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REVIEW ARTICLE

Emerging Role of Bispecific Antibodies (BsAbs) in Cancer Treatment

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ABSTRACT: Bispecific monoclonal antibodies (BsAbs) have emerged as an important development in the field of cancer immunotherapy. Multiple BsAbs have gained FDA approval recently, and many are in the pipeline with substantial research potential. This narrative review article explains the evolving structural designs, mechanism of action, and expanding clinical applications of BsAbs. The literature published in the English language between 2000 and the present was reviewed in different electronic scientific databases. BsAbs are manufactured by combining antigen-binding parts of two monoclonal antibodies (mAb) to engage two targets simultaneously. Two antigen-binding sites of BsAb create a bridge between cancer cells and the T cells, resulting in the destruction of cancer cells by overcoming immune evasion. BsAbs can also inhibit cancer growth by simultaneously blocking two different growth receptors on cancer cells, tackling tumor resistance. BsAbs encounter challenges of manufacturing complexities, risk of immune attack on healthy cells, paucity of tumor-specific antigens, and limitations in pharmacokinetics. Future innovations in protein engineering, discovery of novel tumor-specific antigens, creation of multiphasic Abs, and development of oral or subcutaneous delivery routes may further enhance the safety and efficacy of BsAbs. BsAbs have the potential to change the treatment goal from cancer care to cancer cure.

KEYWORDS: Biomedical and Health Sciences, Immunology, Cancer Immunotherapy, Bispecific Antibodies, Bispecific T-Cell Engagers (BiTEs).

Introduction

For decades, cancer has been treated with surgery, radiation, and chemotherapy.[1] However, in the past decade, immunotherapy has become the fourth standard modality of treatment for various types of cancers. It is a groundbreaking approach that empowers the body's own immune system to fight cancer. Immunotherapy uses cytokines, chemokines, and immune cells to fight against cancer cells. Some of the recent developments in cancer immunotherapy include adoptive cell therapy, including genetically engineered T-cells; oncolytic viruses; cancer vaccines; and monoclonal antibodies (mAbs), including immune checkpoint blockers and the bispecific antibodies (BsAbs).[1,2]

Traditional mAbs bind to a single antigen/epitope, with limitations of immune evasion and resistance, resulting in incomplete tumor eradication. Though the effects of immune evasion and resistance are both context-dependent and do not apply to all mAbs. BsAbs are designed in a lab by combining two mAbs with two different antigen-binding sites to engage two different targets at the same time. BsAbs can have better tumor targeting, immune cell engagement, and signaling modulation than mAbs. BsAbs have shown excellent results in hematological malignancies. Blinatumomab, a novel treatment for Acute Lymphoblastic leukemia, binds CD19 on tumor cells and CD3 on T-cells to begin and amplify cytotoxic activity against tumor cells.[3] Recently, the FDA has approved a few BsAbs for some solid tumors, also. Despite different challenges such as the cytokine release syndrome (CRS), engineering innovations and clinical trials are being conducted to improve the efficacy and safety steadily.[4,5] As the field advances, BsAbs may play an increasingly important role in next-generation cancer immunotherapy.

As a result of enormous potential and expanding research, recent years have seen a surge in the development of BsAbs as a transformative approach in cancer immunotherapy. The rapid expansion of diverse BsAb formats, mechanisms, and targets has created a fragmented body of knowledge. A comprehensive literature review and secondary analysis are needed to clarify the design principles, risks, and benefits of different formats, therapeutic mechanisms, and the evolving clinical landscape.

Methodology

Given the rapid expansion of BsAb formats and clinical applications, this review article aims to focus on the production design strategies, mechanisms of action, clinical uses, current challenges, and future directions of the BsAb-based cancer therapy. This review is based on a narrative approach to analyze and summarize the existing literature on BsAbs' role in cancer treatment. This article is a literature review paper. We performed detailed Literature searches in different electronic databases, e.g., PubMed, Scispace, clinicaltrials.gov, Scopus, and Google Scholar. The search was performed between 2000 and the present date using the keywords Bispecific Antibodies and cancer. A manual search was performed on the references of related original research. Studies were included if they were specific to our topic and published in the English language in the above-specified time period. Studies that were mere commentaries, editorials, had poor methodology, or were

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published in non-peer-reviewed sources were excluded. The selected studies were reviewed and grouped according to common themes. Data from these groups of studies were extracted and organized according to major themes such as structure and design, clinical applications, advantages, limitations, and future research of BsAbs. *The American Chemical Society format was applied for citation of references*. New innovative diagrams were created to depict scientific knowledge in a simple way using the software Biorender. This is a narrative review article with a broad qualitative summary of research without a rigid search process. No formal quality tools, such as PRISMA Guidelines, were applied, which are reserved for systematic review or meta-analysis. This review article is based entirely on previously published studies and does not include any new experimental data or unpublished findings; therefore, it does not require ethical review or approval by an Institutional Review Board.

Discussion

Bispecific Antibodies: Structure and Design Strategies:

The antibody has a Y-shaped structure. Each arm of the Y comprises part of one heavy chain and one complete light chain (Figure 1). It has a central constant and a peripheral variable region. It makes the fragment antigen-binding region (Fab), which is responsible for recognizing a specific antigen. The stem of Y is made up of parts of both heavy chains. It makes the fragment crystallizable region (Fc), which interacts with immune cells and complement proteins.[6]

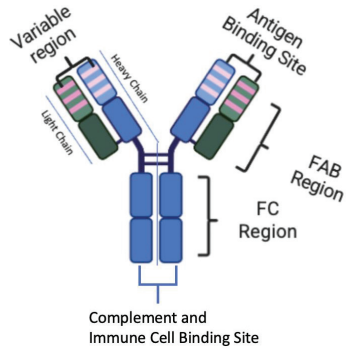

Figure 1: This figure illustrates the Y-shaped structure of an Antibody. Each arm of the Y makes the Fab region, which contains the specific antigen-binding site. The stem of Y makes the Fc region, which interacts with immune cells and complement proteins. This diagram was created using BioRender.

The immune system naturally produces polyclonal antibodies to provide broader protection against pathogens with multiple antigenic sites, which attach to different antigens/epitopes. The mAbs are only produced within the lab, and are highly specific and ideal for targeted therapy. The mAbs are produced by a single clone of B-lymphocytes and bind to a single specific antigen/epitope. A specific antigen is introduced in a mouse to stimulate B-lymphocytes, which turn into plasma cells. The plasma cells (usually splenocytes) are harvested and fused with immortal myeloma cells to create hybridomas. These hybridomas are cloned, and single clones producing the desired antibody are selected and expanded to produce monoclonal antibodies in bulk.[7]

Conventional mAbs are limited in their approach as they can bind to a single antigen/epitope. BsAbs are engineered to recognize and bind to two different targets simultaneously. Scientists use techniques of Quadromas, which is a hybrid of two hybridomas, chemical conjugation, and genetic recombination to produce BsAbs. The manufacturing process starts with genetic engineering and fusion of genes of different mAbs or their fragments to generate a genetic code for a single BsAb. This genetic material is transfected into an expression system such as Chinese hamster ovary (CHO) cells for IgG-like BsAbs or prokaryotic systems (e.g., *E. coli*) for fragment-based BsAbs. This transfected genetic information translates into the production of the desired protein, the BsAbs. Chromatography and Peptide tagging techniques are used to isolate and purify the BsAbs from the expression system. Over 100 distinct structural formats of BsAbs exist to optimize and integrate key functional properties such as stability, half-life, tumor penetration, and immune effector engagement. BsAbs can be categorized into two broad structural design formats, which are IgG-like and non-IgG-like.8

IgG Like BsAbs:

This design constructs a BsAb consisting of a full Y-shaped structure with 3 unique binding sites, one Fc region, and two Fab arms that bind to two different antigens. It has 2 different heavy chains and 2 different light chains as it originates from two different mAbs (Figure 2). These BsAbs have a stable structure with a long half-life. However, the correct pairing of the different heavy chains along with corresponding light chains can be challenging. Two approaches are used to prevent mismatched pairing.[9] The 'knobs into holes' (KiH) technique prevents unwanted homodimer of heavy chains (Figure 2). It introduces a mutation for a large amino acid in the heavy chain from one mAb, creating a "knob," and a mutation for a small amino acid in the heavy chain originating from the other mAb, making a "hole." The "knob" heavy chain preferentially pairs with the "hole" heavy chain. This arrangement forces the production of the desired heterodimers.[10] The CrossMab technique prevents the pairing of the wrong light chain with the wrong heavy chain (Figure 2). It swaps a few domains between one heavy chain and its corresponding light chain so that they fit with each other better.[11]

Non-IgG-like BsAbs:

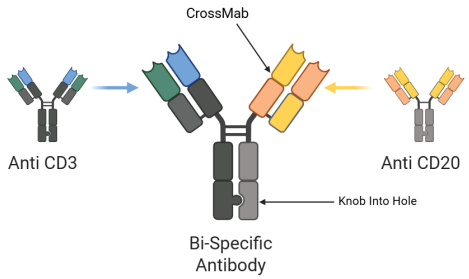

Figure 2: This figure illustrates the construction design of Y-shaped IgG-like BsAb, originating from two different mAbs with 2 different heavy and light chains. The stem of Y depicts the KiH technique to prevent unwanted homodimers of heavy chains, and the right limb of Y shows the CrossMab technique to prevent mismatched pairing of light and heavy chains. This diagram was created using BioRender.

These BsAbs lack an Fc region but have two complete or partial Fab regions and have two antigen-binding sites. These are smaller engineered fragments or fusions designed for a smaller size and better tumor penetration. These are less stable, have short half-lives, and need to be given in continuous intravenous infusion. The following examples will explain the structural design for better understanding.[12]

BiTE (Bispecific T-cell Engagers) are two single-chain variable fragments (scFv) joined by a linker protein without an Fc region in one polypeptide chain (Figure 3a).[13] One scFv binds CD3 on T cells, and the other binds a tumor antigen. They redirect T-cells to kill tumor cells. These are very potent but less stable and sometimes misfold. A practical example is Blinatumomab (CD19 x CD3), which is approved by the FDA for treatment of B-cell acute lymphoblastic Leukemia.

DARTs (Dual Affinity Re-Targeting antibodies) use 2 separate polypeptide chains, each chain contains a single antigen-binding site, which consists of crossed-over variable domains (Figure 3b).[14]

(VL1)-----S-S—--(VH2)

(VH1)-----S-S—--(VL2)

DARTs are more stable and correctly manufacturable than BiTEs. One practical example is Floletuzumab (CD123 x CD3), which is an investigational drug that received orphan drug status by the FDA for the treatment of Acute Myeloid Leukemia.

TandAbs (Tandem Antibodies), on the other hand, contain 4 scFvs arranged in tandem without a functional Fc region. These are engineered to have homodimers of two diabody-like polypeptide chains with a total of 4 binding sites, two binding sites for each target antigen. One practical example is AFM13 (CD30 x CD16A, NK cell engager), which is being investigated in the treatment of CD30-positive lymphomas such as Hodgkin lymphoma and peripheral T cell lymphoma. The drug acts as a bridge by connecting CD30-positive cancer cells with NK cells and macrophages via their CD16A receptors.[15]

scFv-Fc (Figure 3c) and minibodies (Figure 3d) have specially engineered Fab arms to create small scFv fragments that can bind to tumor receptors. These scFv fragments are fused to the Fc domain to improve half-life and can enhance immune engagement effects. A practical example is XmAb platform-based Cibistamab (CEA xCD3, scFv-Fc based), which is investigated for the treatment of CEA antigen-containing solid tumors. It makes a bridge between the CEA expressing tumor cells and the CD3 glycoproteins of T cells, while the Fc portion provides stability and improves half-life.[16]

Nanobody-based BsAbs are built from a single variable domain (VH) containing camelid heavy chain Antibodies called nanobodies (VHH) (Figure 3e). These single-domain small-sized nanobodies do not contain a light chain but have full antigen-binding capability. These nanobodies make BsAbs by linking with each other or by fusion with half-life extenders (Fc) or T cell engagers (Anti-CD3). A practical example is Ozoralizumab (TNF alpha x albumin xTNF alpha), which is approved for the treatment of Rheumatoid arthritis in Japan. It is a trivalent BsAb that includes two anti-TNF Alpha heavy chain antibodies (VHHs) and one anti-human serum albumin (VHH).[17]

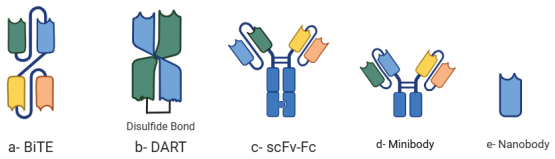

Figure 3: This figure illustrates various designs of non-IgG-like BsAbs. BiTE consists of two single-chain variable fragments (scFv) joined together in one polypeptide chain. DART contains 2 separate polypeptide chains with crossed-over variable domains. Construction of scFv-Fc and Minibody involves fusion of fragments of the Fab region to the complete or partial Fc region, respectively. Nanobody is a camelid-derived single-domain heavy-chain antibody fragment, which can be linked to other mAbs to make BsAb. This Diagram was created using BioRender.

Mechanism of Action in Cancer Therapy:

BsAbs eradicate cancer cells primarily by engaging and activating the immune system, acting as a bridge between tumor cells and immune effector cells. This creates a forced physical connection between a tumor cell and an immune cell, and eventually, the activated immune cell causes lysis of the tumor cell.[18] One arm of BsAb targets a specific antigen on the tumor cell (e.g, CD19 on B cell lymphomas) while the other arm attaches to the CD3 complex on the surface of the effector T cell. This indirect connection causes activation of T cells by bypassing the need for recognition of tumor antigen by the T cell receptor. The activated T cell secretes cytotoxic substances (perforins and granzymes), which cause apoptosis of cancer cells. T cells disengage from dead tumor cells and serially kill additional tumor cells one after the other as long as the BsAb is present.[19] This process is specific to BsAbs that engage with T cells and does not apply to all BsAbs formats. CD16 receptors of NK cells, on the other hand, simultaneously trigger antibody-dependent cellular toxicity.[20] Tumor cells have macrophage evasion receptors such as CD47, which send "do not eat me" signals to prevent phagocytosis by macrophages. Some BsAbs can block CD47 receptors on tumor cells, enhancing phagocytosis of tumor cells by macrophages. BsAbs can also bind to macrophages either via Fc receptors or activating receptors (e.g., MerTK).[21] Immune checkpoints are protein receptors (PD-1 and CTL-4) present on immune cells or ligands (PD-L1and CD28) present on normal cells or antigen-presenting cells; their interaction recognizes the body's own healthy cells and prevents them from immune attack. Tumor cells often trick immune cells by overexpressing these immune checkpoint ligands (PD-L1) or recruiting cells that express these ligands in the tumor microenvironment (TME).[22] BsAbs can simultaneously bind to tumor antigen and an immune checkpoint receptor (e.g., PD-1) on T cells. This checkpoint inhibition is limited to the TME, so that systemic immune activation-associated side effects can be prevented. BsAbs can also bind to two checkpoint inhibitors, PD-1 and CTLA-4, simultaneously to cause dual checkpoint inhibition, thereby enhancing T cell activity more effectively.

BsAbs can also inhibit tumor growth by a different mechanism, which does not involve the immune system, by simultaneously targeting two different growth factor receptors

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on tumor cells, which can stunt tumor growth and overcome tumor resistance mechanisms. For example, Amivantamab binds to the Epidermal growth factor receptor (EGFR) and MET receptor on non-small cell lung cancer and significantly inhibits tumor growth and survival by blocking two different growth signaling pathways. BsAbs are designed to bind to two different antigens on the same tumor cell. Dual antigen-binding makes a stronger connection than a single antibody. It also reduces "on target, off-tumor" toxicity by enhancing specificity to the cancer cells.[23] BsAbs can simultaneously inhibit two signaling receptors of two different growth pathways in a tumor cell and drastically reduce the risk of tumor resistance and tolerance compared to single-target therapy.[24]

Clinical Applications of Bispecific Antibodies:

A good number of BsAbs have been approved for the treatment of different cancers, and many more are in the pipeline.

Treatment of Hematologic Malignancies:

BsAbs have shown a profound impact on certain Hematologic malignancies listed below.

Blinatumumab is a BiTE that engages CD3 on T cells and targets CD19 on cancerous B-cells. It is FDA-approved to be used in relapsed or refractory B-Cell Acute Lymphoblastic Leukemia (B-ALL). It is also used for patients in remission with minimal residual disease to achieve complete remission.[25]

Teclistamab, Elranatamab, and Linvoseltamab are BiTEs that target B-cell maturation antigen (BCMA), highly expressed on multiple myeloma cells, on one side, and CD3 on T-cells on the other side. These have FDA accelerated approval to be used in relapsed or refractory multiple myeloma. These BsAbs redirect T-cells to kill multiple myeloma cancerous cells.[26]

Mosunetuzumab and Epcoritamab are BiTEs that target CD20 on lymphoma cells and CD3 on immune T-cells. These have FDA accelerated approval for relapsed or refractory follicular lymphoma.[27]

Epcoritamab and Glofitamab are BiTEs that target CD20 on lymphoma cells and CD3 on T-cells. These BsAbs have FDA accelerated approval for relapsed or refractory Diffuse Large B-cell Lymphoma with promising responses.[28]

AFM13 is a BsAb that bridges CD30-positive Hodgkin lymphoma cells with NK cells and macrophages, which leads to antibody-dependent cytotoxicity. It is in phase 2/3 clinical trials for relapsed or refractory Hodgkin lymphoma.[29]

Codanilimab (AK104) is a dual checkpoint inhibitor that targets PD-1 and CLT4 simultaneously. This BsAb is at the phase 2 clinical trial stage for relapsing or refractory Hodgkin lymphoma.

Flotetuzumab and Vibecotamab are BsAbs that redirect CD3 T cells to CD123-tagged Acute Myeloid Leukemia (AML) cells.[30] BsAbs redirecting (CD3 T cells to CD70 tagged AML stem cells), (CD3 cells to CLL-1 marked AML blast and stem cells) are at the preclinical stage of development. Dual checkpoint BsAbs (PD-1 and TIM-3) are being tested in AML as an immune modulator.[31] FDA has approved many BsAbs for the treatment of various hematological malignancies and some solid tumors (Table 1).

Table 1: FDA-approved bispecific antibodies (BsAbs) for hematologic malignancies and a few solid tumors. The table lists BsAbs that have received U.S. Food and Drug Administration approval after phase III clinical trials. For each cancer, the specific BsAbs, target antigens, antibody format, and approval status are shown. The target pairings highlight the mechanism of action of BsAbs, most commonly redirecting T cells via CD3 to kill tumor cells.

Cancer Type	BsAb	Targets	Type of BsAb	FDA Status
B-Cell Acute Lymphoblastic Leukemia (RR)	Blantumomab	CD19 x CD3	non-IgG (BiTE)	2014 TA
Multiple Myeloma (RR)	Teclistamab Elranatamab Linvoseltamab Talquetam	BCMA x CD3 BCMA x CD3 BCMA x CD3 GPRC5D x CD3	non-IgG (BiTE) non-IgG (BiTE) non-IgG (BiTE) IgG	2022 AA 2023 AA 2025 AA 2023 AA
Diffuse Large B-Cell Lymphoma (RR)	Epcortitamab Glofitamab	CD20 x CD3 CD20 x CD3	non-IgG (BiTE) non-IgG (BiTE)	2023 AA 2023 AA
Follicular Lymphoma (RR)	Mosunetuzumab Epcortitamab	CD20 x CD3 CD20 x CD3	non-IgG (BiTE) non-IgG (BiTE)	2022 AA 2024 AA
Non-Small Cell Lung Cancer EGFR Exon 20 mutation	Amivantamab	EGFR x c-MET	IgG	2021 TA
Uveal Melanoma (unresectable metastatic) (HLA-A*02:01 positive)	Tebentafusp	gp100 x CD3	non-IgG (fusion protein)	2022 TA
Small Cell Lung Cancer (RR)	Tarlatamab	DLL-3 x CD3	non-IgG (BiTE)	2024 AA
(Non-Small Cell Lung Cancer, Pancreatic Adenocarcinoma) with NRG1 Fusion (RR)	Zenocutuzumab	HER2 x HER3	IgG	2024 AA
Biliary Tract Cancer (HER2-Positive) (RR)	Zanidatamab	HER2 x HER2 (Biparatopic)	IgG	2024 AA

RR= Relapsing Remitting, TA =Traditional approval, AA= Accelerated approval, BCMA = B-cell maturation antigen, GPRC5D =G protein-coupled receptor class C Group 5 member D, EGFR= Epidermal growth factor receptor, NRG-1 Fusion = Nuregulin-1 Fusion, HER =Human epidermal growth receptor

Treatment of Solid Tumors by Bispecific Antibodies:

BsAbs face multiple challenges in the treatment of solid tumors. Solid tumors have immunosuppressive tumor microenvironments (TME), including high expression of checkpoint molecules, myeloid-derived suppressive cells, and immunosuppressive cytokines. Solid Tumors lack a universal tumor-specific antigen and share antigens with healthy cells, which can lead to "on-target, off-tumor" toxicity. Most solid tumors have dense stroma and extracellular matrix, which physically block immune cell infiltration. However, newer BsAbs are designed to solve these problems and have potential for success.[32]

Amivantamab is an IgG-like BsAb; its two arms target two separate receptors on tumor cells to block two different growth pathways. This BsAb blocks the Epidermal growth factor receptor (EGFR) and MET receptor. Dual blockage decreases the chances of tumor escape and resistance. Its Fc portion can also enhance antibody-dependent cellular toxicity. It is FDA approved for a specific Non-Small Cell Lung Cancer (non-SCLC) which harbors EGFR exon 20 insertion mutation.[33]

Tebentafusp targets CD3 T cells and gp100-expressing melanoma cells. The FDA approves it for the treatment of a specific

metastatic uveal melanoma, which is HLA-A*02:01 positive.[34] Tebotelimab is a DART molecule that simultaneously blocks two immune checkpoint inhibitory receptors, PD-1 and LAG-3, on T cells. This leads to reactivation of exhausted T cells against cancer cells. This BsAb is in early-phase trials for resistant metastatic melanoma.[35] 6 Brenetafusp (IMC-F106C) redirects CD3 cells to PRAME antigen- associated melanoma cells. It is under phase 1/2 trials for cutaneous melanoma and other PRRAME-positive tumors such as NSCLC, ovarian, and endometrial cancers.[36]

Cadonilimab (AK104) is a dual checkpoint inhibitor (PD-1 and CLT4). It is approved in China for recurrent metastatic cervical cancer.[37] Tarlatamab is a BiTE that redirects CD3 T cells to DLL3 protein-bearing SCLC cells. It has FDA accelerated pathway approval for metastatic recurrent SCLC.[38] Acapatamab (AMG 160) is a half-life extended BiTE which targets CD3 T-cells and Prostate-specific membrane antigen (PSMA) tagged Prostate cancer cells. It has shown promising results in phase 1 clinical trials for the treatment of metastatic castration-resistant prostate cancer.[39] Cibisatamab is an IgG-type BsAb with a disabled Fc region. It has two domains to bind with CEA on Colorectal cancer cells and CD3 of T-cells. It has completed phase 1 study for the treatment of metastatic colorectal cancer.[40]

Zenocutuzumab is a BsAb that targets both HER2 and HER3 receptors on tumor cells simultaneously. HER2 and HER3 and their heterodimers are growth factor receptors that play an important role in tumor growth. NRG1 ligand drives tumor growth through HER3 receptors in certain Pancreatic adenocarcinomas and NSCLC, which have NRG1 fusion genetic alteration.[41] FDA has granted Zenocutuzumab accelerated approval for the treatment of resistant NSCLC and Pancreatic adenocarcinoma that harbor NRG1 fusion.

Zanidatamab is an IgG-like BsAb that has two antigen-binding sites, which target two different domains (ECD2 and ECD4) of the HER2 receptor on tumor cells. This dual binding causes enhanced HER2 downregulation, inhibiting tumor growth signals. Activated Fc portion of this BsAb ignites both complement-mediated cytotoxicity and antibody-dependent phagocytosis and cellular Cytotoxicity. The FDA has granted Zenocutuzumab accelerated approval for the treatment of previously treated unresectable metastatic HER2-positive biliary tract cancer.[42]

Advantages of Bispecific Antibodies:

The fundamental difference between monoclonal BsAbs and conventional mAbs is that the former binds to two antigens or epitopes, while the latter binds to only one. This dual target capability provides the following key advantages.

Conventional mAb does not activate T-cells directly, as its Fab regions are specific to the tumor antigen and are used up in binding to the tumor. mAb can stimulate antibody-dependent cytotoxicity via its Fc portion. BsAb has two diverse Fab arms, one arm binds to the tumor antigen while the other arm binds to the Immune effector T-cells. This creates a physical synaptic connection between cytotoxic T cells and tumor cells by bypassing the need for direct detection of cancer cells by T-cells. This phenomenon is very important as many cancer cells evade T cells through immune checkpoints.[18]

BsAbs reduce on-target off-tumor toxicity. Some BsAbs may bind to two tumor-specific antigens moderately and achieve high affinity only when both targets are present. This enhanced specificity for tumor cells spares those healthy cells that may have only one out of the two tumor antigens. This widens the therapeutic index and decreases potential damage to healthy cells.

Some BsAbs provide tumor-targeted immune activation. Attack on healthy cells is minimized as T-cells are activated by these BsAbs only when they are attached to the tumor antigen.[43]

Cancer growth and spread are often dependent upon multiple signaling receptors affiliated with different growth pathways. Traditional mAb can block only one receptor and pathway, and cancer cells can escape blockage via another preexisting pathway or develop resistance to a single mAb by evolving a newer growth pathway. BsAb can inhibit two different growth factors or ligands simultaneously, e.g., Amivantamab inhibits both the EGFR and MET receptors in NSCLC. This synergistic approach can be more efficacious and can prevent tumor escape and resistance.[14] BsAbs are highly potent because of their synergistic effects on cancer cells by engaging multiple mechanisms, e.g., immune activation and growth pathway blockade. In preclinical studies, BsAbs outperform and can be 100 to 1000 times more effective than traditional mAbs alone or even the additive effects of combination therapies.[13] Combination of two mAbs has been found more effective than a single mAb, eg, anti-PD-1+anti-CTLA-4 in metastatic melanoma. A single BsAb with dual effect can simplify dosing, lower cost, and may avoid antagonistic PK/PD interactions. For example, Cadonilimab is a dual checkpoint inhibitor (PD-1 and CTLA-4) approved for metastatic cervical cancer in China.[44]

BsAbs can be engineered in multiple formats. Fragment-based small-sized designs can better penetrate solid tumors. The addition of an inactive Fc portion can increase the half-life without increasing the undesired side effects of attacking healthy cells. IgG-like formats with an active Fc portion can stimulate antibody-dependent cytotoxicity as well.[8] BsAbs can act as delivery vehicles for payloads such as toxins, cytokines, drugs, or radionuclides. BsAb conjugated to a drug targets two different tumor-specific antigens on the same tumor cell, which improves internalization into the cancer cell. Pretargeting is a different approach by which BsAb attaches to a specific antigen on a tumor cell with one arm. A radionuclide payload is introduced, which gets captured by the other free arm of the pretargeted BsAb. This widens the therapeutic index and spares normal tissue.[45]

Limitations of BsAbs:

BsAbs can have manufacturing complexities. E coli and CHO cells are used for fragment-based and IgG-like antibodies, respectively, as gene expression systems to produce protein structures of BsAbs from the engineered genetic code. Platform optimization with special techniques, such as transposon systems, is often needed to correctly integrate genes of interest

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into transcriptionally active, stable regions of the host genome to achieve high expression levels.

BsAbs production requires complex engineering to yield a high ratio of correctly paired light and heavy chains for both antigen-binding sites. Formation of undesired inactive homodimers and mispaired chains can lead to non-functional BsAbs. Technologies like KiH, crossMab, and common light chains are used to solve this problem, which adds to the complexity of production. To separate desired BsAb from mispaired byproducts requires multiple chromatography steps. The non-native unnatural structure of some BsAb formats is prone to aggregation and reduced efficacy.[9]

BsAbs face intricate pharmacokinetics and biodistribution issues. IgG-like BsAbs have a larger size due to the presence of the Fc region and may struggle to penetrate the solid tumors due to dense tumor stroma. Fragment-based BsAbs (e.g., BiTEs and DARTs) lack an Fc region, which can improve tumor penetration. However, the lack of the Fc region prevents FcRn-mediated recycling. This results in degradation of these BsAbs in intracellular endosomes, rapid clearance, and short half-life. Due to short half-life, fragment-based BsAbs need frequent dosing or continuous infusions.[16]

BsAbs face unique challenges in clinical trials and drug development programs. Balancing efficacy and toxicity is difficult, which makes it complex to determine and develop optimal dosing. Complex step-wise dosing regimens are required. Lack of predictive biomarkers makes patient selection for clinical trials difficult. Comparative trials with dual mAb therapy are costly and lengthy.[46] The FDA requires meticulous characterization of structure-function relationships, potency assays, and immunogenicity assessment. This demands novel clinical trial designs and endpoints. Complex manufacturing requiring specialized platforms, lengthy drug development programs, and extensive regulatory processes makes BsAb research, development, and production very costly.[47]

BsAbs structure makes them prone to having a higher risk for toxicity and a narrow therapeutic index. T-cell engager BsAbs can cause Cytokine Release Syndrome (CRS) due to generalized immune system activation. This systemic inflammatory response can be severe and fatal, requiring careful dosing and management. Tumor-associated antigens are sometimes present on certain healthy tissue cells. BsAbs can bind to these antigens expressed on healthy tissues, causing on-target, off-tumor effects.[48] Some formats of BsAbs often incorporate murine-derived DNA sequences or novel scaffolds, which can be recognized as foreign by the patient's immune system, leading to anti-drug antibodies (ADAs) that neutralize the BsAb or cause adverse effects.[48]

BsAbs face unique challenges against Solid tumors. Dense stroma and abnormal vasculature in solid tumors impede BsAb delivery and act as a physical barrier. TME contains regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and checkpoint molecules (e.g., PD-L1) that inhibit effector T cells. T-cell engager BsAbs often fail to overcome this suppression. Solid tumors have very few purely tumor-specific antigens. These antigens can have low-level expression in normal tissues, which can narrow the therapeutic index. Furthermore, solid tumors have a high mutational burden. Tumor cells often downregulate or mutate target antigens, resulting in escape from BsAb-mediated killing.[32]

Future Directions:

Innovations and advances in protein engineering will create novel BsAb formats with improved efficacy and safety profiles. Immunogenicity against BsAb can be reduced by using humanized DNA sequences and scaffolds. A third target can be added to BsAbs to make triphasic or multiphasic antibodies, which may enhance precision and overcome resistance. For example, triphasic antibodies targeting BCMA, GPRC5D, and CD3 are in development for multiple myeloma. Designing switchable BsAbs that become active only in TME after attaching to a tumor can minimize off-tumor toxicity.[49] Research is being conducted to develop tools to enhance the efficacy and lower the toxicity of BsAbs. Adding turn-off switches or control mechanisms to deactivate the BsAbs in case of severe side effects, such as CRS, is under investigation. Research is being conducted to develop BsAb designs which can be administered subcutaneously to reduce peak serum concentrations and systemic toxicity.[50]

Research is ongoing to discover novel tumor-specific antigens, e.g., Claudin 18.2 in gastric and pancreatic cancers, DLL3 in SCLC, and GPC3 in hepatocellular carcinoma. BsAbs are being developed against neoantigens and fusion proteins present on certain cancer cells due to genetic alterations.[51] Various fragment-based BsAbs are under development, which can penetrate the stromal barrier and survive in immunosuppressive TME of solid tumors.

BsAbs are being developed, which can simultaneously attack both tumor-associated antigens and stromal cells, creating barriers around solid tumors. For example, BsAbs are under development, which will incorporate Abs against fibroblast activation protein, which is highly expressed in cancer-associated fibroblasts. Intratumoral BsAbs are in the pipeline, where BsAbs are directly delivered inside the solid tumor. Delivery of the BsAb gene incorporated in the genetic code of the oncolytic virus is under investigation.[52]

BsAbs are currently approved for recurrent tumors as last-line therapy. Clinical trials are being conducted to use BsAbs as a front-line therapy. BsAbs Teclistamab and Elrantamab are being tested in newly diagnosed multiple myeloma. Amivantamab (EGFR × c-MET) is being studied in combination with chemotherapy or Lazertinib as frontline therapy for NSCLC.[53] Conjugation of BsAbs with radioligands and drugs can enhance precise payload delivery. BsAbs can enhance Chimeric antigen receptor (CAR) T-cell therapy by simultaneously targeting tumor cells and CAR T-cells, amplifying their anti-cancer effects through increased T-cell activation and expansion. BsAbs in combination with immune checkpoint inhibitors can cause stronger immune engagement. BsAbs can be combined with radiotherapy or chemotherapy to increase tumor antigen exposure and enhance BsAb activity.[54] Algorithms are being developed to stratify patients by using biomarkers, e.g., soluble BCMA levels or immune signatures, e.g., certain T-cell counts, to identify and predict responders and non-responders. Plat-

forms are being developed to produce unique patient-specific BsAbs against neoantigens or fusion proteins.[55]

Using novel platforms like DuoBody or CrossMab can simplify the manufacturing process and reduce costs. Developing oral BsAbs can cut the cost of infusion centers and improve patient convenience.[5] Expanding clinical trials and tumor registries across various geographic and racial boundaries can increase the external validity of certain BsAbs. It will provide information on response rates for different genetic backgrounds.[56] Multiple phase 1 & 2 trials are underway for various BsAbs for the treatment of cancer (Table 2).

Table 2: Ongoing phase I and II clinical trials investigating novel bispecific antibodies (BsAbs) for primarily solid tumors. These studies explore innovative strategies such as targeting newly identified tumor antigens, combining BsAbs with chemotherapy or other monoclonal antibodies to modify the tumor microenvironment (TME) for better penetration, and conjugating BsAbs with radioisotopes for targeted payload delivery.

BsAb ID	Trial ID & Phase	Cancer Type	Target	Innovation
QL 1706	NCT0678602 Phase 2	Triple Neg Metastatic Breast Cancer	PD-1 and CLTA-4	Combination with Chemotherapy (paclitaxel) plus or minus mAb (Bevazmuzab)
BGB-B455	NCT06803680 Phase 1	Advanced metastatic solid tumors	CLDN6 and CD3	Novel Tumor-specific onco-fetal antigen (CLDN6)
PT217 (Peluntamig)	NCT05652686 Phase $\frac{1}{2}$	Neuroendocrine Carcinomas	DLL3 and CD47	Novel Tumor specific antigen DLL3 and macrophages evasion receptor (CD47)
FPI-2053 [111In]-FPI-2107 [225Ac]-FPI-2068	NCT06147037 Phase 1	Solid or Metastatic Tumors	EGFR and cMET	Conjugation with Radioisotopes Indium-111 & Actinium-225
Teclistamab	NCT07110844 Phase 2	AL amyloidosis Plasma/B-cell clonal disorder	CD3 and BCMA	Combination with another mAb (Daratunmubab)

PD-1 =Programmed Cell Death Protein 1, CLTA-4 = Cytotoxic T-lymphocyte associated protein -4, CLDN-6 = Claudin-6, DLL3 = Delta-like ligand 3, EGFR= Epidermal growth factor receptor, BCMA= B-cell maturation antigen.

BsAbs have a huge advantage over the mAbs because of higher potency, efficiency, and versatility in the treatment of cancer. BsAbs engage with tumor antigen and immune effector cells simultaneously, leading to activation of T cells by bypassing the immune system evasion mechanisms of tumor cells. BsAbs can also target two different growth factor receptors on tumor cells, which can stunt tumor growth and overcome tumor resistance mechanisms. Dual tumor-specific antigen targeting may enhance safety by lowering on-target, off-tumor toxicity, as healthy cells may not possess both tumor antigens. BsAbs can also be created in a plethora of formats, including small fragments that consist of modified complete or partial Fab regions. Although a smaller size can optimize the penetration of solid tumors, it comes at the expense of stability. Parts of Fc regions can be added to the above-mentioned Fab region designs to enhance stability and extend half-life. Risk of generalized immune system activation and CRS related to the functional Fc region can be minimized by using an inactive Fc region or turning off switches. BsAbs face certain challenges, including manufacturing complexities, limitations in pharmacokinetics and distribution, risk of CRS, and paucity of tumor-specific antigens present on solid tumors. The above-mentioned challenges provide opportunities for future innovations, including improved areas for manufacturing BsAbs, the discovery of new tumor-specific antigens, and sensible combinations with well-established treatments. Future research holds potential for increasing the safety, efficiency, and universal usage of BsAbs.

Conclusion

BsAbs represent a revolutionary avenue in cancer immunotherapy and are currently reshaping the oncology practice. The FDA has approved multiple BsAbs for the treatment of hematologic malignancies. Although few BsAbs have FDA approval for solid tumors, there is an expanding list in the pipeline. Continued innovations in design, optimization of safety profiles, and integration with other treatment modalities will further expand and uncover the ultimate role of BsAbs in Cancer treatment. In conclusion, while further research and progress remain to be seen, due to the diverse mechanisms of action and engineering potential to target multiple antigens simultaneously, BsAbs can play a pivotal role in the next-generation treatment of cancer. BsAbs have the potential to change cancer care to cancer cure.

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