overall survival outcomes (Roost 2022).

A rationale for using BsAbs as a first-line treatment in multiple myeloma is that the immunosuppressive tumor microenvironment poses challenges to the efficacy of BsAb immunotherapy. T-cell exhaustion as a consequence of multiple lines of treatment can result in lower response rates and poorer outcomes (Omer 2023). Also, cytotoxic T-cells may be more functional at earlier stages of disease thus supporting the earlier administration of BsAbs to improve the therapy response. Another method to possibly reprogram the immunosuppressive tumor microenvironment would be to establish treatment-free intervals, which could possibly reduce T-cell exhaustion.

A research question now under investigation is what sequence to use BsAbs. For example, should patients with r/r LBCL receive CAR T-cell therapy, BsAbs or autologous stem cell transplantation and in what sequence? It may be helpful to mix lines to target different tumor associated antigens: target CD20 when using BsAbs and CD19 when using CAR-T cell therapy. Irrespective of costs of treatment, both BsAbs and CAR T-cell therapy may be alternatives to conventional treatments. The lack of real-world data makes it difficult to confirm durability of response with BsAbs and verify whether this treatment is a viable alternative to CAR T-cell therapy (Gurumurthi 2023). In any case, prognostic tools play an important role in identifying patients at high risk of relapse to subsequently offer them CAR T or BsAbs at an earlier line of therapy.

Studies have combined BsAbs with conventional chemoimmunotherapy or novel therapies, such as polatuzumab, immunomodulators or Bruton's tyrosine kinase inhibitors, for earlier lines of therapy for treatment naïve patients and in the r/r setting to improve response rates and survival (Gurumurthi 2023).

Blinatumomab, for example, is currently approved for the treatment of r/r B-cell lymphomas. Clinical studies are being conducted to evaluate blinatumomab as first-line treatment in combination with conventional chemotherapy. A 2022 randomized phase 3 study showed that the addition of blinatumomab to consolidation chemotherapy resulted in a statistically significantly better overall survival in patients with newly diagnosed Ph(-) precursor B-ALL aged 30 to 70 years (Litzow 2022). Blinatumomab monotherapy followed by chemotherapy maintenance was well tolerated in older patients with Ph (-) ALL (Advani 2022). Promising results have also been shown in chemotherapy-free combinations of blinatumomab with a tyrosine kinase inhibitor in patients with newly diagnosed Ph (+) ALL (3-year overall survival rate of 80% in combination with dasatinib), which could reduce the need for stem cell transplantation (Foa 2020; Jabbour 2023).

In patients with r/r B-cell NHL, BsAbs (i.e., CD20 x CD3 molecules) are being studied in combination with other anti-lymphoma therapies such as chemotherapy, immunotherapy, checkpoint inhibitors, ibrutinib, or polatuzumab vedotin. Preliminary study results have shown efficacy with the combination of a CD20 x CD3

BsAb and the immunomodulatory drug lenalidomide in r/r follicular lymphoma leading the way for phase 3 studies to investigate whether this novel combination is superior to lenalidomide plus rituximab.

Changing targets to improve efficacy

Defining the most appropriate target antigen is a major challenge for the successful development of BsAbs and is key to creating safe and effective molecules for clinical use (Goebeler 2024). To avoid on-target off-tumor adverse events and antigen loss, the antigen targets should ideally be expressed on the target cells but not on the surface of non-malignant cells.

Currently, T-cell engaging BsAbs bind to antigens on tumor cells and CD3 antigens on T-cells whereby

T-cells are then redirected to kill tumor cells. T-cell engaging BsAbs are the most common format of BsAbs currently used in the treatment of hematologic malignancies. More precisely, these molecules target CD19 in acute lymphoblastic leukemia, CD20 in B-cell non-Hodgkin lymphoma, and BCMA and GPRC5D in multiple myeloma (van de Donk 2023). New formats of BsAbs that target other proteins are being developed (**Table 1**). Among these new formats are BsAbs that target aberrantly expressed intracellular oncogenic antigens, tumor-associated antigens, mutant oncogenes, and tumor suppressor genes (van de Donk 2023). However, a disadvantage of these formats, which are HLA-associated, is that they are restricted to patients expressing the relevant HLA allele.

Research is underway to investigate BsAbs for the treatment of lymphoma that target ROR1, CD22, or CD79b. CD19 T-cell-redirecting antibodies with longer half-lives than blinatumomab, for example, are also in development (Reusch 2015). Advances in selecting the most appropriate target are likely to gain importance in future BsAb immunotherapy development. This knowledge will aid in identifying which antigen or antigens should be targeted to eliminate the cellular compartments associated with tumor growth, recurrence and/or metastasis (Goebeler 2024). Obviously, more precise targets may also reduce the risk of on-target off-tumor events.

Natural killer cell engagers

Bispecific killer engagers (BiKEs) are agents that engage NK cells and not T-cells to enhance tumor cell lysis. Of interest, in comparison to T-cells, NK cells do not require antigen priming and thus might avoid some of the toxicities associated with T-cell-based therapies. Incorporating NK-cell engagers may also synergize with bispecific T-cell engagers and potentially enhance the anti-tumor immune response (Omer 2023).

Acimtamig is a tetravalent CD30 x CD16A BiKE and is designed to recruit NK cells and other innate immune cells to CD30-positive tumors, such as Hodgkin lymphoma (Goebeler 2024). Acimtamig has been evaluated in several phase 1 and 2 trials. The most promising results have been shown in clinical trials in which the overall response rate was 92.8% and a complete response rate was 66.7% at a median follow-up of 14 months in patients with r/r CD30+ lymphomas (Kerbauy 2021). Another tetravalent BiKE designed to stimulate NK cell-mediate BCMA-targeted cytotoxicity, AFM24, demonstrated good tolerability but modest tumor activity in patients with multiple myeloma (Surowka 2021).

Mechanisms of immune escape

Tumor heterogeneity is a key determinant of treatment resistance. During treatment, malignant cells diversify to adapt to the often highly specific selective pressures caused by targeted therapies leading to resistance. Tumor cells can utilize a large selection of options to withstand the selective pressures caused by agents targeting a single antigen. The bulk of research to date has focused on identifying which regimens and doses of available agents are most likely to prevent immune evasion and simultaneously enable the successful recruitment of effector cells to the tumor site without systematic T-cell activation or T-cell exhaustion (Goebeler 2024).

Like other forms of anticancer therapy, tumors can become resistant to BsAbs. Antigen escape is a major resistance mechanism to BsAb immunotherapy. Finding and attacking additional tumor-associated target antigens by identifying combinations of multi-antigenic BsAbs may help to offset antigen escape (Omer 2023). CD20 down-regulation has emerged as an evasion mechanism, prompting the need to target alternative antigens. AZD0486 is a novel IgG4 CD3 x CD19 BsAb with a low affinity CD3 part (intended to decrease CRS). This molecule has been evaluated in patients with LBCL and with follicular lymphoma. While efficacy results were very good, the median follow-up (6 months) was too short to assess the durability of response.

As previously mentioned, another contributor to resistance of BsAbs is the immunosuppressive tumor microenvironment in hematologic malignancies. Measures to normalize the tumor microenvironment by using immune checkpoint inhibitors and immunomodulatory agents may help to strengthen the efficacy of BsAbs and lower therapeutic resistance (Omer 2023).

Table 1. Investigational Bispecific Antibodies in Hematologic Malignancies

Agent (Study)	Target	Indication	Comments
Odronextamab[1] (ELM-2, phase 2)	CD20 x CD3	r/r DLBCL	48% probability of maintaining CR for 2 years in hard-to-treat patients; CRS 98% (low-grade) with optimized step-up dosing; no ICANS; improved PRO of pain and emotional functioning. Approval review (FDA & EMA)
Linvoseltamab (LINKER-MM1, phase 2)[2]	BCMA x CD3	r/r MM	Better efficacy with 200 mg vs 50 mg; 200 mg showed consistent efficacy across high-risk subgroups. TEAs in 95%; CRS with 200 mg was 37%. Approval review (FDA & EMA)
Acimtamig (phase 1b)	CD30 x CD16	r/r HL	ORR 83%. Generally well-tolerated. Used in combination with pembrolizumab
Acimtamig (phase 1-2)	CD30 x CD16	Refractory CD30+ lymphoma	ORR 92.8%, CR 66.7%. No incidence of CRS or ICANS. Used in combination with allogeneic NK cells
Acimtamig (REDIRECT, phase 2)	CD30 x CD16	r/r T-cell lymphoma	ORR 32.4%. TEAs 73.1%, serious 8%; infusion-related reactions 31.5% (grade 3, 5.7%)
Felzartamab	CD38	r/r MM	Evaluated in combination with lenalidomide and dexamethasone. Studies being conducted in China
Cevostomab (phase 1)	CD3 x Fc receptor homolog 5	r/r MM	Single and double step-up dosing strategies. ORR 54.5%. No dose-dependent increase in CRS, low rate of adverse events
ISB1342 (phase 1)	CD3 x CD38	r/r MM	CRS in 34% (grade 1-2), low rate of adverse events
ABBV-383 (phase 3 as of June 2024)	BCMA x CD3	r/r MM	Does not require step-up dosing. ORR 57%, CR 29% in phase 1 trial
JNJ-67571244 (phase 1)	CD33 x CD3	r/r AML	Completed trial, safety & efficacy evaluation
JNJ-75348780 (phase 1)	CD3 x CD22	r/r B-cell malignancies (NHL and CLL)	On-going, evaluating safety and determination of recommended dose for phase 2 and optimal dosing schedule
AMV564 (phase 1)	CD33 x CD3	r/r AML	Completed trial, safety & efficacy evaluation
Flotetuzumab (phase 2)	CD123 x CD3	r/r AML	Recruiting, safety evaluation
XmAb14045 (phase 2)	CD123 x CD3	r/r/ AML	Recruiting, safety evaluation
APVO436 (phase 1)	CD123 x CD3	r/r AML	Recruiting, safety evaluation
MGD024 (phase 1)	CD123 x CD3	r/r AML, HL, B-cell ALL, CML	Recruiting, safety evaluation
JNJ-63709178 (phase 1)	CD123 x CD3	r/r AML	Completed trial, safety evaluation
CLN-049 (phase 1)	FLT3 x CD3	r/r AML	Recruiting, safety evaluation

[1] Marketing application submitted for regulatory review: on-going evaluation in patients with FL, AML, acute myeloblastic leukemia; CML, chronic myeloblastic leukemia; DLBLC, mantle cell lymphoma, marginal zone lymphoma, B-cell NHL. [2] Phase 3 trial (LINKER-MM3) on-going: regulatory submission expected by end of 2024.

AML, acute myeloid leukemia; DLBCL, diffuse B-cell lymphoma; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; EMA, European Medicines Agency; FDA, Food and Drug Administration; FL, follicular lymphoma; HL, Hodgkin lymphoma; ICANS, immune effector cell-associated neurotoxicity syndrome; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; ORR, overall response rate; PRO, patient-reported outcome; r/r, relapsed/refractory; TEA, treatment-emergent adverse event

Adapted from: Goebeler 2024; Omer 2023

Trispecific and multispecific antibodies

Trispecific antibodies are being engineered to allow for optimal immunological synapse formation, that is, the enabling of signaling between different immune cells to reduce immune evasion. Because these antibodies can improve selectivity for cancer cells, they may cause fewer toxicities and, as a result, expand the therapeutic window (Mazor 2017). In pre-clinical trials of B-NHL, CMG1A46, an CD3 x CD19 x CD20 trispecific antibody and JNJ-80948543, an CD3 x CD20 x CD79b trispecific antibody showed evidence of superior potency and safety as compared with CD3 x CD20 BsAbs (Zhang 2020). These trispecific antibodies are being investigated for safety and efficacy in patients with r/r B-cell lymphoid malignancies in phase 1 studies (Braun 2024).

Trispecific antibodies also have the potential to enhance pharmacokinetic properties. HPN217, for example, is a trispecific antibody targeting albumin, CD3, and BCMA and is designed to extend the half-life of the molecule. Its safety profile is being investigated in patients with r/r MM. Preliminary results show that 28% of patients experienced CRS and dose-limiting toxicity was mainly reversible transaminitis. Other trispecific antibodies including CD3 x BCMA x CD38 and CD3 x BCMA x GPRC5D are currently under investigation in phase 1 trials for patients with r/r MM. Currently, 30 trispecific antibodies are being investigated.

The manufacturing of trispecific antibodies presents challenges, for example compromised stability or non-desired byproducts arising due to incorrect assembly. These issues may be solved through good manufacturing practices (Tapia-Galisteo 2023).

Multispecific antibodies, which can target multiple antigens simultaneously, are also moving forward. There is an astonishing array of potential formats for multispecific antibodies, which may lead to treatments for diseases, malignant and non-malignant, with no or few effective therapies.

Improving access to BsAbs in the community

As more clinical results on the efficacy and safety of BsAbs become known and greater knowledge of their side effects and management thereof becomes available, the incorporation of BsAbs as standard-of-care will increase, and treatment with these agents will move from academic/acute care institutions to community-based oncology practices (Braun 2024). Because the adverse effects associated with BsAbs are fewer and less severe in general in comparison to those associated with CAR T-cell therapies, Risk Evaluation and Mitigation Strategies (REMS) is not obligatory for BsAb administration as is the case with CAR- T cell therapies, thus easing their administration in the community.

Despite the off-the-shelf availability of BsAbs and their less toxic safety profile, there remain significant hurdles to their widespread use in community oncology practices. One obvious challenge is the lack of "real life" research that addresses the use of these molecules in community-based settings. And/or the logistical issues in terms of the availability of an inpatient setting (possibly with intensive care) and the transportation of patients to these acute care settings if required. The handling and administration of tocilizumab, often used to resolve symptoms of CRS, in a real-world setting has not been thoroughly investigated.

Another challenge to widespread use of BsAb and multispecific antibody immunotherapy is the cost of treatment. At present, cost-effectiveness analyses favor CAR-T cells over blinatumomab, for example, as a comparator on parameters such as incremental quality-adjusted life years (Forenza 2020). This relationship could change with the further advancement of T-cell engager molecules once production costs, logistics, days of hospitalization and short- and long-term adverse events have been considered (Tapia-Galisteo 2023). More longer-term data on treatment response is needed to make a true comparison of the two types of treatment.

To aid and support the educational needs of healthcare professionals involved in the administration of BsAbs and the monitoring of patients receiving these molecules, the Lymphoma Research Foundation has created evidence-based clinical guidelines on the management of CD20 x CD3 toxicities (Crombie 2024; Raje 2023). These guidelines require validation in the community practice setting.

Closer collaboration between academic and community practices can help to improve timely BsAb access for patients in community settings. A shared care model that involves community oncologists referring patients to academic centers for initial treatment with subsequent treatment cycles taking place in a community practice, may be an acceptable option to better manage known early onset adverse events in the community. Furthermore, the expansion of BsAb therapy into community practices may serve to underscore the shift toward patient-centered care (Braun 2024) and help to ensure that a broad spectrum of patients will benefit from advancements in cancer treatment.

Conclusions

As bispecific antibody immunotherapies continue to evolve, they will certainly become an important addition to available anti-cancer treatments. Problems associated with the overlapping expression of target antigens on malignant cells as well as normal cells, such as hematopoietic stem cells, causing on-target off-tumor toxicities, particularly in this case, hematologic toxicity and cytopenias, still require attention to ensure that these agents not only reach their cytotoxic goal, but are also safe. Better identification of patients at risk for CRS and further development of prophylaxis and treatment guidelines will certainly aid in abating the severity of this adverse effect. Lastly, continuing randomized as well as real-life clinical studies are required to evaluate areas of uncertainty in BsAb to gather and analyze data on important outcome criteria such as duration of response (**Table 2**) (Falchi 2023).

Remarkable advances in the immunotherapy of hematologic malignancies are having a large impact on outcomes in patients with relapsed/refractory disease. Instead of considering one immunotherapy over another, greater consideration should be made to considering using these therapies in combination or sequentially to achieve maximum treatment benefit (Tapia-Galisteo 2023). Both bispecific and multispecific antibody immunotherapy will continue to change the treatment landscape in hematologic malignancies.

Table 2. Summary of Areas of Uncertainty in BsAb use in the Clinical Setting

Area of uncertainty	Challenge
Management of T-cell overactivation syndromes	Identify risk factors for CRS Optimal step-up dosing, drug formulation, prophylaxis Outpatient administration Patient and provider education
Duration of response	Optimal duration of BsAb therapy Predictors of durable response
Beginning BsAb at an earlier stage of treatment	Competitive landscape Selecting the most appropriate patient populations (eg, high-risk disease)
Optimal treatment combinations	Moving beyond cytotoxic agents as partner Rational, rather than expedient, combinations
Understanding mechanisms of resistance	Identifying tumor-resistant mechanisms Detailed characterization of T-cell function (and dysfunction) during BsAb therapy Analyzing the role of other players in the lymphoma immune microenvironment

BsAb, bispecific antibody; CRS, cytokine release syndrome
Adapted from Falchi 2023

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Glossary of Terms

Term	Definition
Antibody	A large protein used by the immune system to identify and neutralize antigens. Antibodies attach to antigens (foreign substances) to remove them from the body. Also referred to as immunoglobulins.
Antigen-presenting cells (APCs)	A heterogeneous group of cells that mediate a cellular immune response by processing and presenting antigens for recognition by T cells
Anti-inflammatory cytokines	Stop or lessen inflammation. They relay messages that prevent an excessive immune response that can lead to tissue damage
Antigenicity	The capacity of a molecule or an antigen to induce an immune response, i.e. to be recognized by and interact with an immunologically specific antibody or T cell receptor.
Autologous	Derived from the same individual and hence genetically identical to the host.
Chemokines	Any of a group of cytokines produced by various cells (as at sites of inflammation) that stimulate chemotaxis in white blood cells (such as neutrophils and T cells)
Clinical response/complete remission	An important indicator of treatment response; often used in clinical trials to identify and quantify anti-tumor activity of new agents; limited value in predicting survival
Colony stimulating factors	Secreted glycoproteins that bind to receptor proteins on the surfaces of progenitors in the bone marrow, thereby activating intracellular signaling pathways that can cause cells to proliferate and differentiate into a specific kind of blood cell
Complete response (CR)	The disappearance of all signs of cancer in response to treatment. This does not always mean the cancer has been cured. Also called complete remission
Cytokines	Signaling proteins that aid in the control of inflammation through cell activation, cell differentiation, and cell proliferation
Disease-free survival	A concept used to describe the period after successful treatment during which there are no signs and symptoms of the disease
Genotoxic	Damaging to genetic material
Human leukocyte antigen (HLA):	Highly polymorphic molecule required for antigen presentation encoded within the human major histocompatibility complex
Immune effector cells	A cell that has differentiated into a form capable of modulating or effecting a specific immune response
Immune escape (also known as antigenic escape, immune evasion, escape mutation)	Occurs when the immune system is unable to respond to an infectious agent: the host's immune system is no longer able to recognize and eliminate a pathogen.
Immunogenicity	The ability of a therapeutic protein product to stimulate an immune response
Interferons	A considerable range of antiviral protein substances produced by cells that have been invaded by viruses
Interleukins	A range of cytokines secreted by white blood cells of the immune system. Effector ells have surface receptors for the various interleukins
Macrophage	Any of the large, mononuclear, highly phagocytic cells derived from monocytes, occurring in the walls of blood vessels and in connective tissue; originate in the bone marrow

Term	Definition
Major histocompatibility complex (MHC)	Proteins that control immune responses, encoded by a genetic locus encompassing a family of highly polymorphic genes.
Measurable (minimal) residual disease (MRD)	A relevant independent prognostic factor used to guide treatment decisions. MRD refers to the number of cancer cells that remain in a person during and following treatment
Molecular response Major molecular response	Analysis of the number of cells in blood and bone marrow that contain the BCR-ABL gene; measured using a polymerase chain reaction (PCR) test. A molecular response is attained when there is a 1000 times decrease in the BCR-ABL gene cells from baseline (pretreatment) measurement
Neo-antigens (or tumor antigens)	Antigenic proteins formed by metabolic pathways (for example, drug metabolism)
Off-target	Unexpected side effects due to the effects from other targets or the structure of the drug
On-target	Side effects of treatment on normal tissues that occurs when the target that's being inhibited in the tumor is also being inhibited in normal tissue
Overall response rate (ORR)	The proportion of patients who have a partial or complete response to therapy; it does not include stable disease and is a direct measure of drug tumoricidal activity
Overall survival (OS)	The length of time from either the date of diagnosis or the start of treatment that patients diagnosed with the disease are still alive; used in clinical trials to measure the efficacy of a treatment
Pro-inflammatory cytokines	Trigger or heighten inflammation. They relay messages that coordinate the immune response to fend off attackers, like germs.
Progression free survival	The time from random assignment in a clinical trial to disease progression or death from any cause
Proto-oncogenes	Any gene capable of becoming a cancer-producing gene (an oncogene)
Tumor immune escape	A process by which tumor cells evade immune surveillance. Remains a significant barrier to cancer therapy. Combining several immunotherapies can boost antitumor efficacy and encourage T cells to play a more active part in the immune assault against tumor cells.
Tumor necrosis factor (TNF)	A protein produced chiefly by monocytes and macrophages in response especially to endotoxins and that mediates inflammation and induces the destruction of some tumor cells and the activation of white blood cells

Notes

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