Molecular Cancer

REVIEW

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Bispecific antibodies: unleashing a new era in oncology treatment

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Abstract

Advancements in diagnostic and therapeutic standards have substantially enhanced the survival of patients with malignant tumors. Nevertheless, the quest for effective strategies to address resistant or recurrent advanced tumors remains a critical and unwavering objective. Bispecific antibodies (BsAbs) unleashed a new era of anti-tumor treatment by simultaneously binding to two distinct targets, thereby enhancing specificity, minimizing off-target toxicities, and synergistically modulating anti-tumor immunity and the tumor microenvironment. Compared with the combination of two monoclonal antibodies, BsAbs represent the physical integration of dual specificities, demonstrating superior binding efficacy, reducing the risk of drug resistance, and enabling unique biological functions such as bridging tumor cells and T cells to achieve precise cytotoxicity. However, limitations such as off-target toxicities, drug resistance and immune-related adverse effects require carefully evaluation and further optimization. Further studies are necessary to explore the potential of combining BsAbs with other anti-tumor strategies, balancing the efficacy and safety, optimizing the outpatient-based administration workflow. By tracking the research advancements of recently approved BsAbs and BsAb candidates in clinical trials, it is evident that BsAbs holds significant promise as a novel and transformative option for improving survival outcomes for patients.

Keywords Bispecific antibody, Anti-tumor treatment, T-cell engager, Drug approval, BsAb resistance

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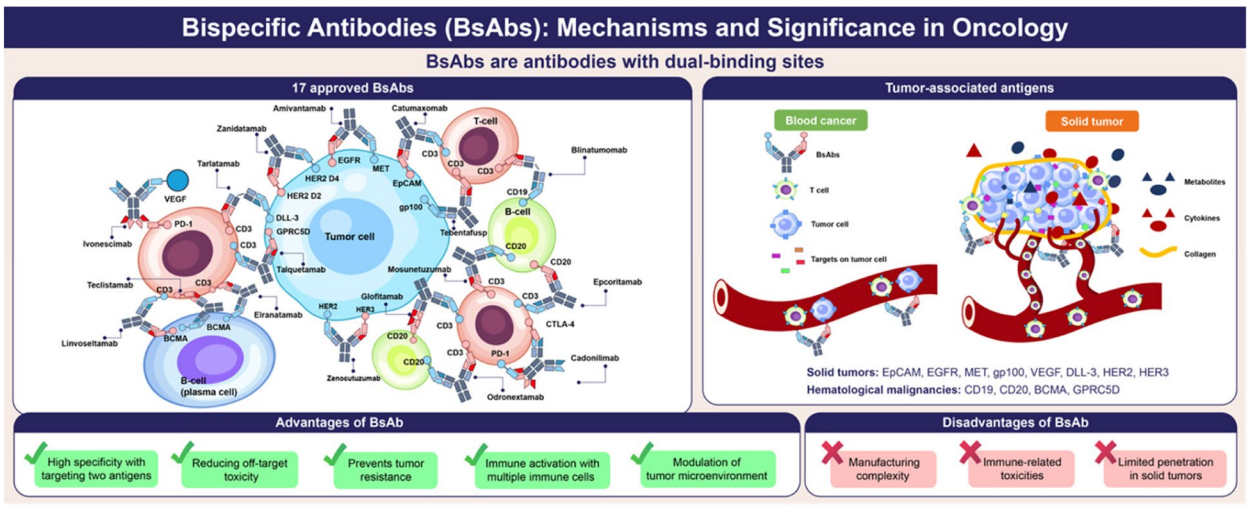
Graphic Abstract



Introduction

Cancer continues to pose one of the most significant public health challenges worldwide. Recent statistics suggest that by 2025, approximately 2,041,910 new cancer cases will be diagnosed in the United States and 618,120 individuals will succumb to cancer [1], suggesting an estimated incidence-to-mortality ratio of approximately 3.3:1. Although conventional anti-tumor interventions, such as surgery, chemotherapy, radiotherapy and targeted therapy, are currently employed, the development of innovative and efficacious anti-tumor strategies has become a critical priority.

In recent years, the number of studies dedicated to the development of anti-tumor therapy employing bispecific antibodies (BsAbs) has substantially increased. A BsAb is a synthetic antibody with two targeted binding units that can simultaneously bind and recognize either two different antigens or two epitopes on the same antigen [2]. BsAbs exhibit properties that extend beyond the superposition of two monoclonal antibodies (mAbs), leading to a synergistic outcome exceeding the sum of their individual components. Compared with the combination of two mAbs, BsAbs enhance targeting specificity through specific dual-targeting, demonstrating superior binding efficacy, reducing the risk of drug resistance, and enabling unique biological functions such as bridging tumor cells and T cells to achieve precise cytotoxicity.

The natural BsAb molecule was first observed by Aalberse et al., who demonstrated the stochastic post-translational formation of bispecific immunoglobulin G4 (IgG4) hybrid molecules [3]. Subsequently, the mechanism of IgG4 antigen-binding fragment (Fab) arm exchange was shown to occur in vivo under specific localized redox conditions. The concept of artificially combining two antigen-binding sites within a single molecule originated with Nisonoff, who cleaved IgG molecules using pepsin to generate univalent $F(ab')_2$, which were then used to create antibodies with mixed specificity [4]. Later, Köhler and Milstein developed the hybridoma technology, an extensively adopted approach for generating BsAbs, known as quadromas [5, 6]. However, the diverse assembly of various heavy (H) and light (L) chains resulted in extremely low yields of the desired bispecific H/L chains. Therefore, subsequent efforts focused on chemically crosslinking $F(ab')_2$ molecules to improve yield.

Owing to advancements in genetic engineering and biological macromolecular recombination, a BsAb targeting cluster of differentiation 3 (CD3) and the epithelial cell adhesion molecule (EpCAM), Catumaxomab (Removab), became the first approved BsAb for treating malignant ascites in epithetial tumors in 2009 [7, 8]. Until 2014, another BsAb, Blinatumomab, targeting CD3 and CD19, was approved by the U.S. Food and Drug Administration (FDA) for treating acute lymphoblastic leukemia (ALL) [9]. Since 2021, there has been a significant increase in the number of BsAbs receiving regulatory approval [10]. As the field progresses, maintaining an updated understanding of approved BsAbs and tracking the development of promising BsAb candidates will be essential for researchers. However, comprehensive and up-to-date summary regarding

globally approved BsAbs and emerging BsAb candidates remains limited. This review offers an in-depth analysis of research advancements in BsAbs with anti-tumor potential up to May 2025, covering the mechanisms of action, clinical efficacy, safety profiles, and specific therapeutic indications.

Category and mechanism of BsAbs

Given significant variability in design and format, BsAbs can be broadly classified into two categories according to the presence of a fragment crystallizable (Fc) domain, which can mediate additional effector functions [2]. The classical structure and schematic representations of several crucial BsAb formats are shown in Fig. 1, including IgG-like BsAb formats (with the Fc region) and non-IgG-like BsAb fragments (without the Fc region).

IgG-like BsAbs (with the Fc region)

IgG-like BsAb is a combination of two mAbs with distinct targets, exerting Fc-mediated effector functions offered by Fc fragments. Full-length BsAbs with Fc regions exhibit longer half-lives, higher solubility, and increased stability due to their larger size and the neonatal Fc receptor (FcRn)-mediated recycling process. Essentially, IgG-like BsAbs may offer significant clinical therapeutic potential by retaining Fc-mediated effector functions,

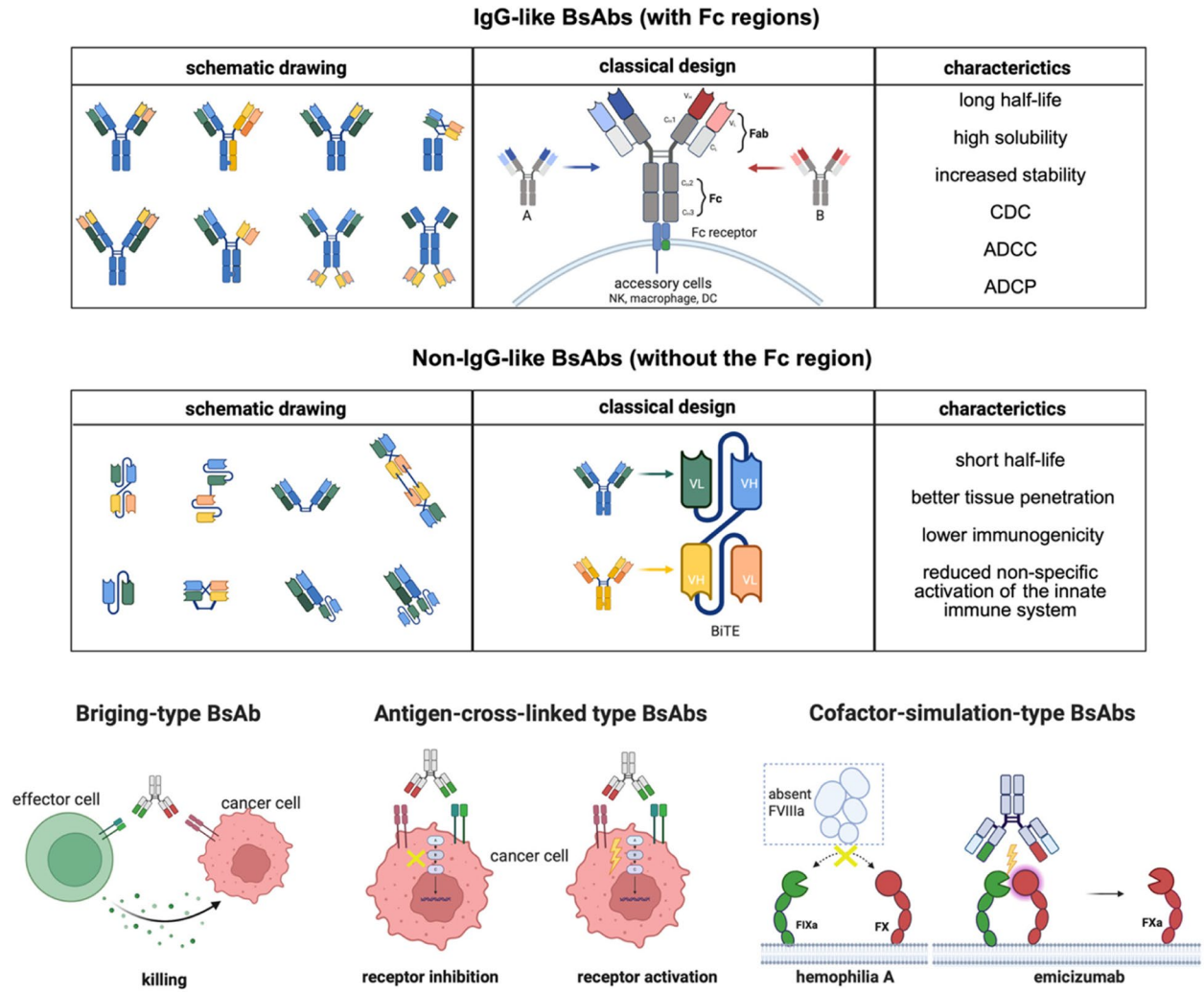


Fig. 1 Classification and mechanism of action of BsAbs. From the perspective of structural design and format variability, BsAbs can be broadly classified into two main types: IgG-like BsAb formats (with the Fc region) and non-IgG-like BsAb fragments (without the Fc region). The classical structure and schematic representations of several crucial BsAb formats are presented. From the perspective of specific mechanisms of action, BsAbs could be further categorized into the three categories: bridging-type, antigen-cross-linked type, and cofactor-sumulation-type BsAbs. The underlying mechanisms of these three types of BsAbs are illustrated respectively. Abbreviations: CDC, complement-dependent cytotoxicity; ADCC, antibody-dependent cell-mediated cytotoxicity; ADCP, antibody-dependent cellular phagocytosis

including antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and antibody-dependent cellular phagocytosis (ADCP). The Fc domain can be further engineered to abrogate Fc-mediated effector functions, thereby preventing T-cell activation via Fcγ receptor-mediated CD3 cross-linking.

Non-IgG-like BsAbs (without the Fc region)

Non-IgG-like BsAbs bind multiple Fabs to molecules lacking Fc regions, avoiding chain cross-linking and the associated Fc-mediated effects. For example, bispecific T cell engagers (BiTEs) are a distinct class of BsAbs, comprising tandem single-chain variable fragments (scFvs) connected via a flexible peptide linker and lacking Fc domains. One binding site recognizes antigens expressed on tumor cells, while the other specifically interacts with CD3. The advantages of BiTEs, including the small size, improved tissue penetration, high flexibility, and high-affinity connection between effector and target cells, are consider to be responsible for their excellent efficacy [11]. With lower immunogenicity, a shorter half-life, and the avoidance of toxicities associated with Fc receptor-mediated effector functions, BiTEs may exhibit enhanced safety profiles. However, the short protein half-life presents a therapeutic challenge due to the rapid dissipation, which complicates the maintenance of consistence serum levels. Another specific structure of is the immune-mobilizing monoclonal T-cell receptor against cancer (ImmTAC) developed by Immunocore, which constitutes a class of bispecific molecules that integrate a high-affinity TCR with an anti-CD3 scFv [12]. This design enables the molecule to target intracellular endogenous antigens while simultaneously recruiting and activating T cells for the precise elimination of tumor cells, thereby augmenting the anti-tumor immune response.

Currently, several challenges remain in optimizing the structural design of BsAbs to achieve a safer profile. For instance, the Duobody platform, which relies on flexible chain exchange, may result in less controlled pairing and increased off-target toxicities. To address this limitation, mosunetuzumab utilizes the "knobs-into-holes" approach, wherein the"knobs" in one CH3 domain are engineered to fit into complementary "holes" in the opposing CH3 domain, ensuring precise heavy chain pairing and minimizing off-target effects [13]. The tetravalent structure of cadonilimab, featuring 4 antigen-binding sites, represents a significant advancement over conventional BsAbs by enhancing antigen binding affinity, minimizing off-target effects, and eliciting a more efficient immune response. Furthermore, charateristics such as complex architectures, precisely engineered sequences and limited humanized components of BsAbs may collectively heighten the risk of immunogenicity [14]. Reverse translation initiatives should be implemented to guide decisions regarding platform and scaffold adjustments.

Based on the functional mechanisms, BsAbs can be categorized into three groups: (1) bridging immune and tumor cells to recruit and activate immune cells for tumor cell elimination, (2) modulating multiple signaling pathways to exert synergistic effects, and (3) facilitating protein complex formation to exert biological effects. The mechanisms of these three functional categories of BsAbs are illustrated in Fig. 1.

Bridging-type BsAbs

Bridging-type BsAbs typically bind to antigens on tumor and effector cells (such as T and natural killer cells) and activate effector cells to recognize and eliminate tumor cells. CD3 is a common surface target on immune cells, known for its strong ability to activate and recruit T cells. T cell engager (TCE), which are BsAbs targeting CD3, can bridge tumor cells and T cells to form a lytic immune synapse and directly activate effector T cells without requiring major histocompatibility complex (MHC)-mediated antigen presentation, thereby inducing cytotoxicity against tumor cells. For instance, talquetamab, a BsAb targeting G-protein-coupled receptor class C group 5 member D (GPRC5D)/CD3, binds to CD3 receptors on T cells and GPRC5D on multiple myeloma (MM) cells [15]. Moreover, BsAbs uniquely connect different target cells within the tumor microenvironment (TME) than the combination of two mAbs. A study demonstrated that cadonilimab could induce the formation of cell doublets and simultaneously bind cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) on separate cells [16]. Strong adhesion between Jurkat-PD-1 cells and Chinese hamster ovary (CHO)-K1-CTLA-4 cells was observed when incubated with cadonilimumab but not when nivolumab and ipilimumab were combined [16].

Antigen-cross-linked BsAbs

Antigen-cross-linked BsAbs can simultaneously bind and recognize two different antigens or two epitopes of an antigen and effectively inhibit two disease-related signaling pathways. This dual action helps avoid drug resistance resulting from single-target inhibition, thus providing a more comprehensive and long-lasting therapeutic effect. For example, the overexpression of the epidermal growth factor receptor (EGFR) is associated with the progression of various epithelial tumors, such as non-small cell lung cancer (NSCLC), ovarian cancer, colorectal cancer, and prostate cancer. Tyrosine kinase inhibitors targeting EGFR (EGFR–TKI), such as gefitinib and erlotinib, have achieved clinical success over the past two decades but also face the challenge of resistance. Relevant studies

have shown that amplification of mesenchymal-epithelial transition (MET) is a critical mechanism of EGFR–TKI resistance, whereas the clinical outcomes of patients with MET amplification can be improved by MET inhibitors [17]. Therefore, BsAbs that target both EGFR and MET, such as amivantamab and EMB01, can effectively control EGFR–TKI resistance caused by MET mutations [18–20].

Cofactor-simulation-type BsAbs

Cofactor-simulation-type BsAbs bind to different molecules to form functional complexes, thereby simulating the function of cofactors and enhancing the immune response. For example, emicizumab bridges activated clotting factor IXa and clotting factor X to replace the absent activated factor VIII (FVIII), thereby promoting thrombin production and reducing bleeding risk. A previous study found that after emicizumab prophylaxis, the annual bleeding incidence in patients with hemophilia was reduced by 68% compared to traditional FVIII treatment [21].

As of May 2025, a total of 17 BsAbs had been approved for anti-tumor treatment applications. Detailed information is provided in Table 1. In the following sections, we will systematically review the research advancements in BsAbs for various tumor types, categorized by hematological malignancies and solid tumors.

BsAbs in hematologic tumors

TCEs, as mentioned previously, is a type of BsAb targeting CD3 and the tumor antigen, which can recruit T cells to the tumor and induce the formation of an immune synapse. When the synapse is formed, activated T cells release perforins and granzymes, resulting in T cell-dependent killing of tumor cell [22]. Hematologic cancers are particularly well-suited for TCE therapies, as malignant blood cells circulate with T cells to avoid the hindrance of the physical barrier and acquire direct killing of tumor cells. CD3-targeting TCEs have shown promising remission rates in patients with R/R ALL, non-Hodgkin's lymphoma (NHL), multiple myeloma (MM), and acute myeloid leukemia (AML). Figure 2 shows the formats and targets of the 9 kinds of TCEs approved for hematological tumors.

B-cell precursor ALL

The prognosis of adults with newly diagnosed ALL has improved over the past three decades. By using intensive chemotherapy regimens, complete response (CR) has been achieved in 85–90% of patients, with long-term survival rates of 30–50% [23]. However, B-cell precursor ALL (BCP-ALL), which originates from B-lymphoid progenitors, has a poor prognosis with less-than-optimal survival outcomes. Among adults with R/R ALL, the overall response rate (ORR) are 18–44% even with aggressive multi-agent chemotherapy, but the duration of response (DoR) is typically short [24].

Blinatumomab

Blinatumomab (Blincyto) was the first approved BsAb for the treatment of CD19 positive R/R BCP-ALL approved in December 2014 by the FDA, in November 2015 by the European Medicines Agency (EMA) and in December 2020 by the China National Medical Products Administration (NMPA) [25]. Blinatumomab is a recombinant murine protein that acts as a CD19-directed BiTE. Given the expression of CD19 on the surface of over 90% of BCP-ALL blasts, blinatumomab is considered to mediate tumor lysis and facilitate the release of cytokines that promote T cell activation and subsequent tumor cell elimination [26, 27]. In a multicenter, randomized, phase III TOWER trial (NCT02013167), which enrolled heavily pretreated patients with BCP-ALL, the blinatumomab group showed a significantly higher median overall survival (OS) of 7.7 months compared with 4.0 months in the chemotherapy group ($p=0.01$). No significant differences in grade 3 or higher treatment-related adverse effects (TRAEs) were observed between the two groups, whereas blinatumomab led to more frequent therapeutic discontinuation than chemotherapy (12% vs. 8%) [28].

Adult patients with BCP-ALL who achieve measurable residual disease (MRD)-negative remission after induction chemotherapy have a better prognosis than those with MRD-positive status. A subsequent study enrolling patients with MRD-positive BCP-ALL showed that 78% of patients returned to an MRD-negative status after one four-week cycle of blinatumomab [29]. These results prompted the FDA to expand in March 2018 the use of blinatumomab to BCP-ALL patients achieving primary or second CR with an MRD $\geq$ 0.1%. However, patients with MRD-negative remission still express relapse [30]. The use of blinatumomab in consolidation chemotherapy in adult patients with MRD-negative remission significantly improved clinical outcomes. A phase III study (E1910) enrolled 224 patients with MRD-negative status after induction and intensification chemotherapy who received blinatumomab and consolidation chemotherapy or consolidation chemotherapy alone [31]. After a median follow-up of 43 months, the three-year OS were significantly higher in the blinatumomab group than those in the chemotherapy group (85% vs. 68%, $p=0.002$) [31]. This results demonstrated that incorporating blinatumomab into consolidation chemotherapy significantly enhances efficacy and maintains a more stable and deeper negative MRD status, thereby improving long-term patient survival. In 2024, the FDA extended the indication to the consolidation chemotherapy phase, marking the evolution

Table 1 Detailed information on the 17 approved BsAbs in oncology treatment as of May 2025

Tumor	Name	Target	Format	Approved indication	Approval time and organization
Hematological cancer	Blinatumomab (Blincyto)	CD19 × CD3	BiTE (two scFvs connected via a linker)	1.R/R BCP-ALL 2. First or second complete remission with MRD-positive (≧0.1%) BCP-ALL	12/2014 FDA 11/2015 EMA 12/2020 NMPA
	Mosunetuzumab (Lunsumio)	CD20 × CD3	Humanized mouse IgG1-based Ab	Patients with R/R FL receiving at least two-line or later therapy	6/2022 EMA 12/2022 FDA
	Epcoritamab (Epkinly)	CD20 × CD3	Humanized mouse IgG1-based Duobody BsAb	Adult patients with R/R DLBCL and R/R FL	5/2023 FDA 9/2023 EMA
	Glofitamab (Columvi)	CD20 × CD3	Fully human IgG1-based Ab with 2:1 configuration (bivalent CD20 and monovalent CD3 binding)	1. Patients with DLBCL refractory to 2 or more prior lines of therapy 2. DLBCL arising from FL	6/2023 FDA 11/2023 NMPA
	Teclistamab (Tecvayli)	BCMA × CD3	Humanized mouse IgG4-based Duobody BsAb	R/R MM received at least four prior therapies including IMiDs, PIs, and anti-CD38 mAbs	8/2022 EMA 10/2022 FDA 6/2024 NMPA
	Elranatamab (Elrexfio)	BCMA × CD3	Humanized IgG2a-based heterodimeric BsAb	R/R MM patients received at least four prior therapies including IMiDs, PIs, and anti-CD38 MAbs	8/2023 FDA 12/2023 EMA
	Talquetamab (Talvey)	GPRC5D × CD3	Humanized mouse IgG4-based Duobody BsAb	R/R MM patients received at least four prior therapies including IMiDs, PIs, and anti-CD38 MAbs	8/2023 FDA
	Odronextamab (Ordspono)	CD20 × CD3	Fully human IgG4-based heterodimeric Ab	Adult patients with R/R FL and R/R DLBCL after two or more lines of systemic therapy	8/2024 EMA
	Linvoseltamab (Lynozyfic)	BCMA × CD3	Fully human IgG4κ-based BsAb	Adult patients with R/R MM who progressed after receiving at least three lines of therapy	4/2025 EMA
Solid tumor	Amivantamab (Rybrevant)	EGFR × cMET	Fully human IgG1-based Ab	1. Locally advanced or metastatic NSCLC patients with EGFR exon 20 insertions	5/2021 FDA 12/2021 EMA 3/2025 NMPA
				2. Locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations	8/2024 FDA 4/2025 NMPA
	Tebentafusp (Kimmtrak)	Gp100 × CD3	ImmTAC (fusion of soluble TCR and the anti-CD3 scFv)	Metastatic uveal melanoma	1/2022 FDA
	Cadonilimab (开坦尼)	PD-1 × CTLA-4	tetravalent 2 + 2 IgG-scFv structure	Recurrent or metastatic CC and GC with prior failure in platinum-based chemotherapy	6/2022 NMPA
	Ivonescimab (依方达)	PD-1 × VEGF	2 + 2 symmetrical IgG1-scFv structure	Locally advanced or metastatic NSCLC with EGFR gene mutation after progression of EGFR TKIs	5/2024 NMPA
	Tarlatamab (Imdelltra)	DLL3 × CD3	BiTE fused with a Fc fragment	Adult patients with extensive stage SCLC with disease progression on or after platinum-based chemotherapy	5/2024 FDA
	Zanidatamab (Ziihera)	HER2 D2 × HER2 D4	Humanized IgG1-based BsAb	$HER2^+$ unresectable, locally advanced or metastatic BTC	11/2024 FDA
	Zenocutuzumab (Bizengri)	HER2 × HER3	Fully human IgG1-based BsAb	Advanced, unresectable, or metastatic NSCLC or PDAC patients harboring a NRG1 gene fusion with disease progression on or after prior systemic therapy	12/2024 FDA
	Catumaxomab (Removab)	EPCAM × CD3	Trifunctional rat-mouse hybrid BsAb	Intraperitoneal treatment of $EpCAM^+$ tumors with malignant ascites who are ineligible for further systemic anticancer therapy	2/2025 EMA

Abbreviation: *BiTE* bispecific T cell engager, *scFv* single-chain variable fragment, *FDA* U.S. Food and Drug Administration, *NMPA* China National Medical Products Administration, *EMA* European Medicines Agency, *MRD* measurable residual disease, *R/R* relapsed/refractory, *BCP-ALL* B-cell precursor acute lymphoblastic leukemia, *EGFR* epidermal growth factor receptor, *MET* mesenchymal-epithelial transition, *NSCLC* non-small cell lung cancer, *CC* cervical cancer, *GC* gastric cancer, *FL* follicular lymphoma, *DLBCL* diffuse large B-cell lymphoma, *MM* multiple myeloma, *IMiDs* immunomodulatory drugs, *PIs* proteasome inhibitors, *PD-1* programmed death-1, *CTLA-4* cytotoxic T lymphocyte antigen 4, *EpCAM* epithelial cellular adhesion molecule, *VEGF-A* vascular endothelial growth factor-A, *BCMA* B cell maturation antigen, *GPRC5D* G protein-coupled receptor, class C, group 5, member D, *TKIs* tyrosine kinase inhibitors, *DLL-3* delta-like ligand 3, *HER2* human epidermal growth factor receptor 2, *BTC* biliary tract cancer, *PDAC* pancreatic adenocarcinoma, *NRG1* neuregulin 1

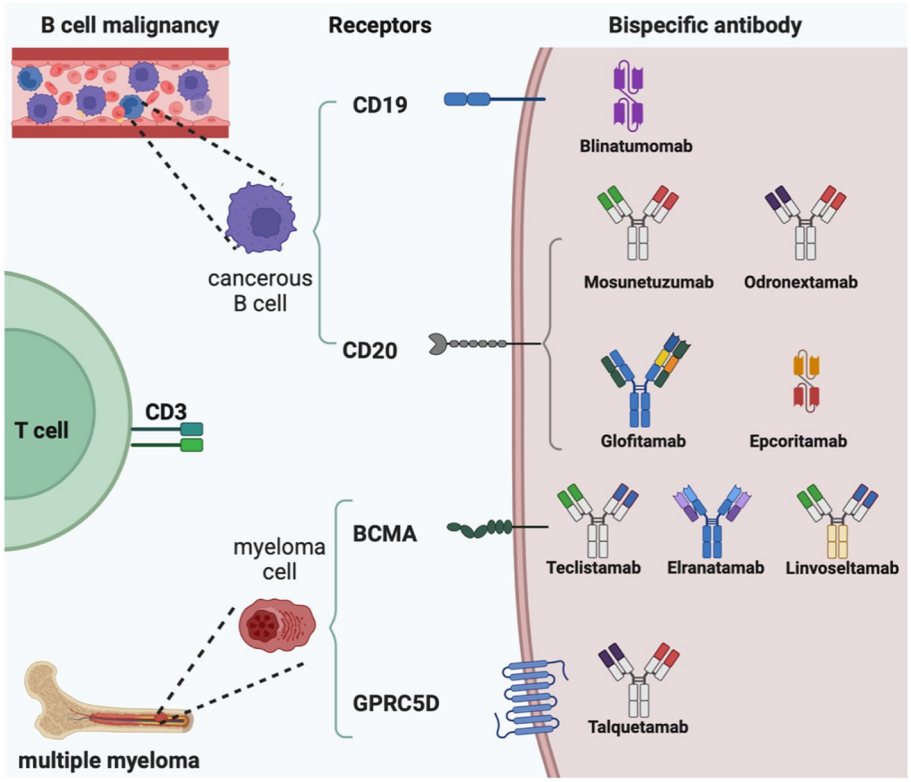


Fig. 2 Dual targets, formats and mechanism of action of approved BsAbs for the treatment of hematological malignancy

of blinatumomab from"rescue therapy"to"full-course therapy". However, the trial excluded patients unable to achieve CR, potentially overestimating its real-world effectiveness. Furthermore, there is a need for additional analysis regarding the necessity of hematopoietic stem cell transplantation (HSCT) following blinatumomab and consolidation therapy. Exploring HSCT-free regimens in the era of blinatumomab remains an important area of investigation. Despite its successes, blinatumomab faces several challenges in clinical application. First, its short half-life necessitates continuous administration to achieve optimal therapeutic outcomes. Second, the central nervous system exhibits a higher risk of recurrence. Third, a higher incidence of neuropsychiatric events was reported in the blinatumomab group than in the chemotherapy-only group [31], possibly attributed to the excessive activation of the immune system [32].

Currently, chemotherapy-free and HSCT-free precision treatments represent a key research focus. Blinatumomab has been widely adopted for treating B-ALL, offering alternative options for patients who respond poorly to traditional chemotherapy or HSCT. Looking ahead, combining blinatumomab with BCL-2 inhibitors, PD-1 inhibitors, and other regimens holds promise for reducing the need for transplantation.

B cell non-Hodgkin lymphoma

Follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL) are the two most common NHL subtypes. FL is a type of indolent B-cell lymphoma that originates in the follicular germinal centers. Among patients with FL, 30–40% eventually develop aggressive DLBCL, which is more intractable and has a poorer prognosis [33]. Additionally, up to 50% of high-risk patients with DLBCL experience disease progression after standard first-line therapy, which consists of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP regimen) plus anti-CD20 mAb (rituximab) [34]. Among patients with R/R DLBCL, despite the implementation of HSCT and chimeric antigen receptor (CAR)-T cell therapy, the recurrence rate remains significantly elevated. Consequently, there remains an unmet need for novel therapies that improve tumor control and clinical survival in patients with R/R B-NHL.

CD20 is a molecule involved in the regulation of B cell activation, proliferation, and differentiation and is specifically expressed in more than 95% of B-cell malignancies. Recently, BsAbs targeting CD20 and CD3 have been investigated for R/R B-cell malignancies, showing promising activity and manageable safety profiles even in multi-refractory patients [35].

Mosunetuzumab

Mosunetuzumab is an IgG1-like humanized BsAb capable of simultaneously targeting the CD20 on B cells and the CD3 antigen on T cells, thereby redirecting T cells to eliminate malignant B cells. Budde et al. presented a dose-escalation phase Ib study and showed an ORR of 34.9% (19.4% CR) in patients receiving mosunetuzumab with aggressive B-NHL, with a DoR of 16.8 months for all responders and 20.4 months for patients with CR, respectively. Moreover, 27.3% of patients had cytokine release syndrome (CRS) with only 1% having grade 3 [36]. These promising results inspired further expansion of this BsAb.

A single-arm multicenter phase II study (NCT02500407) enrolled 90 patients with R/R FL after two or more previous lines of treatment, including anti-CD20 therapy and an alkylating agent [37]. The CR was significantly higher than that of the PI3K inhibitor control group (60% vs. 14%, $p < 0.0001$). CRS occurred in 44% of patients but was predominantly grade 1 or 2. The most common grades 3 or higher TRAEs were neutropenia or decreased neutrophil count (27%), hypophosphatemia (17%), hyperglycemia (8%), and anemia (8%). Recently, updated three-year follow-up data showed that after a median follow-up of 37.4 months, the CR and ORR rates were 60.0% and 77.8%, respectively. Among the 54 patients who achieved CR, 49 remained in CR at the end of treatment. The estimated 36-month OS was 82.4% and the mPFS was 24.0 months. No new CRS events or grade 3 or higher TRAEs were reported [38]. Therefore, mosunetuzumab has a favorable CR-inducing rate and safety profile, allowing its potential administration in patients with R/R FL. In June 2022, the EMA approved mosunetuzumab for adult patients with R/R FL who had received two or more lines of systemic therapy. Subsequently, in December 2022, mosunetuzumab was approved also by the FDA for the same indication [39].

Epcoritamab

Epcoritamab (Tepkinly) is a humanized mouse lgG1-based BsAb created using DuoBody technology. As the first CD3×CD20 TCE for the treatment of DLBCL via subcutaneous injection, epcoritamab binds to the CD20 antigen via a distinctive epitope, unlike other common anti-CD20 mAbs.

Two years of follow-up data from the EPCORE NHL-1 trial underscored the deep and durable response to epcoritamab monotherapy in patients with R/R DLBCL. The estimated 24-month PFS and OS were 27.8% and 44.6%, respectively, with an ORR of 63.1% and CR rate of 40.1% at 24 months, the estimated 24-month PFS and OS were 27.8% and 44.6%, respectively [40]. Recent data from the phase II expansion cohort of the EPCORE NHL 1 confirmed the effects of epcoritamab in R/R FL, with an ORR of 82%, 60% achieving CR, and 22% achieving partial response (PR) after a median follow-up time of 14.8 months. The most common TRAEs were CRS (66%) and were mostly low-grade (65% grade 1 or 2) [41]. Epcoritamab was initially approved by the FDA in May 2023, and by the EMA in September 2023, for the treatment of patients with R/R DLBCL who received two or more lines of systemic therapy. Subsequently, in June 2024, the FDA approved epcoritamab for the treatment of patients with R/R FL, followed by the EMA's approval in September 2024 [42]. Consequently, epcoritamab reprents the first BsAb to receive approval for both R/R DLBCL and R/R FL.

Glofitamab

Glofitamab (RO7082859) is a novel fully humanized mouse IgG1-based BsAb characterized by 2:1 structure, which is bivalent CD20 and monovalent CD3 binding [43]. In a phase I study including patients with different heavily pretreated B-NHL subtypes, considerable efficacy of glofitamab was observed in R/R DLBCL: an ORR of 55% (CR 42.1%) with 5.5 a of mDoR. Of the 63 patients with CR, 53 (84.1%) had durable CR with a maximum of 27.4 months of observation [44]. CRS occurred in 50.3% patients (3.5%, grade 3 or 4). Extended results from the pivotal phase II study, which enrolled 155 R/R DLBCL patients treated with glofitamab, showed durable responses with an ORR of 51.6% (39.4% CR) and a mDoR of 12.6 months [45]. In conclusion, glofitamab showed favorable activity in patients with predominantly refractory aggressive B-NHL, with frequent and durable CR and a predictable and manageable safety profile. The phase III, randomized, open-label STARGLO trial evaluated the application of glofitamab plus chemotherapy in adult HSCT-ineligible patients with R/R DLBCL after one or more lines of treatments [46]. The enrolled patients were randomized into two groups: glofitamab plus gemcitabine-oxaliplatin (Glofit-GemOx) and rituximab plus GemOx (R-GemOx). After a median follow-up of 20.7 months, Glofit-GemOx consistently showed a significantly longer OS than the R-GemOx group (25.5 months vs 12.9 months, $p < 0.0001$). Glofit-GemOx was well tolerated in the safety sets, with a safety profile consistent with the known risks of each drug [46]. These results support the use of glofitamab in HSCT-ineligible patients with R/R DLBCL after one or more lines of therapy. In June 2023, the FDA approved Columvi (glofitamab-gxbm) for the treatment of adult patients with R/R DLBCL after two or more lines of systemic therapy, followed by the NPMA's approval in November 2023 [47].

Odronextamab

Odronextamab (Ordspono) is a hinge-stabilized, fully human IgG4-based CD20×CD3 BsAb. The ELM-2 study showed that in patients with R/R FL who received intravenous odronextamab in a 21-day cycle, ORR was 80% at a follow-up of 20.1 months with 73% of patients achieving CR. Among CR patients, the mDoR was 25 months, and the mPFS was 20.7 months. Odronextamab-related adverse events induced discontinuation in 16% of the patients. The most common TRAEs were CRS (56%), neutropenia (39%), and pyrexia (38%), most of which were grade 1–2 [48]. A total of 127 patients were enrolled in the DLBCL cohort. With a median follow-up of 26.2 months, the ORR and CR were 52% and 31%, respectively. Among the CR patients, the mDoR was 18 months [49]. The probability of achieving 24-month-CR was 48%. Owing to its promising clinical efficacy and manageable TRAEs, odronextamab was approved by the EMA in August 2024 for the treatment of adult patients with R/R FL and R/R DLBCL after two or more lines of systemic therapy [50].

Multiple myeloma (MM)

MM is a malignant disease characterized by the massive proliferation of monoclonal plasma cells in the bone marrow. As the second most common hematological tumor, MM occurs mostly in the elderly and remains incurable. With the advent of new drugs and improvements in detection methods, the diagnosis and treatment of MM have continuously improved. Immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and anti-CD38 mAbs have become therapeutic mainstays for newly diagnosed diseases and early lines of R/R MM. However, patients who are refractory to triple-class refractory (PI/IMiD/anti-CD38 refractory) have poor clinical outcomes, with a mPFS of 3.9 months and a mOS of 11.1 months [51]. Although these three classes of drugs have markedly improved long-term outcomes, the management of triple-class refractory and penta-drug refractory disease (lenalidomide, pomalidomide, bortezomib, carfilzomib, and anti-CD38 mAb) has proven difficult, with limited therapeutic options and a short survival duration [51–53].

BCMA×CD3 BsAbs

B-cell maturation antigen (BCMA), a membrane protein belonging to the tumor necrosis factor (TNF) receptor superfamily, is widely expressed in MM cells, rendering it a promising immunotherapeutic target for patients with R/R MM.

Teclistamab

Teclistamab (Tecvayli) is a humanized IgG4 BsAb created by DuoBody technology targeting CD3 and BCMA. Approved by the EMA in August 2022, the FDA in October 2022, and the NMPA in June 2024, it is the first BsAb for the treatment of patients with heavily pretreated MM. Patients with triple-class refractory MM (77.6%) were enrolled in a phase II study and received weekly subcutaneous injections of teclistamab. With a median follow-up of 14.1 months, ORR was 63.0%, with 39.4% of patients achieving CR. The MRD negativity rate among patients with a CR or better was 46%. The mDoR was 18.4 months. The mPFS was 11.3 months. Common TRAEs included CRS, neutropenia, anemia, and thrombocytopenia. Teclistamab treatment resulted in a high rate of deep and durable responses in patients with triple-class refractory MM. The treatment was well tolerated, with hematological toxicity and CRS (mostly grade 1 or 2) being the most common TRAEs [54].

A real-world analysis of treatment pattern enrolled 501 MM patients who received at least one treatment course with teclistamab before the data cutoff date of July 2024 [55]. The median treatment duration for patients receiving teclistamab was 3.9 months. The mOS for teclistamab-treated patients was 22 months [55]. Research has demonstrated that the dosing of teclistamab exhibits substantial heterogeneity, with treatment intervals for individual patients varying from weekly administration to exceeding once every four weeks. These findings suggest that additional efforts are warranted to optimize the dosing strategy, specifically by refining protocols for dose escalation and maintenance therapy, with the aim of enhancing therapeutic efficacy and quality of life.

Elranatamab

Elranatamab, a BCMA-targeting TCE, is a humanized IgG2a-based BsAb. MagnetisMM-3 (NCT04649359) is an open-label, multicenter, single-arm, phase II study that evaluated the safety and efficacy of elranatamab in patients with R/R MM [56, 57]. A total of 123 patients were enrolled and received elanatamab QW after the two step-up dosing. The updated results showed that after a median follow-up of 28.4 months, ORR was 61.0%, 37.4% of patients achieved CR, and the 24-month ORR was 66.9%. The mPFS was 17.2 months and the mOS extended to 24.6 months [57]. Grade 3 or 4 TRAEs were reported in 100% and 74.8% of the patients, respectively [56].

With promising activity and a manageable toxicity profile, elranatamab (Elrexfio) received approval from the FDA in August 2023 and from the EMA in December 2023 for the treatment of adult patients with R/R MM who had received at least four prior lines of therapy [58].

Linvoseltamab

Linvoseltamab (REGN5458) is a IgG4κ TCE targeting BCMA and CD3 [59, 60]. The LINKER-MMI study, a

phase II clinical trial of linvoseltamab, enrolled patients with R/R MM who had received ≥ 3 prior lines of therapy [61]. In this study, patients treated with linvoseltamab demonstrated a ORR of 71%, with 46% achieving CR or better at a median follow-up of 11 months. Among those achieving CR, the MRD negativity rate was 41% (24/58 patients). The mDoR was 29 months. 85% of patients experienced grade 3 or 4 TRAEs. 46% of patients experienced CRS, with 35% classified as grade 1. Compared with other similar agents, linvoseltamab exhibited a relatively low CRS incidence. The infection was occurred in 74.4% patients, of which 35.9% were grade 3 or higher [61]. Based on these promising results, the EMA granted approval for linvoseltamab (Lynozyfic) in April 2025 for the treatment of adult patients with R/R MM who had progressed after at least three lines of therapy.

The ORR of linvoseltamab was among the highest observed in similar therapies, positioning it as a promising"best-in-class"BsAb targeting BCMA and CD3. An open-label, randomized phase III LINKER-MM3 trial (NCT05730036) is ongoing to compare linvoseltamab with a combination of elotuzumab, pomalidomide, and dexamethasone.

GPRC5D × CD3 BsAbs

Given the overflow of BCMA-targeted therapies in MM, which can decrease BCMA expression or cause complete antigen loss, resulting in drug resistance, additional targets are required. Cell surface expression levels of GPRC5D, an orphan G protein-coupled receptor, were significantly higher in MM cells than in normal plasma cells [62]. Whereas in normal tissues, GPRC5D is only expressed in cells that produce hard keratin, such as hair follicles [63], explaining the specific on-target, off-tumor-related adverse effects such as dysgeusia, skin disorders, and nail changes. Currently, the safety and efficacy of two BsAb products targeting GPRC5D have been reported as promising immunotherapeutic targets for patients, and many targeted drugs are being investigated in preclinical trials.

Talquetamab

Talquetamab (JNJ-64407564), with a proline-alanine-alanine scaffold designed to minimize Fc-receptor binding, is the first BsAb that binds to both GPRC5D and CD3 to induce the killing of GPRC5D-expressing MM cells [64]. Talquetamab shows unprecedented therapeutic potential and remains highly effective in patients who have received many previous treatments. A phase I/II MonumenTAL-1 study enrolled 232 R/R MM patients and found that with median follow-ups of 11.7 months, the percentages of patients with ORR were 70% and the mDoR was 10.2 months [65]. The most common grade 3/4 TRAEs were hematology-related and included anemia, neutropenia, lymphocytopenia, and thrombocytopenia. The most common non-hematological TRAEs were skin-related events, nail-related events, and taste disorders, while dermatological events were mostly of grade 1/2 [65]. The updated results from the phase II MonumenTAL 1 study, which was denounced at the 2023 American Society of Clinical Oncology (ASCO) Annual Meeting, showed that talquetamab maintained its efficacy even in patients who had previously received T-cell redirected therapy. In this cohort, 71% of the patients had previously received CAR-T therapy, 35% had previously received BsAb therapy, and 6% had received both therapies. Among patients who had previously received BsAb or CAR-T therapy, the ORR was 63% for talquetamab at a median follow-up of 11.8 months, and the mPFS was 5.1 months [66]. Based on these results, the FDA approved talquetamab-tgvs (TALVEY) for the treatment of adult patients with R/R MM in August 2023 [67].

Ongoing studies are evaluating talquetamab in combination with other anti-MM drugs, such as CD38 antibodies (e.g., daratumumab) and other BsAbs. Early data from the TRIMM-2 study showed that teclistamab could be effectively combined with daratumumab without overlapping toxicities in patients with heavily pretreated MM [68]. The combination of talquetamab and teclistamab can further enhance therapeutic efficacy, maximize tumor eradication in heterogeneous cell populations, prevent drug resistance due to tumor antigen escape, and prolong the DoR. The RedirecTT-1 is a multicenter, non-randomized, open-label phase Ib/II clinical study designed to evaluate the efficacy and safety of talquetamab in combination with teclistamab [69], enrolled 94 patients with heavily pretreated MM. Among the 44 patients who received the recommended phase II dose (RP2D) of 0.8 mg/kg talquetamab + 3.0 mg/kg teclistamab Q2W, the ORR was 80%. Moreover, 34 patients (77%) achieved very good partial response (VGPR), and 23 patients (52%) achieved CR. The 12-month PFS was 74% [69]. Notably, three patients experienced dose-limiting toxicities. These findings suggest that the combination of talquetamab and teclistamab exhibits robust anti-tumor activity in the majority of R/R MM patients, with TRAEs consistent with those observed during monotherapy. A phase III study evaluating the efficacy and safety of a combination of talquetamab and teclistamab for patients with R/R MM patients received 4-line therapy is ongoing (NCT05552222).

BsAb candidates in clinical stages

Several promising BsAb candidates are currently in phase III clinical trials but have yet to receive regulatory approval. Consequently, it is crucial to track the results

of these large-scale key trials, as they may pave the way for novel treatment paradigms and improve patient outcomes. In the following sections, we will examine specific examples of these promising BsAbs for the treatment of hematological tumors, detailing the mechanisms of action, indications and research advancements. A comprehensive summary of these BsAb candidates is presented in Table 3.

ABBV-383

ABBV-383 (Etentamig) is a BCMAxCD3 TCE that incorporates a bivalent high-affinity BCMA-binding domain and a low-affinity CD3-binding domain, designed to mitigate the risk of CRS [70]. Additionally, ABBV-383 features a silent Fc tail engineered to extend its half-life, enabling a dosing schedule of once every four weeks (Q4W). This regimen enhances patient convenience while reducing the frequency of clinic visits and overall treatment burden [71].

In patients with R/R MM, ABBV-383 demonstrated robust safety and efficacy in the first-in-human phase I study (NCT03933735), conducted [72]. The results of this study indicated that ABBV-383 monotherapy elicites durable responses, with a mPFS of 13.7 months and a 12-month DoR of 70%. Notably, the ORR was 65%, with approximately 53% of patients achieving MRD negativity. The results of further phase Ib study (NCT05650632) into the efficacy and safety of ABBV-383 were presented at the 2024 American Society of Hematology (ASH) Annual Meeting [73]. These data revealed that among the patients ($n=70$) treated with ABBV-383 in the dose optimization and expansion cohorts, the ORR reached 69%, with 56% achieving VGPR. In this study, the introduction of a modified, higher-dose dexamethasone pretreatment during the first cycle successfully reduced the incidence of any-grade CRS from 71 to 43%, with only 1% experiencing grade 3–4 CRS.

In June 2024, a phase III clinical trial of ABBV-383 (CERVINO) was initiated to comprehensively evaluate the efficacy and safety of ABBV-383 administered monthly compared to available standard therapies in R/R MM patients who had received at least two prior lines of treatments. Further clinical results from the CERVINO trial are eagerly anticipated, as they hold the potential to redefine the standard of care for R/R MM patients and offer new hope for those in need of effective and well-tolerated treatment options.

Alnuctamab

Alnuctamab, a TCE with a 2:1 structure, targets BCMA and CD3. It incorporates a low-affinity CD3 binding domain and a modified Fc region to enable bivalent binding to BCMA, thereby reducing the required dosage and mitigating the risk of CRS. In a phase I study (NCT03486067) evaluating subcutaneous administration of alnuctamab for R/R MM, ORR was 53%, with a VGPR rate of 47% among the 73 evaluable patients. The mPFS across all dose groups was 10.1 months, with a 12-month PFS of 53%. Subcutaneous administration demonstrated enhanced safety and operational convenience compared to intervenous administration. However, infection remains a notable concern within the overall safety profile, as 59% of patients experienced infections, predominantly grade 1 to 2, with a lower incidence of grade 3/4 (17%). Additionally, 55% of patients developed CRS, all of which were grade 1 to 2, indicating that the overall safety profile is manageable. A phase III, randomized, multicenter, open-label study (ALUMMINATE trial) to evaluate the efficacy and safety of alnuctamab compared to standard regimens in participants with R/R MM is currently ongoing and expected to provide critical insights into the potential of alnuctamab as a novel therapeutic option.

BsAbs in solid tumors

BsAbs in gynecological tumors

Endometrial, cervical, and ovarian cancers are the most common gynecological malignancies. The primary therapeutic strategies for these tumors include surgery, chemotherapy, radiotherapy, and targeted therapy. However, frequent postoperative recurrence or metastasis often occurs in the advanced stages of the disease. Emerging therapeutic strategies are needed to enhance the survival outcome of patients with advanced disease. The research advancements of various currently available BsAbs in clinical studies for gynecological tumors are outlined in Table 2 and Fig. 3.

Cervical cancer

The proportion of patients with MSI-H cervical cancer (CC) is relatively low at 2.62% [74], whereas the proportion of patients with TMB-H is 14.9% [75]. However, PD-L1 expression is high in CC, ranging from 34.4 to 96.0% [76], suggesting that the immune checkpoint inhibitors (ICIs) could be a breakthrough treatment for metastatic or recurrent CC. However, the response rate of ICI monotherapy is relatively low. According to the KEYNOTE study, the ORR of PD-L1$^+$ metastatic or recurrent CC patients receiving pembrolizumab treatment was 14.3%−17.0% [77]. Additionally, multiple clinical studies have shown that nivolumab is effective in treating metastatic or recurrent CC, with an ORR ranging from 4.0–26.0% [78, 79]. Therefore, novel strategies targeting immune checkpoints are warranted to improve the prognosis of advanced CC patients.

Cadonilimab (AK104)

Cadonilimab (AK104) is a tetravalent BsAb developed utilizing the tetrabody technology platform from

Table 2 Detailed information on clinical studies involving promising BsAbs in gynecological tumors

Tumor	Name	Target	Trial design	Enrolled population	Outcomes
Cervical cancer	Cadonilimab	PD-1/CTLA-4	phase II	the first-line treatment of R/R CC	ORR of cadonilimab plus platinum-chemotherapy is nearly 70%. [84]
	SHR-1701	PD-L1/TGF-βR2	phase/II	the first-line treatment of advanced CC	The ORR was 77.4%, the DCR was 93.5%, and the 6-month PFS was 93.5%. [162]
Ovarian cancer	Navicixizumab	DLL4/VEGF	phase Ib	combined with paclitaxel in heavily treated platinum-resistant OC patients	ORR is 43.2%, mDoR was 6 months. mPFS was 7.2 months. [163]
	Ivonescimab	PD-1/VEGF	phase I	platinum-resistant or refractory epithelial OC	ORR is 29.4%, DCR is 76.5%. [86]

Abbreviation: *DLL4* notch ligands delta-like 4, *TGF-βR2* TGF-β receptor II, *CC* cervical cancer, *OC* ovarian cancer, *ORR* overall response rate, *DCR* disease control rate, *DoR* duration of response, *PFS* progression-free survival, *OS* overall survival

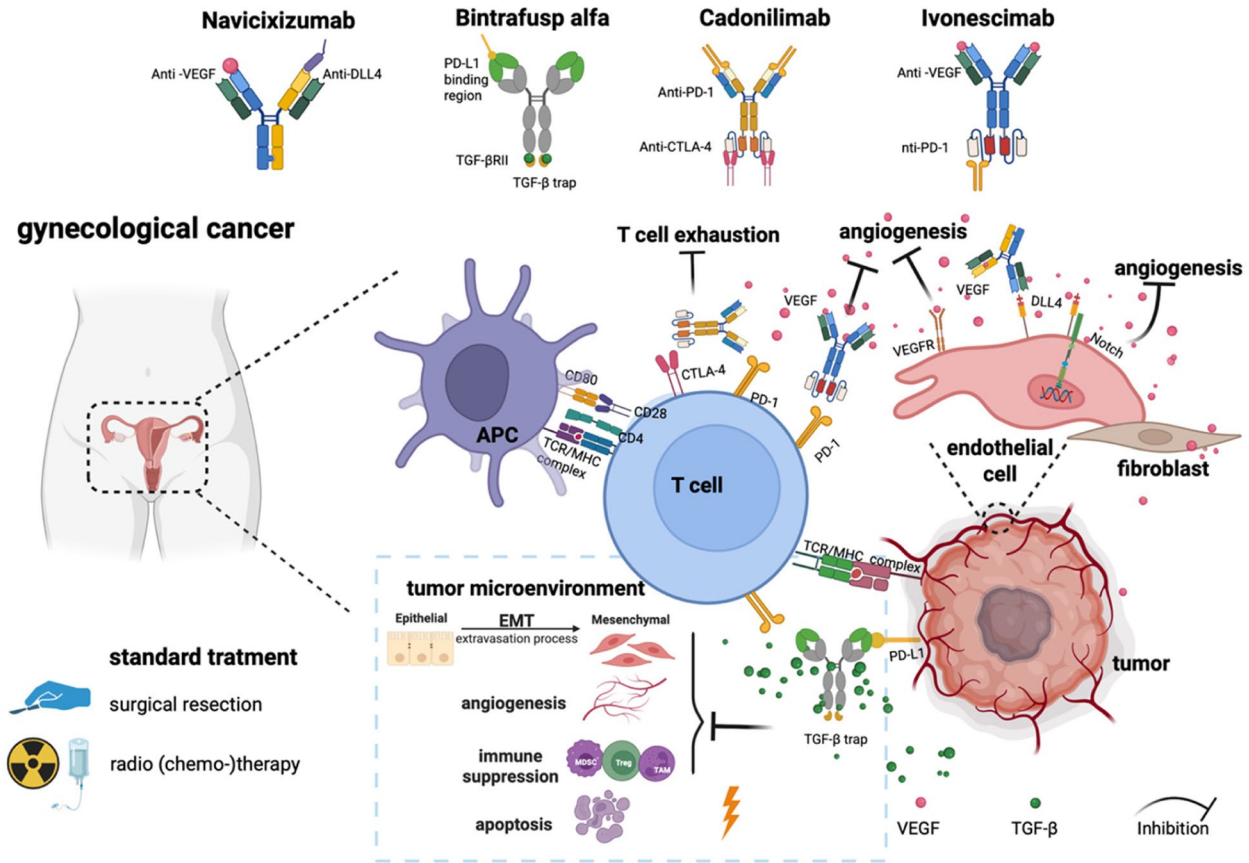


Fig. 3 Structure and mechanism of action of BsAbs in the clinical trials for gynecological cancers

CanSino Biologics. It features a 2+2 symmetrical IgG-scFv structure, wherein the scFv targeting CTLA-4 is fused to the C-terminus of the heavy chain [16]. Without binding to Fc receptors, cadonilimab shows minimal ADCC, ADCP, and the release of interleukin-6 (IL-6)/IL-8, which contributes to significantly lower toxicities. Cadonilimab exhibits a higher binding affinity in environments with high-density of PD-1 and CTLA-4, potentially enhancing infiltration and retention at tumor sites [16]. Clinical studies have shown that combination therapy with ICIs targeting CTLA-4 and PD-1 significantly improves clinical benefits compared with the PD-1 mAb alone [80]. However, its widespread application is limited by toxicity [81]. In addition to mimicking the biological activity of combination of anti-CTLA-4 and PD-1, cadonilimab has a higher binding affinity in TME with high-density of PD-1 and CTLA-4 than in low-density TME. Unlike conventional mAbs, cadonilimab has a higher affinity for high PD-1 levels while exhibiting relatively lower binding affinity at low PD-1 levels.

This characteristic may increase the activity of cadonilimab in the TME characterized by high PD-1 expression, while reducing binding activity in normal tissues, thereby reducing the toxicity associated with the PD-1/CTLA-4 blockade. A previous study verified that cadonilimab significantly decreased Fc-mediated effector function and pro-inflammatory cytokine release compared with the combination of nivolumab and ipilimumab [16].

The AK104-201 trial is a phase I/II multicenter clinical study (NCT04380805). A total of 111 patients with advanced CC who had previously failed platinum-based chemotherapy were included in the study and received cadonilimab monotherapy. The ORR is 33%, while 43.8% in PD-L1-positive patients with a combined positive score (CPS) ≥ 1, and 16.7% in PD-L1 negative patients. The mPFS was 3.75 months, and the mOS was 17.51 months [82]. A phase II study (COMPASSION-13) was conducted to evaluate the efficacy and safety of AK104 combined with standard therapy for the first-line treatment of recurrent or metastatic CC (NCT04868708) [83]. The ORR was 66.7% in the cadonilimab + chemotherapy cohort and 92.3% in the bevacizumab cohort. Cadonilimab plus platinum-based chemotherapy with or without bevacizumab showed surprising anti-tumor effects regardless of the expression of PD-L1. Any grade of immune-related adverse events (irAEs) occurred in 29 (64.4%) patients; however, grade 3 irAEs only occurred in 9 (20.0%) patients [83, 84]. According to the results, cadonilimab combined with standard therapy exhibits well-tolerated adverse effects and enhanced anti-tumor efficacy than the combination of PD-1 blockade and CTLA-4 blockade. The NMPA approved in June 2022 cadonilimab for patients with recurrent or metastatic CC who did previously not response to platinum-based chemotherapy. However, further research is crucial for long-term safety monitoring and OS outcomes. A phase III clinical study investigating cadonilimab plus platinum-based chemotherapy, with or without bevacizumab, as first-line treatment for persistent, relapsed, or metastatic CC was launched in 2021 (NCT04982237). We anticipate obtaining the final survival data and safety profile from this randomized clinical trial (RCT).

Cadonilimab is the only approved BsAb indicated for gynecological tumors. However, multiple start-up pharmaceutical and biotechnology companies have recently been funded to continue this exciting research and promote the bench-to-bedside translation of BsAbs. The translation of BsAbs into clinically applicable drugs is time-consuming and requires considerable effort.

Ovarian cancer

Platinum-resistant or refractory epithelial OC is a serious issue with limited clinical interventions and a median survival of merely 12–15 months. The ORR of PD-1/PD-L1 inhibitors was less than 10%, whereas nivolumab combined with bevacizumab achieved a 16.7% ORR in patients with platinum-resistant OC, suggesting a synergistic effect between PD-1 inhibition and anti-angiogenesis.

An innovative humanized tetravalent BsAb, ivonescimab (AK112), can simultaneously bind to PD-1 and vascular endothelial growth factor (VEGF) as a single agent. Owing to the co-expression of VEGF and PD-1 in the TME, ivonescimab is enriched in tumor sites and targets PD-1 and VEGF with high affinity, inhibiting PD-1/PD-L1 binding and VEGF-A-mediated angiogenesis, thus promoting T cell tumor invasion, restoring immunosuppression, and enhancing anti-tumor activity more effectively. 19 patients with platinum-refractory OC were involved in this phase I study of ivonescimab (NCT04047290) [85]. After a median follow-up of 4.5 months, the ORR was 29.4%, the disease control rate (DCR) was 76.5%. TRAEs occurred in 63.2% of the patients, whereas grade 3 TRAEs were observed in only 15.8%. The most frequently reported TRAEs were hypertension (15.8%), arthralgia (15.8%), and fatigue (15.8%) [85, 86]. Initial results indicated that ivonescimab has gained importance in the treatment of platinum-resistant or refractory epithelial OC. A phase II trial on the combination of ivonescimab and chemotherapy and/or olaparib in OC is currently ongoing (NCT06686030).

BsAbs in lung cancer

Figure 4 listed the detailed information of approved BsAbs in solid tumors including lung cancer. Lung cancer, which originates primarily from the bronchial mucosa or glandular tissues, is one of the most prevalent malignant tumors. Lung cancer is histologically categorized into two subtypes: small-cell lung cancer (SCLC) and NSCLC. NSCLC is the more common subtype, encompassing varieties such as squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. SCLC is a more aggressive subtype characterized by rapid growth and desperate survival outcome [87].

Amivantamab

Molecular segmentation of advanced NSCLC based on oncogenic driver mutations has improved the OS and quality of life of patients with actionable driver mutations and solidified solid tumor-targeted therapy. Mutations in the EGFR gene constitutively activate downstream growth and survival signaling pathways, leading to dependency on the EGFR pathway for tumor growth. Activating somatic mutations in the TKI domain of EGFR are present in nearly 50% of Asian patients with advanced NSCLC. Therefore,

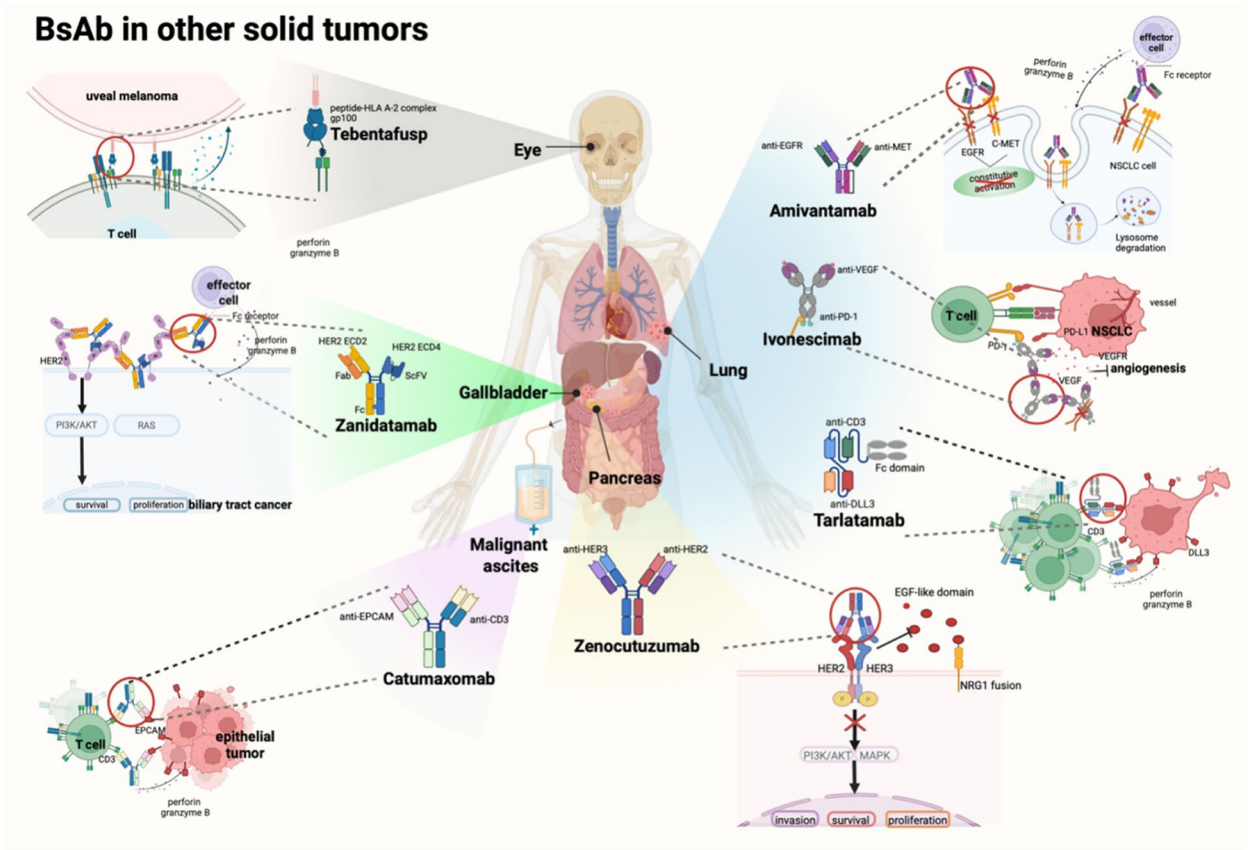


Fig. 4 Detailed formats and mechanism of action of the remaining approved BsAbs in other solid tumors

several EGFR-targeting drugs, such as gefitinib, erlotinib, afatinib, and osimertinib, cover a variety of first-to third-generation TKIs. Among them, osimertinib, a third-generation EGFR-targeting drug, directly refreshed the survival records of patients with NSCLC.

Resistance to EGFR-TKIs and chemotherapy is inevitable in all patients with EGFR-mutated NSCLCs. Insertions in exon 20 account for up to 12% of all EGFR-mutated NSCLC cases, with a five-year OS of 8% [88]. Owing to the altered conformation at the kinase active site that limits the binding of TKIs, NSCLC with insertions in EGFR exon 20 (EGFR 20 ins) is largely insensitive to TKIs approved for the treatment of patients with common EGFR-mutated NSCLC [89, 90]. Therefore, the first-line standard therapy for locally advanced or metastatic NSCLC with EGFR exon 20 insertions is platinum-based chemotherapy, which is associated with an ORR of 23–29% and a mPFS of 3.4–6.9 months [91]. In addition to EGFR-dependent resistance, alterations in the MET receptors are common resistance pathways. Moreover, EGFR and MET dimerize to promote carcinogenic signaling and TME remodeling. BsAbs that simultaneously target EGFR and MET may improve clinical outcomes by inhibiting both pathways and reducing the occurrence of MET and/or EGFR-mediated resistance.

Amivantamab (JNJ-61186372) is a fully human IgG1 BsAb targeting EGFR and MET mutations and amplifications. These mechanisms include the inhibition of ligand binding, endocytosis, and degradation of receptors, and the engagement of macrophages, monocytes, and NK cells through the Fc domain [20, 92, 93]. Collectively, these mechanisms can bypass ligand-site resistance against TKIs in NSCLC patients with EGFR 20 ins mutations, address MET as a bypass resistance mechanism, and recruit effector cells to exert anti-tumor effects.

Based on the results of the phase I CHRYSALIS trial, amivantamab received approval from the FDA in May 2021 and from the EMA in December 2021 for the treatment of patients with EGFR 20 ins following progression after platinum-based chemotherapy [94]. In this trial, patients receiving amivantamab had an ORR of 40%, a mDoR of 11.1 months, a mPFS of 8.3 months and a mOS of 22.8 months [95]. Subsequently, Zhou et al. conducted

a phase III, international, randomized PAPILLON trial to assess the efficacy and safety of amivantamab plus chemotherapy compared with standard chemotherapy alone as a first-line treatment in patients with advanced NSCLC patients with EGFR 20 ins [96]. In total, 308 patients were enrolled in this study. With a median follow-up of 14.9 months, the mPFS was significantly longer in the amivantamab chemotherapy group than in the chemotherapy group (11.4 months vs. 6.7 months, $p < 0.001$). The ORR of the two groups was reported to be 73% and 47%, respectively ($p < 0.001$) [96]. Based on these impressing results, the FDA approved In March 2024 amivantamab combined with chemotherapy as a first-line therapy for the locally advanced or metastatic NSCLC in adult patients with EGFR 20ins. Subsequently, amivantamab received its first approval in China by the NMPA in February 2025.

In August 2024, the FDA approved a third indication for amivantamab in combination with lazertinib for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR 19del or EGFR 21 858R mutations. MARIPOSA is a randomized, international, multicenter phase III trial designed to evaluate the efficacy and safety of amivantamab in combination with lazertinib (A + L) versus third-generation EGFR-TKI monotherapy (osimertinib and lazertinib) as the first-line treatment for advanced EGFR-mutant NSCLC [97]. Patients with EGFR mutations (Exon19 del or Exon21 L858R) in locally advanced or metastatic NSCLC were randomly assigned 2:2:1 to the A + L, osimertinib, and lazertinib groups. At a median follow-up of 22.0 months, the mPFS was 23.7 months in the A + L group and 16.6 months in the osimertinib group ($p < 0.001$). The ORR was 86% and 85% in the A + L and osimertinib groups, respectively. The mDoR was 25.8 months in the A + L group and 16.8 months [98]. Compared with osimertinib, the A + L regimen can further improve PFS and DoR and has a trend of OS benefit. However, the A + L group had a higher incidence of EGFR- and MET-associated adverse effects than the osimertinib group.

In September 2024, the FDA approved the fourth indication for amivantamab: combination chemotherapy (carboplatin plus pemetrexed [CP]) for adult patients with locally advanced or metastatic NSCLC with EGFR 19del or 21 858R mutations that had progressed despite EGFR-TKI therapy, followed in April 2025 by the NMPA' approval in China. MARIPOSA-2 is a randomized, open, controlled, international, multicenter phase III trial designed to evaluate the efficacy of amivantamab + lazertinib + carboplatin + pemetrexed (LACP) versus CP in patients with locally advanced or metastatic NSCLC with an EGFR mutation (Exon19 del/Exon21 L858R) [99]. The study also established an amivantamab + carboplatin + pemetrexed group (ACP) to evaluate the efficacy of lazertinib in patients treated with LACP. The MARIPOSA-2 study was presented for the first time at 2023 European Society for Medical Oncology (ESMO) Annual Congress. A total of 657 patients were randomly assigned to the LACP, CP, or ACP groups in a 2:2:1 ratio. At a median follow-up time of 8.7 months, the mPFS in the ACP and LACP is significantly longer than the CP groups (6.3 months and 8.3 months vs. 4.2 months, respectively; $p < 0.001$ for both). ORR was significantly higher for ACP and LACP versus CP group (64% and 63% vs. 36%, respectively; $p < 0.001$ for both). Results of the second interim analysis, released at the 2024 ESMO Congress, showed improved OS in the ACP group compared with chemotherapy, with a mOS of 17.7 months versus 15.3 months, respectively ($p = 0.039$) [100].

Overall, amivantamab combined with lazertinib became the first multi-target, chemotherapy-free combination regimen that proved to be superior to osimertinib and was approved for first-line treatment of EGFR-mutated NSCLC patients, marking the first-line treatment of EGFR-mutated advanced NSCLC into the chemotherapy-free era.

Ivonescimab

In preclinical studies, anti- vascular endothelial growth factor (VEGF) and anti-PD-(L)1 mAbs were found to have synergistic activity. Anti-VEGF not only inhibits angiogenesis but also increases immune effector cell trafficking and infiltration into the TME and modulates T-regulatory cells and myeloid-derived suppressor cells, allowing for an immunoresponsive environment, which leads to the enhanced efficacy of anti-PD-(L)1 inhibitors [101, 102].

Ivonescimab (AK112) is a humanized IgG1-scFv BsAb and an innovative quadrivalent antibody designed using tetrabody BsAb development technology. It can simultaneously target PD-1 and VEGF-A and plays a dual therapeutic role in immunity and anti-angiogenesis [103]. The HARMONi-5 trial enrolled 108 patients with advanced immunotherapy-naïve NSCLC receiving ivonescimab as first- or second-line monotherapy. The median follow-up was 10.4 months. For all the patients, the ORR and DCR were 39.8% and 86.1%, respectively. Grade 3/4 TRAEs were observed in 24 patients (22.2%). TRAEs leading to treatment discontinuation or death occurred in four patients (3.7%) [104].

To compare the efficacy of ivonescimab plus chemotherapy with chemotherapy alone in patients with relapsed or metastatic NSCLC that progressed after EGFR-TKI therapy. HARMONi-A (AK112-301) is a double-blind, randomized, phase III trial involving 322

patients [105]. The mPFS was significantly higher in the ivonescimab group than in the control group (7.1 months vs. 4.8 months, $p<0.001$). The ORR was 50.6% for ivonescimab and 35.4% for chemotherapy alone ($p=0.006$). Grade 3 or higher TRAEs occurred in 61.5% of patients in the ivonescimab group versus 49.1% of patients in the control group, most commonly chemotherapy-related. Grade 3 or higher irAEs occurred in 6.2% of patients in the ivonescimab group and 2.5% in the chemotherapy-only group. Ivonescimab plus chemotherapy significantly improved PFS with a tolerable safety profile in patients with NSCLC who previously underwent EGFR-TKI treatment, and may offer a new treatment option for patients with TKI resistance. Based on these results, ivonescimab in combination with CP received its first approval in May 2024 in China for the treatment of patients with EGFR-mutated locally advanced or metastatic non-squamous NSCLC who had progressed after TKI therapy [106].

A phase III clinical study (HARMONi-2/AK112-303) comparing ivonescimab or pembrolizumab monotherapy in the first-line treatment of locally advanced or metastatic NSCLC with positive PD-L1 expression (TPS ≥ 1%) in China were presented [107]. The results showed that, ivonescimab demonstrated a clinically significant improvement in PFS in patients with intermediate and high PD-L1 expression compared with pembrolizumab (11.14 vs. 5.82 months, respectively; $p<0.001$) [107, 108]. Based on these impressive interim results, the NMPA granted approval for a new indication of ivonescimab in April 2025. The approved indication is for first-line monotherapy in patients with locally advanced or metastatic NSCLC who are PD-L1-positve (TPS ≥ 1%), EGFR gene mutation-negative, and ALK-negative. Awaiting the OS results and confirmatory studies outside China, the first-line treatment landscape of locally advanced or metastatic NSCLC without a driver mutation may change.

Tarlatamab

SCLC is an aggressive disease associated with poor prognosis and accounts for approximately 15% of all newly diagnosed lung cancers. Although most patients with extensive-stage SCLC respond to initial therapy, progression usually occurs within months [109, 110]. Second-line treatment options are limited, with a short DoR (3.6–5.3 months) and an OS rarely exceeding 8 months [111, 112]. Delta-like ligand 3 (DLL3), a protein that inhibits Notch signaling, is typically localized intracellularly in normal cells but is abnormally expressed on the surface of SCLC cells [113].

Tarlatamab is a BiTE antibody fused with an IgG Fc fragment. The outer scFv specifically targets DLL3 whereas the inner scFv binds to the CD3, thereby facilitating the T cell-mediated lysis of cancer cells. In 2023, a phase II trial (DeLLphi-301) involving previously treated patients with SCLC indicated that tarlatamab exhibited anti-tumor activity and durable responses. ORR is 40% and the mPFS was 4.9 months. The estimated OS at 9 months was 68%. Moreover, this study revealed no new safety concerns compared with the phase I trial [114]. Based on the favorable outcomes of this clinical study, the FDA expeditiously approved in May 2024 tarlatamab as an innovative therapy for extensive-stage SCLC, suitable for patients progressed after platinum-based chemotherapy. This approval also signified the introduction of the first BsAbs targeting DLL3 for SCLC treatment [115]. Updated data from the phase II DeLLphi-301 trial of tarlatamab in advanced SCLC were reported at the WCLC 2024. At a mean follow-up of 20.7 months, the patients had a mOS of 15.2 months, with an estimated 18-month OS of 46%. In the chemotherapy-free interval cohort, the OS at 6, 12, and 18 months was 73.4%, 57.0%, and 46.0%, respectively. This indicates that the interval between chemotherapy is no longer a key factor in judging the effectiveness of treatment, and patients can be treated with tarlatamab more flexibly.

BsAbs in biliary tract cancer

Biliary tract cancer (BTC), including gallbladder cancer and intrahepatic, extrahepatic, and perihilar cholangiocarcinoma, accounts for nearly 3% of gastrointestinal cancer [116, 117]. Most patients are initially diagnosed with incurable, locally advanced, or metastatic disease, with a five-year OS of only 3.0% for distant disease [118]. Molecular profiling has revealed that human epidermal growth factor receptor 2 (HER2) is mutated, amplified, or overexpressed in approximately 5–15% of patients with BTC [119, 120]. However, HER2-targeted therapies, including trastuzumab, pertuzumab, lapatinib, neratinib, and trastuzumab emtansine (T-DM1), have not yet been approved for BTC treatment.

Zanidatamab

Zanidatamab, a humanized IgG1-like BsAb, binds via its scFv to the extracellular juxtamembrane domain (ECD4) of HER2 and via its Fab region to the HER2 dimerization domain (ECD2). This dual binding induces the cross-linking of zanidatamab and HER2 to form a polymer that elicits potent CDC-related activity [121]. By targeting two different epitopes of HER2, zanidatamab exhibits a higher binding affinity for HER2-positive tumors. Moreover, zanidatamab mediates HER2 internalization and downregulation, ADCC, and phagocytosis, showing superior anti-tumor activity than that of the traditional HER2 mAb (trastuzumab and pertuzumab) [121].

A phase I dose-escalation and expansion trial showed that zanidatamab is well tolerated and shows promising

activity in patients with heavily pretreated, advanced, HER2-overexpressing BTC [122]. HERIZON-BTC-01 is a multicenter, single-arm, phase IIb trial of zanidatamab in patients with HER2-amplified, unresectable, locally advanced, or metastatic BTC who have disease progression on gemcitabine-based therapy. The results showed that after a median follow-up of 12.4 months, the confirmed ORR was 41.3%, the mPFS was 5.5 months, and only 18% of patients experienced grade 3 or higher TRAEs [123]. These trial results led in November 2024 to the approval of zanidatamab by the FDA for treating advanced and metastatic BTC with HER2- positive expression in patients who had not responsed to prior chemotherapy.

A phase III trial exploring the efficacy of zanidatamab in combination with standard first-line chemotherapy for HER2-positive BTC is currently ongoing (NCT03929666). Additionally, the application of zanidatamab has been evaluated in other HER2-expressing solid tumors, including a phase III trial for the first-line treatment of gastroesophageal adenocarcinoma (NCT05152147). Further studies are required to verify the efficacy and safety of zanidatamab.

BsAbs in pancreatic adenocarcinoma

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive tumor with high mortality. Owing to its asymptomatic onset, many patients are initially diagnosed at an advanced or metastatic stage, with a five-year OS below 9% [1]. Given the poor prognosis, novel treatment strategies are essential to improve outcomes for patients with unresectable PDAC.

Neuregulin 1 (NRG1), a member of the EGF family, is crucial in the development and homeostasis of the nervous and circulatory system. NRG1 gene fusions are oncogenic drivers in the recurrence of various solid tumors, leading to the production of chimeric proteins that bind to HER3 via the EGF-like domain, thus activating downstream growth and proliferation signaling pathways [124]. Although NRG1 fusions are rare and occur in less than 1% of solid tumors [125], research indicates that certain cancer subtypes have a higher rate of NRG1 gene fusion. For instance, the incidence is 27% to 31% in invasive lung mucinous adenocarcinoma and 6% in PADC [126].

Zenocutuzumab is a novel humanized full-length IgG1 BsAb targeting HER2 and HER3. It inhibits tumor cell proliferation and survival by blocking HER2–HER3 dimerization and the interaction between NRG1 fusion proteins and HER3. On February 2025, The New England Journal published a phase II clinical study (eNRGy), which evaluated the efficacy and safety of the zenocutuzumab targeting HER2 and HER3 in patients with advanced solid tumors carrying the NRG1 fusion gene [127]. The study demonstrated that zenocutuzumab exhibited significant therapeutic effects, particularly in patients with NSCLC and PDAC, with most adverse events classified as grade 1 or 2. A total of 204 patients with 12 distinct solid tumors with NRG1 fusion received zenocutuzumab treatment. Among them, the most common tumor types were NSCLC (94 cases) and PDAC (36 cases), with a median age of 62 years. In the 93 patients with NSCLC, the ORR was 29%, and the mDOR was 12.7 months. Among the 36 patients with PDAC, the ORR was 42%, and the mDOR was 7.4 months [127]. In the 204 patients treated with zenocutuzumab, 194 (95%) experienced TRAEs, mainly of grade 1 or 2. The most common TRAEs associated with zenocutuzumab were diarrhea (29%), fatigue (21%), and nausea (20%). Based on these clinical results, the FDA approved in December 2024 zenocutuzumab for the treatment of adult patients with advanced, unresectable, or metastatic PDAC or NSCLC carrying an NRG1 gene fusion who have experienced disease progression during or after systemic therapy. Zenocutuzumab is the first FDA-approved drug targeting NRG1 fusions and HER3.

BsAbs in uveal melanoma

Uveal melanoma is the most common primary intracranial cancer in adults; it begins in melanocytes in the uvea and accounts for 3–5% of all melanomas. Despite good local tumor control with surgery or radiation, approximately 50% of patients eventually develop metastasis. The most common sites of metastases were the liver (60.5%), lungs (24.4%), skin/soft tissue (10.9%), and bone (8.4%). The 5-year OS after initial diagnosis ranges from 51–69%, whereas OS is below 8% in metastatic uveal melanoma (mUM) [128, 129]. Given its low TMB and reduced immunogenicity compared with cutaneous melanoma, UM exhibits lower clinical response to ICIs, In mUM, the clinical benefit of ICIs is particularly limited, in contrast to their significant impact on improving the clinical outcomes of cutaneous melanoma [130]. Glycoprotein 100 (gp100) is a lineage antigen expressed in melanocytes and melanomas. Considered to be a melanoma-associated tumor antigen, gp100 is significantly increased during the development of melanoma and is highly expressed in UM cells.

Tebentafusp

Tebentafusp is a specific BsAb developed utilizing the ImmTAC technology platform. Formed by the fusion of soluble TCR and the anti-CD3 immune effector domain, tebentafusp mimics a natural TCR protein, with one end capable of highly specific recognition of the target polypeptide-HLA complex and an anti-CD3 scFv added

to the other end. Owing to the MHC limitations of the TCR, the selection of HLA subtype matching needs to be considered during drug development. Of all the alleles at the HLA-A locus, HLA-A*02:01 is present in approximately 45% of the Caucasian population, showing a high concentration and being an ideal candidate. Once tebentafusp binds to the MHC complex of HLA-A*02:01-positive patients, it recruits and activates polyclonal T cells through CD3 to release cytokines and cytolytic mediators against target cells [131, 132].

In January 2022, tebentafusp received its first approval from FDA for the treatment of HLA-A02:01-positive adults with unresectable or mUM [133], based on the results of a phase III clinical trial. In this trial, 378 untreated patients with mUM were randomly assigned to either the tebentafusp or the control groups, which received single-agent of pembrolizumab, ipilimumab, or dacarbazine [134]. At a median follow-up of 43.3 months, the mOS was 21.6 months in the tebentafusp group than 16.9 months in the control group. The three-year OS were 27% and 18%, respectively. Regarding ORR, the tebentafusp group outperformed the control group (11% vs. 5%). One-third of the responders in the tebentafusp group responded at 18 months [135]. The most common TRAEs in the tebentafusp group were cytokine-mediated events and skin-related events (due to gp100-positive cutaneous melanocytes), including rash (83%), pyrexia (76%), and pruritus (69%) [134]. Therefore, tebentafusp significantly prolonged OS in patients with mUM than existing standard therapies, thus providing a new and effective treatment option for these patients.

BsAbs in malignant ascites

The formation of malignant ascites is attributed to the dissemination of tumor cells within the peritoneal cavity, leading to fluid accumulation in the abdominal region. During the invasion of the peritoneum by tumor cells, the physiological regulation of fluid dynamics in the abdominal cavity becomes compromised. This disruption in the balance between fluid influx and efflux can result in the gradual accumulation of several liters of fluid within the abdominal space [136]. In clinical settings, various tumors, including ovarian, gastric, endometrial, breast, colon, and pancreatic cancers, are associated with the development of malignant ascites [137]. Malignant ascites is often indicative of disease progression and correlates with a poor prognosis. The presence of ascites can induce distressing symptoms such as abdominal distension, persistent fullness, pain, nausea, dyspnea, insomnia, and fatigue, thereby considerably impairing patients' quality of life. Epithelial cell adhesion molecule (EpCAM) is a member of the adhesion molecule family and functions as a transmembrane glycoprotein. Overexpression of EpCAM has been closely associated with tumor invasion, metastasis, and poor clinical outcomes [138]. EpCAM is highly expressed in most epithelial cancers, rendering it an attractive target for anti-tumor therapies. In 70%–100% of cases involving malignant effusions, tumor cells are EpCAM-possitive [139].

Catumaxomab

As the first-in-class rat-mouse hybrid trifunctional BsAb, catumaxomab incorporates two Fab domains that specifically target EpCAM on tumor cells and CD3 on T cells. Additionally, its Fc domain engages Fcγ receptor-positive accessory cells, facilitating the close interaction between immune effector cells and tumor cells to enhance tumor destruction via multiple immunological mechanisms [140]. Intraperitoneal administration of catumaxomab provides localized and regional targeted immunotherapy against EpCAM-positive tumor cells within the abdominal cavity. A phase II/III trial evaluating catumaxomab for the treatment of malignant ascites in epithelial cancers (NCT00836654) demonstrated its significant efficacy in reducing the frequency of paracentesis, alleviating patient discomfort, and enhancing quality of life [141]. Notably, catumaxomab exhibited a marked advantage in puncture-free survival, achieving a duration four times longer than that of the control group (paracentesis alone). Based on these findings, the EMA approved in April 2009 catumaxomab for treatment of malignant ascites [142]. As the first commercially available BsAb, catumaxomab was withdrawn from the market in 2017 due to limited market acceptance, suboptimal commercial performance, and technical and conceptual limitations. With advancements in medical technology and the increasing availability of approved BsAb products, the EMA reapproved catumaxomab in February 2025, for intraperitoneal treatment of malignant ascites in adult patients with EpCAM-positive epithelial cells who are not eligible for further systemic anti-tumor therapy [143].

BsAb candidates in clinical stage

The following section describes several promising BsAb candidates that are currently in phase III clinical trials for solid tumors but have yet to receive regulatory approval. A comprehensive summary of all these BsAb candidates is provided in Table 3.

M701

M701 is a recombinant BsAb targeting EpCAM/CD3, designed for intraperitoneal administration to treat malignant ascites. Compared with catumaxomab, M701 has undergone humanization modifications, which significantly reduce its immunogenicity and enabling sustained dosing. Furthermore, the asymmetric structural

design of M701 optimizes the affinity of the CD3-binding domain, effectively balancing efficacy and safety.

At the 2024 ASCO Annual Meeting, interim analysis data from a phase II clinical trial of M701 were presented [144]. This study concluded that the intraperitoneal infusions of M701, in addition to systemic tumor therapy, was well tolerated and did not pose a higher risk than systemic tumor therapy alone in the control group. In total, the 84 enrolled patients received an intraperitoneal infusion of M701 ($n=43$) or abdominal paracentesis alone ($n=41$). The median puncture-free survival (PuFS) was significantly longer in the M701 group (54 days) than in the control group (24 days, $p=0.001$). The mOS was 113 days versus 76 days, respectively ($p=0.0575$). The 6-month survival was 35.2% versus 15.8%, respectively. Subgroup analyses revealed that patients with different cancer types, including gastric cancer, colorectal cancer, and ovarian cancer, all derived clinical benefits from M701 treatment. In the M701 group, 52% of patients experienced grade 3 or higher TRAEs, whereas this proportion was 57.5% in the control group [144]. M701 has now progressed to a phase III clinical trial (NCT06432296) which is actively recruiting patients with advanced epithelial solid tumors with malignant ascites. Final data from this trial are anticipated with interest.

Volrustomig (MEDI5752)

Volrustomig is a PD-1/CTLA-4 BsAb engineered to preferentially bind CTLA-4 on PD-1-positive activated T cells, thereby enhancing T-cell proliferation more effectively. Unlike conventional PD-1 mAbs, volrustomig inhibits the PD-1 pathway by mediating its internalization and degradation in a CTLA-4-dependent manner [145].

Preliminary data from a Ib/II phase study (NCT03530397) showed encouraging anti-tumor activity and acceptable tolerability with NSCLC first-line treatment using volrustomig plus CP, particularly in patients with PD-L1 expression on < 1% of tumor cells. More recent findings presented at the 2024 WCLC confirmed that volrustomig combined with chemotherapy remains effective in patients with PD-L1 expression below 1%, a population for whom traditional immunotherapy has shown limited efficacy [146]. Specifically, the ORRs were 43% for patients with non-squamous cell carcinoma and 50% for those with squamous cell carcinoma patients [146].

Based on these results, volrustomig holds promise as a more precise and efficacious treatment option for NSCLC and is currently advancing into phase III trials. NCT05984277 (eVOLVE-Lung02) is a phase III, two-arm, parallel-group, randomized, multicenter, open-label clinical trial designed to evaluate the efficacy and safety of volrustomig combined with chemotherapy in comparison to that of pembrolizumab combined with chemotherapy in the first-line treatment of metastatic NSCLC with PD-L1 expression on < 50% of tumor cells [147]. Additionally, volrustomig is being investigated for multiple indications, including CC, pleural mesothelioma, and head and neck squamous cell carcinoma, all of which have entered phase III clinical evaluation [148].

Erfonrilimab (KN046)

Erfonrilimab (KN046) is a humanized BsAb with a 2 + 2 symmetrical design, targeting PD-L1 and CTLA-4 [149]. Recently, the results of the open-label phase II KN046-202 trial (NCT04054531) have been published, evaluating the efficacy, safety, and tolerability of erfonrilimab in combination with chemotherapy as first-line therapy for metastatic NSCLC [150]. The results demonstrated an ORR of 46.0%, a mDOR of 8.1 months, a mPFS of 5.8 months, and a mOS of 26.6 months, with a 12-month OS of 74.2%. For patients with squamous NSCLC, the ORR was 50%, the mDoR was 7.3 months, the mPFS was 5.7 months, and the mOS was 26.6 months. KN046-related adverse events (AEs) were observed in 83 patients (95.4%), including grade 3 or higher KN046-related AEs in 30 patients (34.5%) [150]. Subsequently, the ongoing randomized, placebo-controlled phase III ENREACH-LUNG-01 study (NCT04474119, CTR20201294) was initiated to further evaluate the efficacy and safety of KN046 in combination with platinum-based chemotherapy as first-line treatment for advanced squamous NSCLC. This study has successfully completed its first interim analysis and met its prespecified endpoint of improving PFS.

KN026

KN026 is a BsAb that simultaneously binds to two non-overlapping epitopes of HER2, thereby effectively blocking HER2 signaling [151]. Compared with the combination of trastuzumab and pertuzumab, KN026 demonstrates enhanced inhibitory and cytotoxic effects on HER2-positive tumor cells. Moreover, KN026 also exhibits inhibitory efficacy against tumors with low level HER2 expression and trastuzumab-resistant cell lines.

HER2-positive gastric cancer (GC) is a highly heterogeneous malignancy characterized by aggressive invasiveness, frequent recurrence, and poor prognosis. Gastroesophageal junction cancer (GEJC) is an aggressive disease of the upper gastrointestinal tract with the fastest-growing incidence and mortality rate in recent years [152]. The current standard first-line treatment for advanced HER2-positive GC/GEJC primarily involves palliative chemotherapy combined with targeted therapy [153]. the prognosis in this setting is inferior. The median survival was about one year with optimal systemic

Table 3 The promising BsAbs currently in phase III clinical development for anti-tumor treatment but remain unapproved

Tumor	Name	Target	Conditions	Intervention	Clinical Trials No.
Hematologic tumors	ABBV-383 (Etentamig)	BCMA × CD3	R/R MM patients who have received at least two prior treatments	ABBV-383 versus standard available therapy	NCT06158841
	Alnuctamab	BCMA × CD3	R/R MM patients who have received not more than 3 prior lines	Alnuctamab versus standard available therapy	NCT06232707
Solid tumors	KN026	HER2 D2 × HER2 D4	First-line treatment of $HER2^+$ recurrent or metastatic breast cancer	KN026 + albumin-bound docetaxel versus trastuzumab + pertuzumab + docetaxel	NCT05838066
			$HER2^+$ advanced unresectable or metastatic GC/GEJC failed first-line therapy	KN026 + paclitaxel/docetaxel/irinotecan versus placebo + paclitaxel/docetaxel/irinotecan	NCT05427383
			Neoadjuvant therapy in patients with $HER2^+$ breast cancer	KN026 + albumin-bound docetaxel ± carboplatin versus pertuzumab and trastuzumab plus docetaxel ± carboplatin	NCT06747338
	Navicixizumab	VEGF × DLL4	Platinum-resistant advanced epithelial ovarian cancer, primary peritoneal, or fallopian tube cancer	Navicixizumab + paclitaxel and navicixizumab monotherapy versus paclitaxel monotherapy	NCT05043402
	Izalontamab (SI-B001)	EGFR × HER2	Advanced or metastatic NSCLC patients without actionable genomic alterations who failed the first-line treatment	SI-B001 + docetaxel versus docetaxel	NCT05943795
	SHR-1701	PD-L1 × TGF-βRII	Unresectable locally advanced or metastatic HER2-negative GC or GEJC	SHR-1701 + oxaliplatin + capecitabine (CAPOX) versus placebo + CAPOX	NCT04950322
			Perioperative treatment of resectable GC or GEJC	SHR-1701 + S-1 + oxaliplatin versus placebo + S-1 + oxaliplatin	NCT05149807 (terminated)
			First-Line treatment in persistent, recurrent, or metastatic CC	SHR-1701 + paclitaxel + cisplatin/carboplatin ± BP102 versus placebo + paclitaxel + cisplatin/carboplatin ± BP102	NCT05179239 (terminated)
			Advanced or metastatic non-squamous NSCLC With EGFR mutation after failure of TKIs	SHR-1701 + pemetrexed disodium + cisplatin/carboplatin ± BP102 versus placebo 1 + placebo 2 + pemetrexed disodium + cisplatin/carboplatin	NCT05132413
			First-line treatment of unresectable recurrent or metastatic CRC	SHR-1701 + BP102 + XELOX versus placebo + BP102 + XELOX	NCT04856787
	Erfonrilimab (KN046)	PD-L1 × CTLA-4	First-line treatment of advanced squamous NSCLC	KN046 + gemcitabine + nab-paclitaxel versus placebo + gemcitabine + nab-paclitaxel	NCT04474119
			First-line treatment of advanced PDAC		NCT05149326
			Resectable stage IB-IIIB (stage IIIB only $T_3N_2M_0$) NSCLC	Preoperative use: KN046 versus axitinib	NCT06020352

Table 3 (continued)

Tumor	Name	Target	Conditions	Intervention	Clinical Trials No.
	Volrustomig (MEDI5752)	PD-1 × CTLA-4	Unresected locally advanced HNSCC who have not progressed after receiving definitive concurrent chemoradiotherapy	Volrustomig versus observation	NCT06129864
			Advanced unresectable pleural mesothelioma	Volrustomig + carboplatin + pemetrexed versus investigator's choice (platinum + pemetrexed/nivolumab + ipilimumab)	NCT06097728
			First-line treatment in participants with mNSCLC in PD-L1 < 50%	Volrustomig + chemotherapy versus pembrolizumab + chemotherapy	NCT05984277
			Locally advanced CC (IIIA-IVA) who have not progressed following platinum-based CCRT	Volrustomig versus placebo	NCT06079671
	PM8002 (BNT327)	PD-L1 × VEGF	Second-line treatment of advanced SCLC	PM8002 + paclitaxel versus investigator's choice (topotecan or paclitaxel)	NCT06616532
			Inoperable locally advanced/metastatic triple-negative breast cancer	PM8002 + nab-paclitaxel versus placebo + nab-paclitaxel	NCT06419621
	Rilvegostomig (AZD2936)	PD-1 × TIGIT	First-line treatment for PD-L1-high mNSCLC	Rilvegostomig versus pembrolizumab	NCT06868277
			HER2-positive locally advanced or metastatic GC/GEJC with PD-L1 CPS ≥ 1	T-DXd + rilvegostomig + chemotherapy versus trastuzumab + pembrolizumab + chemotherapy	NCT06764875
			First-line treatment of squamous mNSCLC with PD-L1 expression	Rilvegostomig + chemotherapy followed by rilvegostomig versus pembrolizumab + chemotherapy followed by pembrolizumab	NCT06692738
			First-line treatment of non-squamous mNSCLC with PD-L1 expression	Rilvegostomig + chemotherapy versus pembrolizumab + chemotherapy	NCT06627647
			Locally advanced or metastatic and/or unresectable HCC	Rilvegostomig + bevacizumab ± tremelimumab versus atezolizumab + bevacizumab	NCT06921785
			BTC after curative intent resection	Rilvegostomig + chemotherapy versus placebo + chemotherapy	NCT06109779
	M701	EPCAM × CD3	Malignant ascites caused by advanced epithelial solid tumors with systemic therapy	M701 versus paracentesis	NCT06432296

Abbreviation: GEJC gastroesophageal junction cancer, *TGF-βRII* TGF-β receptor II, *TKI* tyrosine kinase inhibitors, *CRC* colorectal cancer, *HNSCC* head and neck squamous cell carcinoma, *TIGIT* T-cell immunoglobulin and ITIM domain, *CCRT* concurrent chemoradiotherapy, *CPS* combined positive score, *HCC* hepatic cell carcinoma

chemotherapy and supportive care [154]. A phase II clinical trial evaluating KN026 monotherapy in patients with advanced HER2-expressing GC/GEJC who had progressed after at least one line of standard treatment enrolled 45 patients. In the high-level HER2 subgroup, ORR was 56%, mDoR was 9.7 months, mPFS was 8.3 months, and mOS was 16.3 months [155], whereas in the low-level HER2 subgroup, ORR was 14%. The most common grade 3 or higher TRAEs were gastrointestinal disorders (11%). A phase II/III clinical study (KN026-001) assessing the combination of KN026 and chemotherapy for second-line or later treatment of HER2-positive GC/GEJC has completed its first interim analysis. Following a thorough evaluation by the Independent Data Monitoring Committee, the study met its prespecified primary endpoint of PFS, demonstrating both statistical significance and clinical relevance.

Another multicenter, open-label, single-arm phase II study evaluated the efficacy and safety of KN026 in combination with docetaxel as first-line treatment for patients with HER2-positive recurrent/metastatic breast cancer (BC) [156]. A total of 57 patients were included in the study, and the ORR was 76.4%. The median follow-up duration was 31.1 months, and the mPFS was 27.7 months. The mOS has not yet been reached, with 12-month, 24-month, and 30-month OS of 93.0%, 84.1%, and 78.5%, respectively. Grade 3 or higher TRAEs occurred in 63.2% of the enrolled patients. The most common grade 3 or higher TRAEs were neutropenia (40.4%) and leukopenia (28.1%). These results demonstrate that KN026 in combination with docetaxel exhibits promising efficacy and a manageable safety profile as a first-line treatment for HER2-positive recurrent/metastatic BC. Currently, a phase III RCT is ongoing to further evaluate this regimen [156].

SI-B001

Approximately 40%–80% of patients with NSCLC show EGFR expression, and the EGFR signaling pathway can be activated by EGFR×HER3 heterodimers [157]. SI-B001 is a recombinant humanized BsAb capable of simultaneously binding to EGFR and HER3, thereby blocking the interaction of EGFR and HER3 with their respective ligands and inhibiting the downstream pathways [158]. Additionally, SI-B001 has the potential to overcome HER3-mediated resistance following EGFR-targeted therapy and exhibits superior efficacy compared to the combination of EGFR and HER3 mAbs.

The results of the phase II study evaluating the efficacy of SI-B001 in combination with chemotherapy were presented at the 2023 ASCO Annual Meeting [159]. This study enrolled 55 patients with locally advanced or metastatic EGFR/ALK wild-type NSCLC who progressed after first-line anti-PD-1/L1 immunotherapy. Results demonstrated that the ORR for patients treated with SI-B001 combined with docetaxel was 43.5% and the mPFS was 7.2 months, surpassing historical data for standard docetaxel monotherapy. Regarding safety, the most common grade 3 or higher TRAEs were bone marrow suppression (17%), neutropenia (15%), and leukopenia (12%) [159]. No drug-related deaths were observed.

Based on these findings, a further randomized phase III trial is currently underway (NCT05943795). If these results are further validated, SI-B001 in combination with docetaxel may emerge as a viable second-line treatment option, addressing the unmet need following immunotherapy resistance.

SHR-1701

SHR-1701, a BsAb independently developed in China, consists of an IgG4 mAb targeting PD-L1 and the extracellular domain of the transforming growth factor (TGF)-β receptor II [160]. This molecule not only promotes the activation of effector T cells but also effectively enhances immune regulation within the TME, thereby improving the immune system to eliminate tumor cells [161]. A phase II trial (NCT05179239) had the primary objective to evaluate the preliminary efficacy and safety of SHR-1701 in combination with BP102 (a biosimilar to bevacizumab) and chemotherapy as first-line treatment for CC, irrespective of PD-L1 expression status [162]. A total of 31 patients with recurrent or metastatic advanced CC were enrolled. With a median follow-up duration of 7.2 months, reductions of target lesion were observed in 30 patients (96.8%). The ORR was 77.4%, the DCR was 93.5%, and the 6-month PFS was 93.5%. TRAEs of grade 3 or higher occurred in 83.9% of patients, with the most common events being neutropenia, leukopenia, and anemia [162]. Notably, the FDA-approved first-line therapy for PD-L1-positive recurrent or metastatic CC (pembrolizumab + chemotherapy ± bevacizumab) has an ORR of 68%. These results suggest that SHR-1701 in combination with platinum-based chemotherapy and BP102 may offer equivalent or superior efficacy, potentially challenging the current standard of care.

Currently, over 20 clinical trials involving SHR-1701 are underway, including phase III studies evaluating its use as first-line or neoadjuvant treatment of colorectal cancer (CRC), NSCLC, GC, or CC, highlighting its broad therapeutic potential across malignancies.

Navicixizumab

An updated BsAb, navicixizumab, was designed to inhibit both Delta-like ligand 4 (DLL4) and VEGF, thereby inducing anti-angiogenetic effects and concurrently eliciting an effective anti-tumor response [163].

DLL4, a Notch ligand, plays a critical role in angiogenesis by coordinating tips and stalk cells and is associated with anti-VEGF resistance [164]. Dysregulation of the Notch pathway occurs in nearly 22% of patients with OC and is associated with poor prognosis, such as limited survival, advanced stages, or lymph node involvement [74]. VEGFR, Notch1, and Notch3 are overexpressed in OC samples [165]. Hu et al. showed that blocking both DLL4 and VEGF with a combination of siRNA and bevacizumab was superior to either strategy alone [166].

Navicixizumab exerts potent anti-tumor activity in xenografts of various solid tumors [167]. A phase Ib study showed promising clinical results for navicixizumab combined with paclitaxel in heavily treated platinum-resistant OC [163]. In this study, 44 patients previously treated for recurrent platinum-resistant OC received bevacizumab and paclitaxel. The ORR was 43.2% and the mPFS was 7.2 months [163]. The most common grade 3–4 TRAEs were hypertension (40.9%), neutropenia (6.8%), and thrombocytopenia (4.5%). Received a fast-track designation by the FDA in 2019 for platinum-resistant OC, navicixizumab combined with paclitaxel has great potential and manageable toxicity in patients with platinum-resistant OC. Further randomized studies are ongoing to verify the synergistic efficacy and limited TRAEs associated with blocking VEGF and DLL4 expression in platinum-resistant advanced epithelial OC (NCT05043402).

PM8002 (BNT327)

PM8002 is the first and currently only BsAb targeting PD-L1 and VEGF to advance into phase III clinical trials. By simultaneously targeting PD-L1 and VEGF, PM8002 addresses immune modulation and anti-angiogenesis, inducing a synergistic anti-tumor effect.

A phase II single-arm study indicated that PM8002 in combination with chemotherapy demonstrates preliminary anti-tumor activity and acceptable safety in patients with advanced NSCLC [168]. Among patients with high PD-L1 expression (≥50% of tumor cells), the ORR is 92.3%. For patients with PD-L1 expression between 1 and 49%, the ORR is 60%, surpassing other comparable treatments. TRAEs occurred in 95.3% of patients, with grade 3 or higher TRAEs reported in 54.7%. However, most TRAEs were attributable to chemotherapy agents and not directly associated with PM8002. Additionally, PM8002 combined with paclitaxel as a second-line treatment for SCLC exhibited encouraging anti-tumor activity and an acceptable safety profile [169]. A phase Ib/II study included 27 patients with advanced SCLC who did not responded to first-line platinum-based chemotherapy. Results demonstrated a DCR of 81.8%, an ORR of 72.7%, and a mPFS of 5.5 months [169]. The subsequent phase III study is currently recruiting patients (NCT06616532). The results of another phase II study indicated that PM8002 plus nab-paclitaxel shows encouraging anti-tumor activity and good safety as a first-line treatment for advanced triple-negative breast cancer (TNBC) [170]. Key data included an ORR of 78.6%, a DCR of 95.2%, a 12-month OS of 80.8%, a 15-month OS of 78.1%, and an 18-month OS of 72.2%. All patients experienced TRAEs, with 59.5% experiencing grade 3 or higher TRAEs [170]. Furthermore, a multicenter, randomized, double-blind phase III clinical trial is ongoing to evaluate PM8002 injection or placebo in combination with nab-paclitaxel as first-line treatment of locally advanced or metastatic TNBC unsuitable for surgery (NCT06419621).

Overall, PM8002 holds broad application potential across various tumor types. However, further clinical trials are warranted to clarify its efficacy, safety, and optimal usage strategy. With continued advancements in clinical research, PM8002 has the potential to receive approval in the near future.

Rilvegostomig(AZD2936)

T-cell immunoglobulin and ITIM domain (TIGIT) is a co-inhibitory receptor highly expressed on tumor-infiltrating lymphocytes (TILs). The interaction between TIGIT and its homologous ligand PVR directly suppresses the activation of CD8 + T cells, representing a novel immune checkpoint following PD-1/PD-L1. Rilvegostomig is a BsAb simultaneously targeting TIGIT and PD-1, thereby achieving enhanced immune activation and producing synergistic anti-tumor effects [171, 172].

The first-in-human study of rilvegostomig (ARTEMIDE-01, NCT04995523) conducted on patients with ICI-resistant metastatic NSCLC demonstrated encouraging safety and anti-tumor activity. Notably, the ORR was 61.8% in patients with high PD-L1 expression and 29.0% in those with low PD-L1 expression [173]. A phase III clinical trial (NCT006627647) was scheduled to compare rilvegostomig in combination with chemotherapy head-to-head with pembrolizumab for the treatment of patients with PD-L1-positive non-squamous NSCLC. Furthermore, three additional phase III trials have been accelerated, targeting hepatic cell carcinoma (HCC), NSCLC, and BTC [174]. If the phase III trials prove successful, rilvegostomig has the potential to change the standard treatment for advanced tumors.

Toxicities and limitations

With the increasing use of BsAbs, managing associated toxicities has become a critical aspect of clinical practice [175]. Owing to the unique structure, BsAbs targeting

the same antigens may exhibit differing levels of efficacy and adverse reactions as a result of variations in production processes and target binding sites. In clinical practice, it is essential to closely monitor adverse events based on the specific targets of BsAbs and promptly adjust the treatment strategy accordingly.

The consensus guidelines for handling toxicities associated with BsAbs as follows: 1) therapeutic strategies should be individualized for each patient, considering factors such as clinical presentation, tumor characteristics, and prior treatment responses; 2) a comprehensive pre-treatment assessment is imperative for every patient; 3) managing and mitigating adverse events is a dynamic and personalized process that necessitates continuous monitoring to optimize anti-tumor efficacy while safeguarding patients from preventable harm; 4) comprehensive patient education is critical for successful BsAb therapy. Prior to initiating treatment, physicians must engage in detailed discussions with patients to ensure they fully comprehend the treatment procedure, actively participate in self-monitoring, and promptly report any adverse events.

On-target off-tumor adverse effects

For the successful development of BsAbs, the selection of appropriate targets represents a critical step that significantly influences both efficacy and safety. An ideal target for BsAbs should exhibit uniform expression on the surface of tumor cells while being absent from essential healthy tissues to mitigate on-target off-tumor toxicities. Given that antigen loss or downregulation is a prevalent resistance mechanism in cancer, the targeted antigen should play a critical role in tumor cell survival or proliferation.

Although most BsAb targets exhibit specific expression primarily in tumor cells, low-level expression may occasionally occur in normal tissues, thereby inducing a certain degree of off-tumor toxicity. The specific symptoms observed are contingent upon the expression profile of the target antigen. For instance, due to gp100-positive cutaneous melanocytes, the off-tumor toxicity associated with the gp100-targeting tebentafusp manifests as skin-related events, including rash, pyrexia, and pruritus [134]. In contrast, GPRC5D is exclusively expressed in hard keratin-producing cells, such as hair follicles, which elucidates the specific on-target off-tumor adverse effects, such as dysgeusia, dermatological disorders, and nail abnormalities [63]. Hypogammaglobulinemia represent an example of off-tumor toxicity linked to BsAbs, which arises due to the presence of target antigens (e.g., BCMA and GPRC5D) in both malignant and normal plasma cells [176]. To mitigate such toxicities, strategies predominantly focus on refining BsAb design. For example, if one binding arm recognizes an antigen also present in normal tissues, the other binding arm can be designed to target antigens highly expressed on tumor cells or tumor-associated stromal cells. This dual-specificity approach increases the likelihood that BsAbs will only engage tumor cells, thereby reducing collateral damage to healthy tissues. Additionally, designing BsAbs as prodrugs that are conditionally activated in the TME represents another promising strategy. By ensuring that BsAbs remain inactive until infiltrating into the tumor site, this approach minimizes systemic exposure and associated toxicities, improving the therapeutic index. Given the heterogeneity of solid tumors, it is imperative to evaluate target expression across various tumor subtypes and locations to improve personalized drug delivery. Leveraging the unique dual-targeting capabilities of BsAbs, a comprehensive assessment of antigen combinations is essential. This includes evaluating critical factors such as internalization kinetics, recycling rates, antigen turnover, lysosomal degradation pathways, and intrinsic cellular mechanisms. Integrating these multifaceted considerations is pivotal for the rational and effective design of BsAbs.

Drug resistance

Compared with single-target mAbs, BsAbs can simultaneously bind to two targets and block two signaling pathways, reducing the risk of drug resistance. For instance, after long-term use of mAbs targeting receptor tyrosine kinases (RTKs), tumor cells can evade immune response by switching signaling pathways or activating intracellular signals through homodimers or heterodimers of HER family members themselves or among different members. The simultaneous blockade of two or more RTKs or their ligands using BsAbs can reduce tumor cell escape and enhance therapeutic efficacy. Nevertheless, resistance to BsAb therapy is a complex process influenced by tumor characteristics, T-cell functionality, and an immunosuppressive TME. With regard to tumor cells, a higher tumor burden generally correlates with a greater likelihood of responding to BsAb therapy. However, prolonged use of the same BsAb can result in the loss of targeted tumor antigens, increasing the risk of non-response or early relapse.

Moreover, pre-existing T-cell dysfunction significantly contributes to resistance against CD3-based BsAbs [177]. During host immune surveillance, T cells function as essential sentinels once antigen-presenting cells present MHC-antigen peptide complexes to the TCR, providing secondary costimulatory signals to activate naïve T cells and promote effector T-cell proliferation. However, if co-stimulatory molecules are absent or replaced by a co-inhibitory molecule (such as immune checkpoints),

T cells become functionally impaired to mediate specific cytotoxicity towards tumor cells. Prolonged exposure to immunosuppressive anti-tumor drugs, along with inhibitory interactions with tumor cells (e.g., PD-L1), further impairs T-cell function. This may explain why BsAbs exhibit superior efficacy when administered earlier in the disease course [178]. Prolonged exposure to T-cell-redirecting antibodies results in sustained T-cell stimulation, leading to T-cell exhaustion. This state of exhaustion is characterized by the expression of inhibitory checkpoint molecules and a progressive decline in T-cell functions, such as proliferation, cytotoxic activity, and cytokine production [179, 180].

Therapeutic strategies that modulate costimulatory and inhibitory pathways to counteract T-cell exhaustion can enhance the anti-tumor efficacy of CD3-targeting BsAbs. In a mouse model, the administration of anti-CD33×CD3 BiTE (AMG330) increased the expression of PD-1 on tumor cells, which substantially compromised T cell-mediated tumor cell lysis. However, inhibiting the PD-1/PD-L1 interaction restored sensitivity to AMG330 and augmented AMG330-induced cytotoxicity. Moreover, BsAbs engineered to target both immune checkpoints and tumor antigens exhibit superior performance compared with combinations of ICIs and BsAbs. Mechanistically, this enhanced efficacy is attributed to their ability to block PD-1/PD-L1 interaction in TAA-positive cancer cells. To further counteract peripheral tolerance and enhance immune checkpoint blockade within tumors, novel BsAbs are being developed to simultaneously target two distinct immune checkpoints, such as the CrossMab format anti-PD-1/TIM-3 BsAbs, or to engage checkpoint inhibitors along with T-cell costimulatory receptors. A phase I study has demonstrated that combining glofitamab with a CD19×4-1BB costimulatory BsAb exhibits a safety profile comparable to that of glofitamab monotherapy while eliciting promising anti-tumor responses in heavily pretreated patients with lymphoma [181–183].

An immunosuppressive TME is characterized by the presence of various immunosuppressive cells, such as regulatory T cells (Tregs) and immunosuppressive molecules, significantly reducing the efficacy of immunotherapies, including CD3-targeting BsAbs. Preclinical and clinical research has shown that Tregs can impair the functionality of BsAbs [184]. Notably, studies have demonstrated that CD38-targeting antibodies can eliminate CD38-positive Tregs, enhancing T-cell performance. This provides a scientific rationale for combining BsAbs with CD38-targeting antibodies in the treatment of MM [68].

Immunogenicity

As exogenous proteins, BsAbs may induce an immune response upon entering the body, leading to the formation of anti-drug antibodies (ADAs). This phenomenon can affect the pharmacokinetic and pharmacodynamic properties of the drug. Immunogenicity generally refers to the ability to stimulate ADA production within the host. Structural modifications, along with potential synergistic immune regulatory mechanisms derived from different domains of BsAbs, are closely linked to the patient's immune status, concurrent use of immunosuppressive agents, dosage regimens, and routes of administration [14, 185]. Zhu et al. analyzed the pharmacokinetic and pharmacodynamic profiles of blinatumomab in patients with R/R ALL, MRD-positive ALL, and NHL by integrating data from six clinical trials. They also investigated the immunogenicity of blinatumomab and its impact on pharmacokinetic and pharmacodynamic properties [43]. The immunogenicity of blinatumomab was evaluated based on the proportion of patients who tested positive for ADAs or neutralizing antibodies. Among the 436 patients who underwent immunogenicity testing across the six clinical trials, only four patients were positive for both binding and neutralizing ADAs, resulting in an overall immunogenicity rate of less than 1%. Moreover, clinical studies have demonstrated that 4-1BB agonists exhibit immunogenic properties. In a phase I study (NCT01471210) involving patients with R/R B-cell lymphoma, 16% to 30% of patients developed ADAs following urelumab administration [186]. In another phase I study (NCT01307267) conducted in patients with advanced cancer, 41.8% of patients developed treatment-induced ADAs after receiving urelumab therapy [14, 187].

As the applications of BsAbs continue to expand, safety standards for the development and clinical application will become increasingly stringent. The influence of immunogenicity on the safety and efficacy of BsAbs must not be underestimated. Strategies such as enhancing the humanized components of BsAb during development, utilizing fully humanized antibodies when feasible, conducting thorough immunogenicity assessments in preclinical and clinical trials, and implementing therapeutic drug monitoring during clinical application to ensure patients remain within the therapeutic window will significantly enhance the safety and clinical effectiveness of BsAbs.

IrAEs

For CD3-targeting BsAbs, the common irAEs including CRS, immune effector cell-associated neurotoxicity syndrome (ICANS) and infection. And the common risk factors associated with the incidence and severity of irAEs include high tumor burden, rapid disease progression, plasma cell leukemia, elevated baseline inflammatory markers, and central nervous system involvement.

CRS

BsAbs targeting CD3, commonly referred to as TCEs, activate immune cells, particularly macrophages, leading to a significant release of cytokines such as IL-2, IL-6, IFN-γ, and TNF-α [188]. Overactivation of immune effector cells and uncontrolled increases in cytokines result in systemic CRS, characterized by acute systemic inflammation and secondary organ dysfunction [188, 189]. CRS is one of the most common TRAEs associated with TCE therapy, with notable variations in clinical presentation and severity among patients. Clinical data indicate that 14% to 35% of patients receiving blinatumomab experience CRS, with approximately 5% exhibiting grade 3 or higher CRS [190, 191]. The incidence of CRS tends to decrease progressively as the treatment cycles advance. To mitigate the risk, step-up dosing during treatment initiation is implemented, and dexamethasone premedication is recommended prior to each administration, particularly when resuming infusion after an interruption of more than 4 h [192]. It is important to note that while the majority of CRS occur during the early stages of dose escalation, delayed-onset cases have also been reported. Moreover, the occurrence of CRS often correlates with a less favorable prognosis. The clinical presentation of CRS often involves multiple organ systems and directly impacts subsequent anti-tumor treatment strategies. Owing to incomplete understanding of the underlying pathophysiological mechanisms, managing CRS effectively remains challenging. The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) provides a grading system specifically designed for CRS associated with antibody-based therapies to optimize immunotherapy outcomes while minimizing the risk of severe CRS complications.

Therapeutic approaches have evolved from rudimentary symptomatic treatments to comprehensive life-support-based interventions. The primary objective is to prevent life-threatening CRS while optimizing the beneficial anti-tumor effects. To mitigate TCEs-induced CRS, strategies such as step-up dosing, subcutaneous administration rather than intravenous delivery, and TCEs with low affinity for CD3 binding have been shown to effectively reduce the risk of severe CRS [72, 193, 194]. For managing CRS symptoms, inhibiting cytokine signaling via blockers such as IL-6, IL-1, IFN-γ, or TNF-α can be beneficial, as cytokines are key mediators of CRS progression. Steroids also serve an important function in controlling excessive inflammation [195]. Current CRS management options include cyclophosphamide, alemtuzumab, antiserum globulin, and hematopoietic stem cell therapy. Additional supportive measures include antipyretics, intravenous fluid administration, and oxygen support. Overall, continuous validation and refinement of CRS mechanisms and resolution strategies are imperative to enhance the efficacy and safety of TCE therapies.

ICANS

ICANS refers to a spectrum of neurological adverse events associated with BsAbs. The incidence of ICANS in patients undergoing BsAbs is significantly lower compared to CRS. Although the exact mechanism remains incompletely understood, it is currently hypothesized that ICANS arises from cytokine-mediated endothelial cell activation, leading to blood–brain barrier disruption and transient cytokine infiltration into the cerebrospinal fluid and brain parenchyma. Clinically, ICANS manifests as a progressive range of neurological symptoms, spanning from subtle signs such as tremors, dysgraphia, aphasia, or mild confusion to severe manifestations including complete aphasia, seizures, decreased levels of consciousness, and cerebral edema. Headache and tremor are the most frequently observed symptoms. Management primarily focuses on symptom control and administration of high-dose glucocorticoids. Tocilizumab, which does not cross the blood–brain barrier, is generally not recommended unless ICANS occurs concurrently with CRS.

Infection

Patients receiving BsAbs exhibit a markedly increased susceptibility to bacterial, viral, or fungal infections, especially BCMA- or CD20-targeting BsAbs. This heightened vulnerability is attributed to various immunological factors, such as T cell redirection, B cell or T cell exhaustion, neutropenia, lymphopenia, and hypogammaglobulinemia. A meta-analysis demonstrated that 50% of patients undergoing BsAbs encountered infection-related complications, of which half were severe grade 3/4 infections. Notably, 25% of fatalities were attributed to infections [196]. General antibacterial prophylaxis is not routinely recommended for patients undergoing BsAb therapy. However, it is advised for patients experiencing prolonged neutropenia, those at high risk of infection, or individuals with a history of recurrent bacterial infections. Antimicrobial prophylaxis should be discontinued once the risk of neutropenia has been mitigated. Furthermore, it is recommende to receive appropriate vaccinations prior to initiating treatment as universal prophylaxis against pneumocystis jirovecii, varicella zoster, and herpes simplex [188, 192]. MM patients often develop secondary immune deficiencies, such as hypogammaglobulinemia, which is characterized by reduced serum IgG levels. A retrospective study indicated that the infection risk associated with anti-BCMA

or anti-GPRC5D BsAb therapy primarily results from treatment-induced severe hypogammaglobulinemia [197]. And patients with higher grade infections were found to have significantly lower serum IgG [197]. The depletion of plasma cells, including those responsible for producing IgG, leads to profound hypogammaglobulinemia in treated patients and potentially exacerbating the risk of infection. One study revealed that all patients receiving anti-BCMA BsAbs experienced profound hypogammaglobulinemia, which persisted throughout the entire treatment period [197]. Consequently, the regular monitoring of IgG levels is essential, and immunoglobulin replacement therapy (IGRT) has been shown to reduce the risk of severe infection by 80% [198], supporting the implementation of primary prophylaxis [188, 199, 200]. However, guidelines for manageing infection risks in MM patients recommend IGRT only for individuals with moderate-to-severe hypogammaglobulinemia (serum IgG < 400 mg/dL) and a history of recurrent, severe infections [201]. This restrictive recommendation is primarily due to the uncertain efficacy of IGRT in preventing infections in the general MM population, along with its potential risks and high costs.

Discussion

As an advanced form of antibody technology, the development of BsAbs remains predominantly in experimental stages. Among the over 300 types of BsAbs that have progressed to clinical trials, approximately 80% are still in early phases. Promising BsAb candidates currently under development in phase III clinical trials are summarized in Table 3. Globally, only 17 BsAbs have received regulatory approval for use in oncology (Table 1).

Specifically, 9 BsAbs have been approved for the treatment of hematological malignancies, all of which are CD3-targeting TCEs. Although TCEs have led to the approval of multiple products for hematological malignancies, their application in solid tumors remains fraught with significant challenges. This disparity is primarily attributed to the highly immunosuppressive TME of solid tumors, which impedes effective interactions between tumor cells and T cells. Furthermore, the dense tumor stroma acts as a physical barrier, hindering T-cell infiltration, while inadequate blood perfusion in solid tumors may compromise drug delivery or lead to non-uniform distribution of the BsAbs within the tumor. The other key barriers is safety, which includes severe CRS and immunogenicity. The clinical dosing of TCEs is often constrained due to CRS, limiting the ability to achieve higher drug concentrations required to overcome ADA levels. Moreover, TCEs directly activate $CD4^+$ T cells, potentially amplifying humoral immune responses and thereby exacerbating immunogenicity.

Compared to mAbs, the techniques involved in the design, construction and development of BsAbs are considerably more complex and sophisticated. The primary objective of developing BsAbs is to provide significant clinical advantages over the simple combination of two mAbs, achieving a synergistic effect that exceeds the sum of their individual contributions. However, some key technical challenges must be addressed during the design and development of BsAbs [202]. One of the most critical challenges in BsAb design is the selection of ideal targets. Ideally, these targets should exhibit specific expression on tumor cells while sparing healthy tissues to minimize off-target effects. Tumor cells often employ immune evasion strategies, such as rapid shedding or internalization of the targeted antigen, which can render BsAbs less effective in eliminating tumor cells. To overcome this limitation, substantial theoretical and practical efforts must be devoted to identifying appropriate antigens that enhance both specificity and feasibility. Developing high-performance BsAb scaffolds and rationally designing the epitope targeting are also crucial steps in maximizing their efficacy. Another challenge in BsAb design is the issue of chain mismatches, which occurs when heavy and light chains from different antibody domains incorrectly pair during recombinant production [203]. This phenomenon can lead to reduced yields and compromised functionality of the final product. To address this limitation, researchers have developed innovative material science approaches, such as chemically coupling polyethylene glycol to small proteins or fusing them with heavy chain fragments (Fc/CH3) or human serum albumin, which significantly extend circulation time while preserving recombinant binding ability [204]. Moreover, as BsAbs are increasingly combined with other agents, such as ICIs and CAR-T cells [205], the safety profiles require careful evaluation [206].

CAR-T cells which are genetic engineered, patient-derived T cells that express chimeric antigen receptor (CARs), enable the recognition and elimination of cancer cells. Both CAR-T and CD3-targeting TCEs are generalized immunotherapeutic approaches that leverage T cell redirection to induce cytotoxicity, with overlapping approved indications in the treatment of B-cell malignancies. A meta-analysis revealed that CAR-T therapy achieved higher CR than TCEs for R/R DLBCL (0.51 vs. 0.36, $p < 0.01$), although with a heightened risk of severe toxicities [207]. However, CAR-T cell manufacturing requires ex vivo genetic modification and autologous T cell expansion, which is a relatively inefficient, resource-intensive, time-consuming and thus costly process. In contrast, off-the-shelf BsAbs allow immediate treatment initiation without personalized manufacturing processes. Furthermore, there may be a synergistic benefit

to using CAR-T cells and BiTEs against tumors. Patients refractory to one therapy may exhibit responsiveness to the other in clinical practice. For example, two patients who were refractory to blinatumomab achieved CR after CD19 CAR-T treatment [208]. Additionally, the cytotoxic effects can be augmented by combining BsAbs or CAR-T targeting two distinct tumor antigens. A preclinical study demonstrated enhanced tumor control through the simultaneous employment of CAR-T cells targeting the alpha folate receptor and EGFR-targeting BiTE [205]. The optimal sequence of BsAbs and CAR-T cell therapy remains unclear. Current evidence suggests that when targeting the same antigen, CAR-T therapy may be suitable for initial treatment, while BsAbs could serve as salvage therapy after CAR-T failure [209, 210]. For instance, epcoritamab is well-tolerated and effective in DLBCL patients relapsing after CAR-T therapy [211]. Glofitamab not only triggered responses after CAR-T therapy but also enhanced the persistence and activity of residual CAR-T cells in peripheral blood [212]. Bridging therapy is essential prior to CAR-T infusion, primarily aimed at reducing tumor burden, as rapidly progressing disease has been associated with shortened survival and increased rates of CAR-T-related toxicities [213]. While preliminary data suggest that prior exposure to BsAbs could negatively impact successful T cell manufacturing and outcomes after CAR-T therapy, [214], BsAbs still serve as a bridging option for patients who have exhausted all other salvage strategies. A retrospective analysis revealed that BsAbs provided a highly effective and safe bridging therapy of CAR-T cells, achieving the highest ORR compared to those of chemotherapy, anti-CD38, and anti-SLA-7 mAb-based regimens (100% vs. 46%) [215]. However, data from two small-scale studies indicate limited PFS when using BCMA CAR-T after BCMA-BsAb [216, 217]. Given the limited number of patients and the heterogeneity of prior treatments, definitive conclusions are challenging to establish. Therefore, direct comparisons of these strategies through prospective trials are essential to determine the optimal sequential approach for CAR-T and BsAbs therapy [218].

The step-up dosing (SUD) regimen of BsAbs has been implemented to minimize the potential for adverse inflammatory responses, like CRS and ICANS [219–221]. SUD entails initiating treatment with a low starting dose, followed by incremental adjustments until the full treatment dose is achieved. SUD facilitates a more gradual"priming"of the immune system, thereby reducing the possibility of triggering an uncontrolled inflammatory response that may lead to CRS or other immune-related toxicities [222, 223]. Despite these advantages, challeges remain in managing CRS during the SUD phase. For instance, inpatient monitoring is often necessary during SUD to ensure timely detection and management of adverse events. In real-world setting, nearly 90% of patients receiving teclistamab have required hospitalization for a week or longer to implement this SUD regimen [224]. However, the rarity of grade 3 or 4 CRS, coupled with enhanced resource utilization and decreased patient satisfaction, necessitates the transition of SUD management from inpatient to outpatient protocolized approaches. Sandahl et al. demonstrated the successful establishment of an outpatient-based workflow for teclistamab administration, highlighting the safety and feasibility of outpatient administration as a potential means to reduce healthcare resource utilization and improve patient experiences [225, 226]. The ongoing expansion of the SUD phase into community practices necessitates a comprehensive strategy that integrates educational programs, operational adaptations, and collaborative networks [227]. Despite the typical premedication being dexamethasone, the prophylactic use of tocilizumab may serve as a valuable consideration when selecting patients for outpatient BsAb administration. A single dose of tocilizumab effectively blocks the IL-6 receptor for approximately 10 days, covering the entire SUD period [228]. Consequently, the prophylactic administrated of tocilizumab prior to step-up dose 1 has been shown to decrease the frequency of CRS without compromising efficacy when tocilizumab is administered prior to the first step-up dose [229–231]. Furthermore, the importance of high-quality symptomatic and supportive care cannot be overstated. Wearable devices, for example, can be employed to continuously monitor vital signs such as body temperature in real-time, enabling the early detection of CRS onset. This proactive approach allows clinicians to intervene promptly, potentially preventing the progression of mild symptoms into more severe complications. Machine learning (ML) algorithms represent yet another innovative advancement in the field of CRS management. By analyzing real-time patient data, ML algorithms can predict the likelihood of CRS onset, providing clinicians with actionable insights to inform personalized treatment decisions. By integrating clinical decision support systems into routine clinical practice, healthcare providers can enhance the quality of care delivered to patients undergoing BsAb. The safety of adopting outpatient SUD for patients with high tumor burden or severe comorbidities, such as organ dysfunction, requires additional evaluation. Institutions utilizing outpatient models often need to establish comprehensive monitoring systems, including wearable technology, daily communications, and routine clinical visits, to identify early signs of CRS, infections, or neurotoxicities and manage symptoms effectively.

Optimizing the dose interval is essential for achieving a balance between therapeutic efficacy and safety. Since dosing intervals vary between different BsAbs, patient

monitoring should be tailored to accommodate individual schedules [195]. For example, talquetamab was approved based on findings from the phase I/II clinical trial MonumenTAL-1, which evaluated two distinct dosing regimens: 0.4 mg/kg weekly after two step-up doses and 0.8 mg/kg biweekly following three step-up doses. Both regimens demonstrated comparable efficacy; however, the biweekly option was deemed more practical due to its reduced frequency of visits and potential to minimize adverse effects [232]. Updated data indicate that biweekly dosing may enhance outcomes in terms of PFS and DoR [233]. Patients in the dose-reduced cohort also showed a trend toward less T-cell exhaustion, which may indicate improved immune fitness for T-cell redirecting therapies [232]. Additionally, reducing the frequency of talquetamab dosing may be a strategy to mitigate the infection risk and GPRC5D-related off-target effects such as dysgeusia, hair loss and nail changes while sustaining treatment response [199, 234–236]. Moreover, during the maintenance therapy phase, patients who received a protocol-permitted dose reduction or less frequent dosing were able to effectively mitigate TRAEs while maintain therapeutic response. For instance, epcoritamab and odronextamab in NHL, and elranatamab in MM, successfully implemented reduced dosing frequencies in persistent responders during maintenance therapy [237]. Similarly, a study supporting the approved transition from weekly to biweekly dosing of teclistamab in patients who maintained CR for at lease 6 months [238]. Furthermore, extending the dosing interval can positively mitigate cytopenia, and this consideration should be incorporated when the expected anti-tumor efficacy is achieved. Currently, ongoing phase III studies of talquetamab are adapting a response-adapted step-down approach from biweekly to monthly dosing. Adjusting the dosing schedule to lower intensity may enhance patient convenience while maintaining an effective therapeutic threshold, though additional research on other BsAbs is needed for validation [239].

During the clinical translation of BsAbs, it is essential to prioritize clinical value by rationally defining research and development objectives based on the structural and mechanistic characteristics, as well as thoroughly exploring, analyzing, and clarifying the clinical advantages. First-in-human study are typically associated with elevated safety risks, necessitating the formulation of stringent risk management strategies. Furthermore, clinical pharmacology studies serve as a critical foundation for determining appropriate dosing regimens for BsAbs, requiring systematic investigations to optimize the dosing strategy. Prior to initiating clinical studies, a comprehensive assessment of the immunogenicity risk should be performed, along with the establishment of corresponding mitigation plans. Simultaneously, during the development process, clinical pharmacokinetic, pharmacodynamic, safety, efficacy, and immunogenicity data should be integrated to comprehensively assess the impact of immunogenicity on the overall efficacy and safety profile of BsAbs.

The development of BsAbs has encountered a multitude of challenges as more candidates progress through rigorous preclinical and clinical evaluations. These challenges encompass serval critical areas, including manufacturing complexities arising from the intricate structural designs required to achieve dual-target specificity, immunogenicity, off-target effects, drug resistance and immunity-related toxicities such as CRS. Looking ahead, the continued optimization of BsAbs holds substantial promise for improving patient care, including refining dosing intervals and administration frequencies, as well as implementing enhanced clinical oversight through real-time monitoring and personalized medicine approaches. Moreover, current studies on BsAbs have several limitations that warrant attention. The relatively small sample size and the limited duration of follow-up may result in an underestimation of long-term recurrence risk. Furthermore, the absence of large-scale RCTs that enable direct comparisons between BsAb candidate and existing standard treatments hinders the comprehensive evaluation of therapeutic efficacy and safety. Additionally, further investigations are needed to explore optimal sequential or combination strategies with other therapeutic modalities, such as CAR-T cell therapy. Simultaneously, efforts to refine the management of adverse events are essential to enhance patient tolerability. In summary, while the development of BsAbs presents numerous challenges, ongoing advancements and strategic optimizations offer substantial hope for transforming cancer treatment paradigms.

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Authors'contributions
R. Yin and Q. Li organized the work and contributed to revising the paper. L. Shui designed the structure and contributed to writing the paper. L. Shui and D. Wu performed the creation of the figures. K. Yang and C. Sun helped revised the manuscripts. All authors read and approved the final manuscript.

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