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Mechanisms and Clinical Breakthroughs of Bispecific Antibody–Drug Conjugates (BsADCs)- Dual-Targeting Strategies Exemplified by EGFR/HER3

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Abstract. Cancer remains a major burden, with conventional and single-target ADC therapies limited by toxicity, heterogeneity, and resistance. The development of bispecific ADCs (BsADCs) is a product of the latest developments in this field, but most of these drugs are still at an early stage of design and clinical evaluation. In this review, the development process, structure, and mechanisms of action of ADCs will be outlined, and a rationale will be provided for the development of BsADCs combining bispecific targeting and targeted delivery of the cytotoxic payload. Different aspects of BsADC design such as target pairs, antibody format, internalization, linker-payload engineering, and optimal drug to antibody ratio will be discussed. Some clinical candidates like BL-B01D1 and DM005 will be analyzed in order to evaluate their efficacy and safety profile. Moreover, this review will discuss major challenges related to manufacturing difficulties, tumor penetration, on-target/off-tumor toxicity, and unpredictable interaction between different targets. BsADCs represent a new promising strategy to address tumor heterogeneity, antigen escape, and bypass signaling as well as improve targeted payload delivery. This review can serve as a theoretical background for designing and testing BsADCs.

Keywords: Bispecific antibody-drug conjugates (BsADCs), Targeted payload delivery, Tumor heterogeneity

1. Introduction

Cancer is one of the major health problems associated with morbidity and mortality across the world. Millions of people develop cancer each year even though there has been significant progress in cancer diagnosis and therapy, according to the American Cancer Society [1]. Even though surgery, radiotherapy, and chemotherapy are among the key components of cancer therapy, the efficiency of these methods is limited due to several reasons [2].

Antibody-drug conjugates (ADCs) are made up of three vital elements, which include a monoclonal antibody (mAb), a linker chemical, and a highly active payload [3]. Using antibodies to deliver cytotoxic drugs specifically to the tumor cells allows for an increase in antitumor activities, while at the same time decreasing the systemic exposure to the drug [4]. The ADCs technology has been improved greatly within the last few decades. First generation ADCs have been limited by

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instable linkers, suboptimal mAbs properties, and the choice of payload types. Second-generation ADCs were developed by using improved mAbs engineering and linkers chemistry, thus increasing pharmacokinetics and therapeutic windows. Trastuzumab deruxtecan (T-DXd), sacituzumab govitecan, and enfortumab vedotin are third-generation ADCs, and they have shown significant clinical efficacy in many types of cancer [3-5]. There have been more than ten ADCs approved, and their indication has gone from hematological cancers to solid cancers such as breast, stomach, lung, and urothelial cancers [4, 5]. Nevertheless, conventional monoclonal antibodies and single-target ADCs remain challenged by tumor heterogeneity, bypass signaling activation, antigen loss, and acquired drug resistance [5]. These limitations have therefore created a strong rationale for the development of next-generation ADC platforms.

Bispecific antibodies (BsAbs) are engineered antibodies capable of simultaneously recognizing two distinct antigens or epitopes. Compared with conventional monospecific antibodies, BsAbs can potentially increase tumor selectivity, enable cooperative binding, promote receptor clustering and internalization, and simultaneously modulate complementary signaling pathways [6-8]. The development of BsAbs has accelerated rapidly in recent years, with an expanding number of products receiving regulatory approval worldwide. As of 2026, 15 BsAbs had received FDA approval, while the global number of approved BsAb products had reached approximately 19 according to recent industry summaries [7, 8].

With the advancement of BsAb engineering, the integration of BsAbs with ADC technology has led to the development of bispecific antibody–drug conjugates (BsADCs). By combining dual-target recognition with targeted delivery of highly potent cytotoxic payloads, BsADCs are designed to address several limitations of conventional ADCs, including tumor heterogeneity, antigen escape, inadequate internalization, and resistance to single-target therapies [6, 8]. Although many BsADCs remain in preclinical or early clinical development, accumulating evidence suggests that this platform has considerable potential as a next-generation targeted cancer therapy [8].

This review summarizes the development, structural characteristics, design strategies, clinical progress, and current challenges of BsADCs. Especially important are the issues related to target selection, antibody formulation, linker-payload conjugation, and the clinical development of selected representatives. A systematic analysis of these developments can help develop a theoretical basis for optimizing and translating the clinical application of BsADCs in precision oncology.

2. Development and composition of ADCs

2.1. Mechanism of action of ADCs

The role played by ADCs can therefore be described as an exacting targeted drug delivery mechanism. ADCs have three key elements, which include an antibody, a linker, and a cytotoxic compound. While each plays a unique role, the three combine to selectively target, deliver, and eliminate cancer cells [3, 4].

Antibody recognizes and binds the antigenic epitopes present on the surface of the cancerous cells. This allows the antibody to target the ADCs specifically to the tumor cells rather than to the surrounding healthy tissues. Hence, an ideal ADC antibody will have high target specificity along with appropriate binding affinity and low off-target binding properties [3, 4]. Therapeutic antibodies are either humanized or full-length human antibodies, which makes them less immunogenic and hence more suitable for repeat dosing [3, 4]. Antigen binding and efficient internalization become imperative following the binding event because this step determines how well the drug payload is able to localize to the target site [3, 4]. Some antibodies are capable of activating the effector

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functions of the immune system, like ADCC, which makes another mode of killing of tumor cells possible [3].

Cytotoxic payload represents the active moiety which is used to kill tumor cells. Since only a small portion of the administered ADC is delivered to individual tumor cells, an ADC payload needs to be highly potent [3, 4]. In addition, it should have enough stability during its circulation and intracellular trafficking until release. Major classes of payloads include tubulin inhibitors like monomethyl auristatin E (MMAE), DNA damaging agents like pyrrolobenzodiazepine (PBD) dimer, and topoisomerase I inhibitors such as deruxtecan (DXd) [3, 4].

The linker is responsible for connecting the antibody to the payload and significantly influences the stability, pharmacokinetics, and intracellular release of the payload [3, 4]. Linkers can be either cleavable or non-cleavable, depending on their mechanism of release [9, 10]. Cleavable linkers are capable of responding to intracellular stimuli such as low pH levels or enzyme-mediated reactions. Following release, the payload can diffuse across the membranes of neighboring antigen-negative tumor cells if its diffusion ability allows this, creating a bystander effect [3, 4, 9]. Non-cleavable linkers typically necessitate the full degradation of the antibody in lysosomes to release the metabolically active payload. This mechanism of release usually allows greater stability in the circulation, yet the metabolites released through this process are generally less membrane-permeable and thus demonstrate a weaker bystander effect [3, 4]. The intensity of the bystander effect does not depend solely on the structure of the linker but also on the properties of the payload.

2.2. Development history of ADCs

The early experience in the clinic with ADCs showed that linker stability played an important role in defining the therapeutic window, as the premature payload release in blood might lead to reduced tumor exposure and increased systemic toxicity, making it hard to escalate the dose [3, 4]. The above problems resulted in the emergence of second-generation ADCs, featuring stable linkers such as thioether and enzyme-sensitive, among other innovations [3, 4].

Subsequent advances in linker chemistry, site-specific conjugation, payload selection, and antibody engineering further improved ADC homogeneity, pharmacokinetics, therapeutic index, and intracellular drug release [4, 10]. These technological advances contributed to the emergence of third-generation ADCs and established ADCs as an important class of targeted anticancer therapeutics.

2.3. Clinical limitations of traditional ADCs

The evolution of third generation ADC technology significantly broadened the applicability of the technology platform. T-DXd is a perfect illustration of this, having proven its clinical efficacy in HER2-low breast cancer, at least partly thanks to its permeable payload that allows for an appreciable bystander effect [3, 4]. It was a breakthrough that opened up new possibilities for HER2-ADCs in low HER2 expressing cancers.

Nonetheless, there have been some limitations of clinical use discovered by researchers. The heterogeneous nature of the tumor is capable of facilitating survival of the antigen negative subclones of tumor under the selective pressure, leading to resistance to treatment and disease progression [6, 11]. In addition, adaptive mechanisms leading to activation of other signaling pathways can affect the efficacy of targeted therapy [6, 11]. Indeed, HER3 signaling pathway activation is likely to lead to resistance in EGFR-dependent tumors [12]. This suggests that depending only on the single recognition of a tumor-associated antigen is not enough.

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3. Bispecific antibodies (BsAbs)

BsAbs have been engineered with remarkable speed and constitute a flexible framework that allows simultaneous targeting of two molecules [6-8]. In contrast to traditional mono-specific antibodies, BsAbs have the ability to recognize two antigens/epitopes in one single molecule, which makes possible mechanisms such as dual pathway inhibition, synergistic binding, and receptor cross-linking [6-8].

BsAbs have shown their efficacy in clinical settings in both hematologic malignancies and solid tumors. Examples of FDA-approved products include blinatumomab (CD3×CD19), emicizumab (FIXa×FX), and amivantamab (EGFR×MET) [6, 8]. The advances made by BsAbs in the clinical setting have become a significant technology platform for

An illustration of the possibility of BsADCs in enhancing tumor selectivity has been presented through molecules that target the expression of co-antigens like pCAD and CDH17 [13]. One such candidate that has been explored in the past is izalontamab brengitecan (iza-bren; BL-B01D1; also called DB-1418). It is a bispecific molecule for EGFR×HER3 [8, 14]. It has been developed as a strategy where there is receptor-mediated internalization along with delivery of toxic cargo, in addition to blocking of complementary pathways through targeting of both the receptors [8, 14].

4. Concept and design logic of BsADCs

4.1. Concepts and potential advantages of BsADCs

BsADCs combine the advantages of BsAbs in target recognition and those of ADCs in delivering the cytotoxic payload. Contrary to the combination of the two technologies, BsADCs are built as integrated molecular structures where target recognition, interaction with the receptor, internalization, intracellular trafficking, and payload release are orchestrated as one single molecule [6, 8]. Typically, a BsADC is made up of a bispecific antibody conjugated to one or more cytotoxic agents via either a cleavable or non-cleavable linker.

Advantages of BsADCs over conventional ADCs include the following factors. Firstly, due to the dual recognition, there is an expansion of tumor cells coverage and lowering the likelihood of the appearance of escape tumors due to the negative selection against antigens [8, 15]. Secondly, the BsADCs will increase tumor specificity if two targets are co-expressed in tumor tissue and not in normal tissue [8].

Second, engagement of both receptors at once would lead to receptor clustering, crosslinking, and better endocytosis. It can be especially effective if one of the targets that has been chosen is characterized by relatively slow internalization [8]. Receptor clustering and cooperative internalization have been identified as key aspects for payload delivery through BsADCs [8].

Thirdly, BsADC may facilitate complementary pathway blockade. Since blocking two parallel or compensatory pathways at once through BsADC will limit the chances of the tumors evading treatments via bypass signaling [8], this can be applicable to treatments like EGFR/HER3, where signaling by HER3 may lead to adaptive resistance to EGFR targeting drugs.

The other possible benefit lies in increasing tumor selectivity via synergistic binding. Should high avidity be obtained only when both antigens are presented at once, the BsADCs will lower the chances of the compound being bound effectively to normal tissue expressing low amounts of either antigen [7, 8]. However, these benefits do not necessarily follow from the combination of any two targets. The success of BsADC creation relies upon target selection, antibody engineering, proper internalization kinetics and proper linker/payload properties [8, 14].

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4.2. Target selection strategy

The choice of targets for BsADCs is supposed to be based on the well-known principles used for regular ADC construction such as high tumor expression, low expression in normal tissue, and ability to internalize [3, 4, 6]. At the same time, there are some other aspects that should be taken into account during BsADC construction [8, 15].

Firstly, co-expression must be high. Preferably, both targets must have good expression in tumor tissues but not in normal tissues. Such a profile would enhance tumor selectivity and expand the therapeutic window [8, 15].

Secondly, cooperative internalization is critical. Co-engagement of the receptors can result in the clustering of the receptors and increased internalization of both receptors, thus counteracting the poor internalization of the receptor via the monotherapeutic approach [8]. This concept holds good especially when there is a highly expressed receptor that is a slow internalizer.

Finally, complementary pathways must be thought about. Target combinations can be used to disrupt the vertical relationships between targets like EGFR and HER3 or the parallel pathway such as TROP2/Nectin-4 [8].

4.3. Antibody format and structural design

The different formats of bispecific antibodies employed in BsADCs can be generally categorized as symmetric and asymmetric designs. The example of symmetric designs includes the scFv-Fc format, while the asymmetric design includes the Knobs-into-Holes and CrossMab engineering approaches [7, 8]. In asymmetric designs, there is the risk of improper heavy and light chain pairing, thus the need for chain-pairing techniques like common light chains [7, 8].

Fc engineering must also be well optimized since the Fc domain affects the pharmacokinetics of an engineered protein through interaction with the neonatal Fc receptor (FcRn) and may provide immune effector functions like ADCC and ADCP [3, 7, 8]. Whether Fc effector functions should be retained, modulated, or eliminated will depend on the intended mechanism of action and payload toxicity of the ADCs [3, 7, 8]. For highly cytotoxic BsADCs, Fc silencing by mutagenesis, e.g., LALA, may be considered [7, 8].

Conjugation of payloads is another significant aspect of BsADC engineering. Enzyme conjugation and disulfide bridging techniques may help to optimize DAR homogeneity, improve ADC stability, and pharmacokinetics [4, 10]. Such technologies will be even more crucial in the case of asymmetric BsADCs due to increased structural heterogeneity.

4.4. Linker and payload design

The balance between systemic stability and payload delivery efficiency must be taken into account in the design of the linker [3, 4]. Enzyme-cleavable linkers and pH-sensitive linkers are some examples of linkers that can facilitate the delivery of the payload in intracellular and tumor environments. Non-cleavable linkers usually involve degradation of the whole antibody before generating the active metabolite [9, 10].

Useful in reducing hydrophobicity and aggregation, as well as increasing pharmacokinetics of ADCs, especially those having relatively high DAR values, are hydrophilic modifications, which include PEG-based strategies [4, 9, 10]. The choice of payload should depend on tumor biology. DXd, topoisomerase I inhibitors, can be considered as an effective option for heterogeneous solid tumors owing to their potency and membrane permeability, leading to a notable bystander effect [3,

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4]. Microtubule inhibitors, such as MMAE, offer potent cytotoxicity and can be considered as good options for target-expressing tumors with intracellular delivery [3, 4].

Optimization of DAR involves trade-offs of antitumor activity and pharmacology of drug conjugates. The increase in DAR could help in increasing the amount of drug payload in each antibody, but excess of DAR could lead to increase in hydrophobicity, aggregation, and systemic clearance [3, 4, 9]. Thus, optimal value of DAR needs to be found out depending on the antibody structure, target, linker chemistry, payload, and pharmacokinetics.

Examples of BsADC drug candidates are as follows. BsADC drug candidate BL-B01D1 has DAR of 8 and the payload is a topoisomerase I inhibitor [14, 15], while BsADC DM005 drug candidate targets EGFR/c-MET and its DAR is 4 [16, 17]. It clearly shows that there is need for considering target selection, antibody structure, linker chemistry, payload, and DAR together.

5. Clinical progress of representative BsADCs

There have been some BsADC drugs developed into clinical trials with promising antitumor activities against several types of solid tumors. Below are examples of representative BsADCs based on target pairings.

5.1. BL-B01D1 (EGFR/HER3)

BL-B01D1 (izalontamab brengitecan; iza-bren) is an EGFR/HER3 bispecific ADC and one of the most clinically advanced BsADCs currently under development. The construct uses a cleavable linker to conjugate the topoisomerase I inhibitor Ed-04 and has a DAR of approximately 8 [14].

In EGFR-mutant NSCLC patients whose disease had progressed following EGFR TKI therapy, a pooled analysis of phase I and phase II trials involving 171 patients reported a confirmed objective response rate (cORR) of 47.4%, a disease control rate (DCR) of 81.3%, a median progression-free survival (PFS) of 6.9 months, and a median overall survival (OS) of 24.8 months [15]. In the chemotherapy-naïve, post-TKI subgroup treated at the recommended phase II dose of 2.5 mg/kg, the cORR increased to 56.0%, the DCR reached 90.0%, and median PFS extended to 12.5 months [15]. Treatment-related adverse events were predominantly hematological; grade ≥3 treatment-related adverse events occurred in approximately 70.2% of patients, while interstitial lung disease (ILD) was uncommon at 0.6%, all of which were grade 1. Treatment discontinuation because of treatment-related adverse events occurred in 1.2% of patients [15].

The combination of BL-B01D1 with osimertinib has also generated notable clinical findings. At the 2025 World Conference on Lung Cancer, a phase II study in first-line EGFR-mutated NSCLC reported an ORR of 100% and a confirmed ORR of 95.0% among 40 patients treated with BL-B01D1 at 2.5 mg/kg in combination with osimertinib [18]. These findings provide an important proof of concept for combining dual-target ADC-mediated cytotoxicity with EGFR pathway inhibition.

BL-B01D1 has also demonstrated clinically meaningful activity in breast cancer. In the phase III PANKU-Breast 02 study presented at the 2026 ASCO Annual Meeting, BL-B01D1 achieved a median PFS of 8.5 months (HR=0.29), a median OS of 15.9 months (HR=0.60), and a confirmed ORR of 51.7% in patients with previously treated metastatic triple-negative breast cancer (TNBC) [19]. Both PFS and OS, the two primary endpoints, were positive. The reported ILD rate was 1.4%, while diarrhea and stomatitis were not reported as common adverse events in the study population [19]. These results represent an important clinical milestone for BsADCs and support further investigation of dual-target ADCs in TNBC.

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5.2. DM005 (EGFR/c-MET)

Beyond EGFR/HER3, other target combinations are progressing rapidly. DM005 is a fully human bispecific ADC targeting EGFR and c-MET. It uses a cleavable linker conjugated to the topoisomerase I inhibitor BLD1102 and has a DAR of 4 [16]. The rationale for selecting EGFR and c-MET is based on their co-expression in multiple solid tumors and the established role of MET signaling in mediating resistance to EGFR-targeted therapies.

In a first-in-human phase I study presented at the 2026 ASCO Annual Meeting, 45 patients with advanced solid tumors were enrolled. Among 32 evaluable patients, 8 achieved partial responses. In the subgroup of 13 patients with EGFR-mutant NSCLC treated at the 3.3, 4.2, and 5.2 mg/kg dose levels, 6 patients achieved partial responses and 5 achieved stable disease, corresponding to an unconfirmed ORR of 46.2% and a DCR of 84.6% [16]. Neither interstitial lung disease nor infusion reactions were found, and a safe profile was indicated for the therapy [16]. Such preliminary results are evidence in favor of further research of EGFR and c-MET dual targeting to overcome the resistance and facilitate intracellular cargo delivery.

5.3. Other BsADC candidates

Additionally, some other Bispecific ADCs have now entered clinical development. The DM002 is a Bispecific ADC that targets MUC1-C and HER3; on the other hand, JSKN016 is a TROP2 and HER3 targeting drug, whereas GenSci139 targets EGFR and HER2 [8]. These drugs show the increasing range of combinations of targets in order to overcome tumor heterogeneity, compensatory signaling and ADC internalization.

Also, AVZO-1418/DB-1418, which is another EGFR/HER3 targeted Bispecific ADC, has been granted FDA Fast Track designation for clinical trial, which once again indicates the increasing interest in this drug class [7]. Overall, the Bispecific ADC Pipeline is growing very fast, though the majority of drugs are still in pre-clinical development stage. Thus, long-term efficacy, safety and clinical differentiation of these drugs will be proven only through clinical trials.

6. Current challenges

Despite the promising initial results seen in clinical trials, however, there are still some major problems that need to be overcome before BsADCs can become clinically applicable [8, 17].

Manufacturing and quality control are critical challenges. Right heavy and light chain paring in particular for the asymmetric bispecific ADC structure may be challenging, and the inherent heterogeneity of ADC conjugation adds to the difficulty in characterizing and performing quality control [4, 7, 10]. Methods of site-specific conjugation such as the glycan-based enzymatic conjugation and disulfide bridging may increase DAR consistency but manufacturing feasibility and economic efficiency remain significant aspects to consider [4, 10].

Safety is another important challenge. BsADCs incorporate the toxicity of highly toxic agents with the biological effects of targeting two antigens. Binding two targets may potentially result in additive or even synergistic on-target/off-tumor effects if both antigens are weakly expressed in normal tissues [7, 8]. In the pooled BL-B01D1 study, approximately 70.2% of the participants experienced grade ≥3 treatment-related adverse events while interstitial lung disease (ILD) was observed in only 0.6% of the patients [15]. Similarly, the PANKU-Breast 02 study reported ILD in approximately 1.4% of patients [19]. Such data underscores the importance of assessing not only the single antigen but both antigens in the context of their distribution.

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The next issue pertains to the low penetration rate of large therapeutics into solid tumors. The dense extracellular matrix, increased interstitial pressure, aberrant tumor vasculature, and heterogeneity of tumor architecture could be some of the factors that may affect the penetration and delivery of BsADCs into the tumor microenvironment [5, 6]. The relatively large molecular size of conventional IgG-like bispecific antibodies could also pose problems in the penetration into avascular tumor areas [6, 8]. Despite the advantages offered by dual-targeting, adequate tumor penetration will still be needed for efficacy.

The unpredictability of synergy for a particular dual-target combination is yet another hurdle. The chosen targets may not have an effective biological interaction between them. BsADCs depend on how well the targeted proteins are co-expressed, distributed in space, internalized, trafficked intracellularly, and how complementary the involved signaling pathways are to each other [8, 15]. The understanding of the mechanistic details of receptor cross-linking, cooperativity in internalization, and signaling crosstalk is limited and does not ensure clinical relevance even if synergy was demonstrated preclinically [8, 20].

Furthermore, target pairing is still more of an empirical process than anything else. Some systematic strategies combining single-cell and spatial transcriptomics and quantitative receptor biology may aid in selecting appropriate targets [15, 20]. This might minimize the risk of failure associated with choosing combinations that work effectively in simple experimental conditions but poorly in real tumors.

7. Future perspectives

A number of directions could be highly relevant for the future development of BsADCs [8, 20].

Dual-payload strategy is one of those directions. It suggests the use of dual BsADCs conjugated with two different drugs with the different modes of action such as microtubule inhibitor and topoisomerase I inhibitor, and, hence, the BsADCs should theoretically provide additional efficacy due to the combination of two complementary effects and decrease the risk of drug resistance to each other [4, 17, 20].

The artificial intelligence and computational biology can serve as useful techniques in the identification of targets and designing of molecules. For example, the single-cell and spatial transcriptomics will be helpful in gaining insights into the expression and the spatial organization of the candidate targets in the tumor tissue as well as in the normal tissue for the rational identification of the target pair [20]. Furthermore, the computation tools will be useful for optimizing the drug-to-antibody ratio (DAR) and pharmacokinetics of novel BsADCs [20].

Another promising direction of innovation is linker technology. A two-way or multistep responder linker would theoretically deliver its payload in response to the receipt of multiple stimuli within the intracellular or tumor environment such as certain enzymes, acid, or oxidative stress [9, 10]. This approach will allow reducing the risk of premature release and increase the spatial selectivity of the drug delivery. Hydrophilic modifications such as PEGylation could still play an important role for high DAR BsADCs by decreasing aggregation and improving pharmacokinetics [4, 9, 10].

Another possible application would be combination with immunotherapy. BsADCs have the capacity not only to kill tumor cells but to activate immunity as well because of tumor cell death and antigen release or modulation of the tumor microenvironment. Combination of BsADCs with immune checkpoint blockade needs further investigation.

Finally, as clinical evidence accumulates, BsADCs may gradually move from later-line treatment toward earlier disease settings, including first-line and potentially adjuvant treatment. The initial

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data on the use of BL-B01D1 along with osimertinib for first-line therapy in EGFR-mutated NSCLC gives some initial insight into this approach [18]. Nonetheless, larger randomized trials with long-term survival data are needed before it becomes a standard treatment regimen.

8. Conclusion

Bispecific antibody-drug conjugates (BsADCs) have been reviewed for their development, structure design, and clinical advances. Starting from the drawbacks of current ADCs, such as tumor heterogeneity, antigen escape, adaptive resistance, and inefficient internalization, BsADCs can simultaneously target multiple sites with efficient drug delivery. The potential benefits of BsADCs may result from coordinated target recognition, cooperative internalization, wide coverage of tumor cells, and concomitant inhibition of complementary signaling pathways.

Important aspects in the design of BsADCs include rational target pairs for their co-expression and internalization kinetics, bispecific antibodies, site-specific conjugation, and properties of linkers and payloads. It is particularly necessary to consider both antigen expression and biological characteristics of two targets, like their coexistence and resistance role.

The clinical advancement of BL-B01D1 is a valuable case study in the field of BsADCs. Its activity in EGFR-mutated NSCLC, including the combination with osimertinib, and the positive phase III results in TNBC demonstrate that dual-target ADCs can potentially translate mechanistic advantages into clinically meaningful outcomes. Other candidates, including DM005 and several early-stage BsADCs, further indicate that the field is expanding toward diverse target combinations.

BsADCs still face core challenges such as manufacturing complexity, poor tumor penetration, on-target/off-tumor toxicity, and an incomplete understanding of dual-target synergy. Future progress will depend on biologically coordinated integration of rational target selection, smart linker–payload design, and patient selection, with further potential unlocked by dual-payload strategies, tumor-microenvironment-responsive linkers, and immunotherapy combinations.

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