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NARRATIVE REVIEW

Bispecific Antibodies in the CAR T-Cell Era: Bridging Therapy, Sequencing, and Emerging Paradigms

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ABSTRACT

Delays in accessing CAR T-cell therapy remain a significant barrier for patients with aggressive hematologic malignancies, with many failing to reach infusion due to manufacturing delays, waitlist mortality, comorbidities, and disease progression. Bispecific antibodies, with their off-the-shelf availability, rapid cytoreductive potential, and manageable toxicity, have emerged not only as a promising bridging modality to preserve eligibility and optimize patients before CAR T-cell therapy but also as standalone therapies. This comprehensive review synthesizes the evolving evidence base surrounding bispecific antibodies across multiple dimensions: their comparative efficacy and safety relative to CAR T-cell therapy, the mechanistic underpinnings of resistance and strategies to circumvent it, and, most importantly, their role as a bridging therapy before CAR T-cell treatment. By integrating structural pharmacology, clinical trial data, real-world outcomes, and emerging combination approaches, this manuscript delineates how bispecific antibodies and CAR T-cell therapy function as complementary modalities whose coordinated deployment may expand access, enhance durability of response, and reshape the structural framework of cellular therapy in hematologic malignancies.

Introduction

For many rapidly progressing hematological malignancies such as multiple myeloma (MM), diffuse large B-cell lymphoma (DLBCL), and follicular lymphoma (FL), achieving and maintaining remission remains a challenging feat. While chimeric antigen receptor (CAR) T-cell therapy represents a potentially curative option for select patients, the availability and applicability of CAR T-cell therapy is often limited by factors such as manufacturing delays, cost, comorbidities, and disease progression. These barriers have created a critical therapeutic gap, one that bispecific antibodies (BsAbs) are uniquely positioned to address. Bispecific antibodies have recently emerged as an effective and versatile therapeutic class, offering an immediate, off-the-shelf alternative or complement to CAR T-cell therapy for patients who are ineligible for or require disease control before consolidation. While there is a growing role for BsAbs as bridging therapy before CAR T-cell administration, the effect of this strategy on the efficacy and safety of subsequent CAR T-cell therapy remains incompletely understood[1]. Bispecific antibodies also represent a growing standalone treatment option, with distinct safety profiles, resistance mechanisms, and management considerations. As the use of both CAR T-cell therapy and BsAbs expands, critical questions have emerged regarding comparative efficacy, toxicity, resistance, and optimal sequencing. This review provides an overview of BsAbs in hematologic malignancies, with a particular focus on their role as a bridging therapy before CAR T-cell therapy. In addition, this review will compare the safety and toxicity profiles of BsAbs and CAR T-cells, examine resistance mechanisms and strategies to overcome them, and discuss evolving considerations for the use of BsAbs, both alongside and in place of CAR T-cell therapy. Rather than positioning BsAbs and CAR T-cell therapy as competing modalities, it is imperative to focus on how best to integrate these platforms. Understanding their complementary strengths and limitations will be essential to advancing equitable delivery, mitigating toxicity, and defining next-generation treatment paradigms in hematologic malignancies.

Overview of Bispecific Antibodies:

To understand the evolving role of BsAbs, it is first essential to characterize the structural and functional diversity of these treatments. Bispecific antibodies are engineered proteins with two distinct binding domains that allow them to bind two antigens simultaneously[2]. These proteins pair a tumor-associated antigen with the cell surface protein complex CD3 on T cells to redirect and activate cytotoxic T cells against malignant cells, thereby facilitating targeted destruction[3]. Structurally, BsAbs exist in various forms: small fragment-based constructs, such as bispecific T-cell engagers (BiTEs), which are comprised of two linked single-chain variable fragments without an Fc domain, as well as full-length IgG-like bispecifics that retain an Fc region and more conventional antibody pharmacology[4,5]. Figure 1 compares the structure and design of BsAbs and BiTEs. Fragment-based BiTEs typically have short serum half-lives (hours) and therefore often require continuous infusion, a limitation that has driven the development of half-life-extended BiTEs and Fc- or albumin-fusion strategies to permit intermittent dosing[6]. Full-length IgG-like BsAbs (for example, epcoritamab, mosunetuzumab, glofitamab) utilize neonatal Fc receptor (FcRn) recycling to achieve prolonged half-lives and allow subcutaneous or intermittent intravenous schedules[7]. These agents have shown durable responses in non-Hodgkin lymphoma and other B-cell malignancies in phase I/II and later-phase studies[8,9]. Ongoing work continues to compare pharmacokinetics and routes of administration and focuses on next generation designs to improve half-life, potency, and safety.

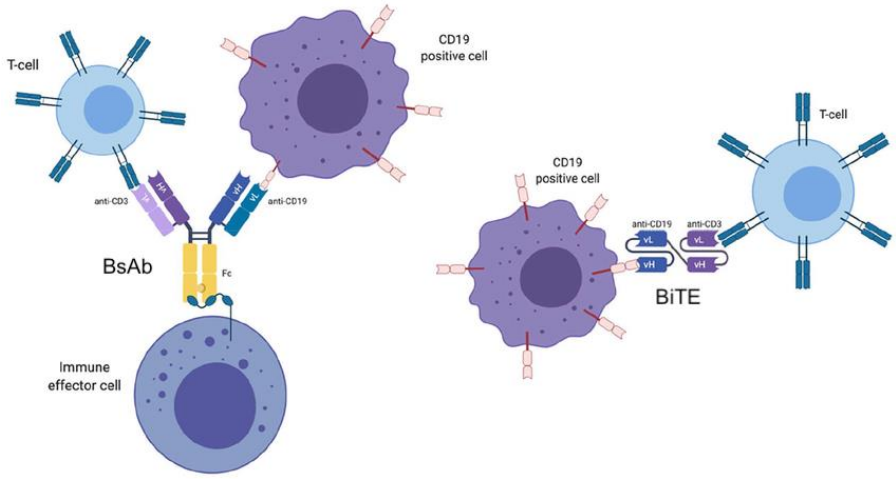

Figure 1: Bispecific antibodies compared with bispecific T-cell engagers (BiTEs). BiTEs link a tumor-specific antigen to CD3 on T cells to promote cytotoxicity but lack an Fc domain and require continuous infusion due to rapid renal clearance. Full-length BsAbs function similarly but retain an Fc region, enabling broader immune effector engagement, a prolonged half-life, and reduced renal excretion due to their larger size. Modified with permission from Rampotas et al. *Ther Adv Hematol.* 2021;12:20406207211053120. doi:10.1177/20406207211053120.

Comparative Efficacy of Bispecific Antibodies and CAR T-Cell Therapy:

As these structural innovations of BsAbs have led to their widespread clinical use, comparisons with CAR T-cell therapy have become increasingly relevant. CAR T-cell products and engineered BsAbs share a common mechanism: redirecting endogenous T cells to malignant targets[10]. However, they differ fundamentally in manufacturing, dosing, kinetics, durability, and toxicity profiles[11]. This section will discuss the differences in efficacy between BsAbs and CAR T-cell therapy in various hematologic malignancies, recognizing that these therapies have not yet been compared prospectively in a head-to-head manner.

Retrospective, non-randomized studies have suggested that CAR T-cell therapies may achieve higher response rates when compared to BsAbs. Meta-analyses of studies in multiple myeloma patients consistently show higher complete response (CR) and overall response rates (ORR) with BCMA CAR T-cell products than with BCMA-targeting BsAbs[12]. Liang et al. found that BCMA-directed CAR T-cell therapy achieved a significantly higher pooled CR rate 0.54 [95% confidence interval (CI) 0.42–0.69] vs. BCMA-targeting BsAbs 0.35 [0.30–0.41], p<0.01 in patients with MM (Figure 2)[13]. A pooled analysis of patients with R/R DLBCL reported similar findings, with CR rates of 36% for CD20xCD3 BsAbs compared to 51% for CAR T-cell therapy[14]. These differences persisted after adjustment for prior therapies and disease characteristics. In heavily pretreated patients with R/R follicular lymphoma, certain trials report CR rates of 94% and 79% for lisocabtagene maraleucel and axicabtagene ciloleucel, respectively, compared to a 62% overall response rate for mosunetuzumab, a CD20xCD3 BsAb[15]. As these agents have not been compared in a prospective, randomized fashion, this data is informative but must be considered in the context of cross-trial comparisons.

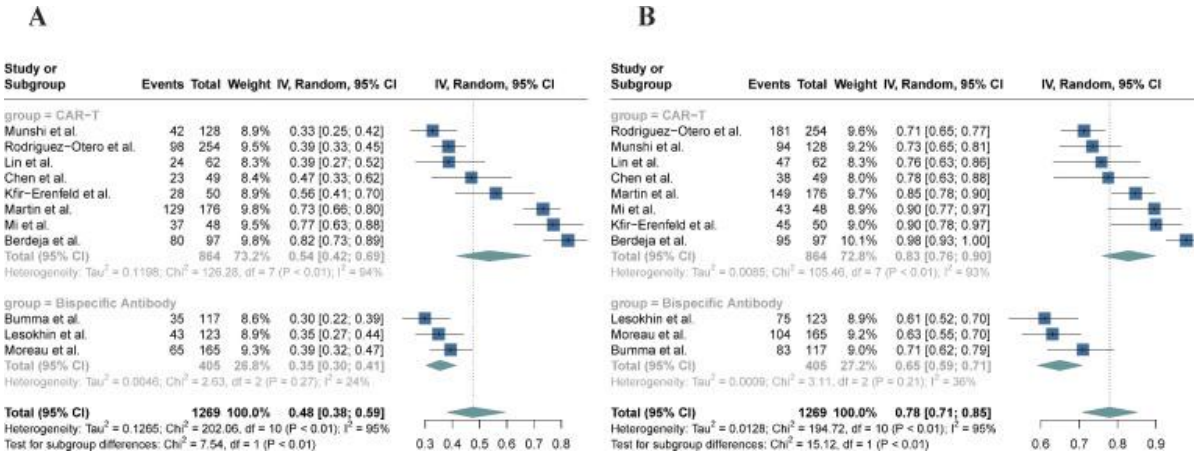

Figure 2: Forest plot comparing efficacy of CAR T-cell and bispecific antibody therapies. (A) Complete response (CR); (B) overall response rate. CAR indicates chimeric antigen receptor. Reproduced with permission from Liang et al. *J Immunother Cancer.* 2024;12:e010064. doi:10.1136/jitc-2024-010064.

Comparative Toxicities of Bispecific Antibodies and CAR T-cell Therapy:

The superior response rates observed with CAR T-cell products may be offset by higher rates of adverse effects, particularly cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS)/neurotoxicity, reflecting rapid in vivo T-cell expansion and high peak cytokine release[16].

Cytokine release syndrome is the most frequently reported adverse event across T-cell-engaging products and has consistently been shown to be more common in patients receiving CAR T-cell therapy compared to those undergoing BsAb treatment[17]. For example, in a meta-analysis by Kim et al. which evaluated patients with DLBCL receiving CAR T-cell or BsAb therapy, grade ≥3 CRS occurred in 2% of patients treated with BsAbs vs. 8% of CAR T-cell recipients[14]. This clinical entity manifests with a broad range of clinical severity and can range from low-grade febrile responses to life-threatening distributive shock and respiratory failure[18]. The onset of CRS is typically within days of initial dosing or dose escalation, although timing varies by agent and dosing schema[19]. The peak cytokine release in CAR T-cell therapy tends to occur a few days after infusion, whereas in BsAbs it occurs within hours of the first few infusions and declines in frequency after repeated treatments[19]. Management of CRS in both CAR T-cell and BsAb therapy is guided by severity, with supportive care alone used for grade 1 CRS and escalation to anti-interleukin-6 (IL-6) therapy (tocilizumab) and corticosteroids for higher-grade CRS[20]. Management of CRS can be more challenging in patients receiving CAR T-cells, as one cannot rely on dose interruption as with BsAb products[21]. Certain strategies such as fractionated dosing, step-up dosing for BsAbs, and preemptive tocilizumab or corticosteroid use in high-risk patients, have shown great promise in reducing severe CRS without clearly compromising efficacy in several studies[22,23]. More recently, early-phase trials have identified the selective janus kinase 1 (JAK1) inhibitor itacitinib as another promising strategy for CRS prevention, demonstrating meaningful reductions in inflammatory cytokine signaling without impairing CAR T-cell expansion or antitumor activity[24,25].

The pathophysiology of ICANS remains incompletely understood, though current evidence emphasizes a complex interplay between cytokine dysregulation, T-cell activation, and blood–brain barrier disruption[26]. Elevation of interleukin-15 has been one of the most consistently identified biomarkers associated with ICANS across multiple studies, though its essential role in CAR T-cell proliferation and long-term survival limits the feasibility of targeted inhibition[27,28]. Interleukin-1 (IL-1) signaling also contributes to neuroinflammation, and thus anakinra, an IL-1 receptor antagonist, has been used both prophylactically and therapeutically to reduce ICANS in patients treated with CAR T-cell and BsAb therapy[29]. Notably, ICANS is far less common in patients receiving BsAb therapy and remains predominantly associated with CAR T-cell therapy[30].

Clinically, ICANS often occurs after clinical signs of CRS, and is characterized by a variety of neurological symptoms, ranging from headache and confusion to life-threatening cerebral edema and seizures[31]. Management prioritizes neurologic monitoring, seizure prophylaxis for high-risk patients, rapid corticosteroid administration for grade ≥2 events, and intensive care support for severe cases[32]. Because tocilizumab has poor central nervous system penetration and may theoretically worsen neurotoxicity by increasing circulating IL-6 levels, it is not recommended for isolated ICANS[33]. Instead, institutions increasingly rely on alternatives such as siltuximab, a monoclonal antibody that binds IL-6, as well as anakinra and intrathecal corticosteroids in severe or refractory cases[34]. Seizure control with levetiracetam and avoidance of medications that lower seizure threshold is recommended in institutional protocols as well[35].

To contextualize these differences in toxicity profiles, Figure 3 summarizes reported CRS and ICANS rates across representative BsAb trials, including both monotherapy and combination approaches. Across these studies, CRS is common but predominantly low grade, while grade ≥2 CRS and clinically significant ICANS remain infrequent. These trends align with pooled analyses showing substantially lower rates of severe CRS and ICANS with BsAbs compared with CAR T-cell products, despite overlapping immune effector mechanisms.

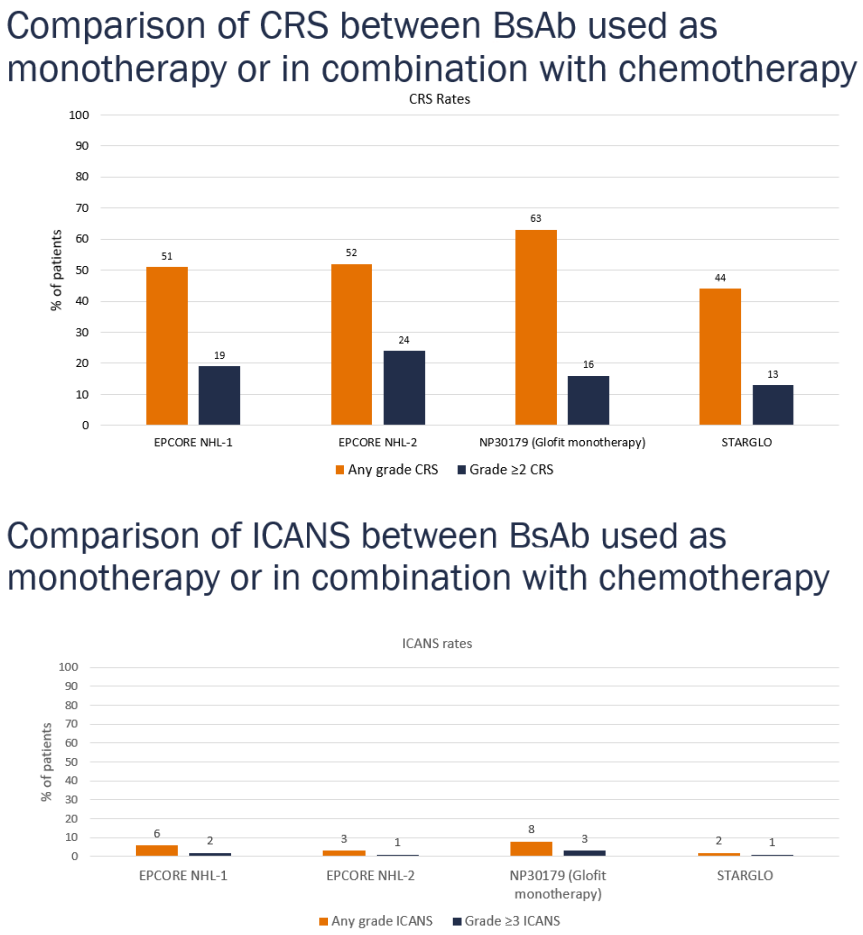

Figure 3: Comparative rates of CRS and ICANS across selected bispecific antibody trials. Incidence of any-grade and higher-grade CRS (top) and ICANS (bottom) are shown for representative monotherapy and combination studies. CRS is common but predominantly low grade, whereas higher-grade CRS and clinically significant ICANS are infrequent. Although these figures provide a useful visual overview of toxicity patterns, direct cross-trial comparisons should be interpreted cautiously, as they are not derived from head-to-head analyses and may be influenced by differences in patient populations, disease burden, prior therapies, dosing strategies, toxicity grading criteria, and supportive care practices.

Infection risk is another significant shared toxicity of BsAb and CAR T-cell therapy. Interestingly, CAR T-cell therapy has been associated with lower overall infection rates compared to BsAb therapy (49% vs. 66%; OR 0.52, 95% CI 0.30–0.91, p=0.023)[36]. Among patients with MM receiving BCMA-directed treatments, severe infections were more common with BsAbs (40%) than with CAR T-cells (26%), including a higher rate of grade 5 infections (7% vs. 0%, respectively)[37]. Similar trends were observed by Van Biesen et al., who reported a significantly higher proportion of patients experiencing grade ≥3 infections with continuous BsAb therapy compared with CAR T-cell therapy in B-cell lymphomas (29% vs 16%; p = 0.003)[38]. Notably, this difference was observed only in patients receiving continuous BsAb dosing and was absent in those treated with fixed duration regimens[38]. Despite these disparities in infection rates, infection-related mortality did not differ between CAR T-cell recipients and either the continuous or fixed-duration BsAb groups[38]. To prevent these side effects, all patients should receive prophylaxis for Pneumocystis jiroveci pneumonia (PJP), Herpes simplex virus (HSV), and Varicella Zoster Virus (VZV) for at least six months after treatment with either BsAb or CAR T-cell therapy[39]. Recent data also argue for proactive infection surveillance and immunoglobulin replacement when indicated.

Overall, CAR T-cell therapy is associated with higher rates of cytopenias when compared to BsAb therapy[40]. This is due to several factors. First, prior treatments such as chemotherapy, immunotherapy, or radiation therapy can damage the bone marrow microenvironment[41]. Further, patients often receive lymphodepleting chemotherapy before CAR T-cell infusions to allow for adequate expansion of infused CAR T-cells[42]. CAR T-cell therapy also generates a more robust immune response when compared to BsAb therapy, triggering greater cytokine release and T-cell expansion that can affect the bone marrow[13]. Some studies report all-grade cytopenia rates of 91% with CAR T-cell therapy vs. just 35% with BsAb therapy (OR 12.4,

95% CI 1.16-134, p=0.037)[36]. Other studies report pooled incidences (proportions of patients affected) of 70% for thrombocytopenia and 59% for lymphopenia following CAR T-cell therapy, compared with 31% and 40%, respectively, with BsAbs (p<0.01)[43]. First-line management of prolonged cytopenias includes transfusion and growth factor support, and refractory cases may warrant stem cell boosts if autologous stem cells are available[44].

Logistical Barriers to CAR T-cell Therapy:

Logistical challenges and differences in treatment availability are evident between the two therapies, with fewer centers offering CAR T-cell therapies than BsAbs[45]. Although CAR T-cell therapy is a potentially curative option for many patients, barriers exist that may prevent patients from receiving this treatment. First, many patients may die from disease progression before receiving CAR T-cell therapy, a phenomenon known as "waitlist mortality", occurring in up to 4% of patients, potentially due to long manufacturing times[46,47]. Across real-world cohorts, the average "vein-to-vein" time, i.e., the time between T-cell collection and CAR T-cell infusion, typically ranges from three to five weeks[48]. Figure 4 highlights the survival function of patients in the JULIET trial who remained eligible for CAR T-cell infusions over time. Further, these treatments are costly, with CAR T-cell therapy alone costing roughly $400,000[49]. In addition, the majority of CAR T-cell therapies are administered inpatient, resulting in prolonged hospitalizations, that incur additional costs. Thus, bridging therapy can play a valuable role in providing disease control, reducing the risk of clinical deterioration, and allowing patients to remain eligible for CAR T-cell therapy.

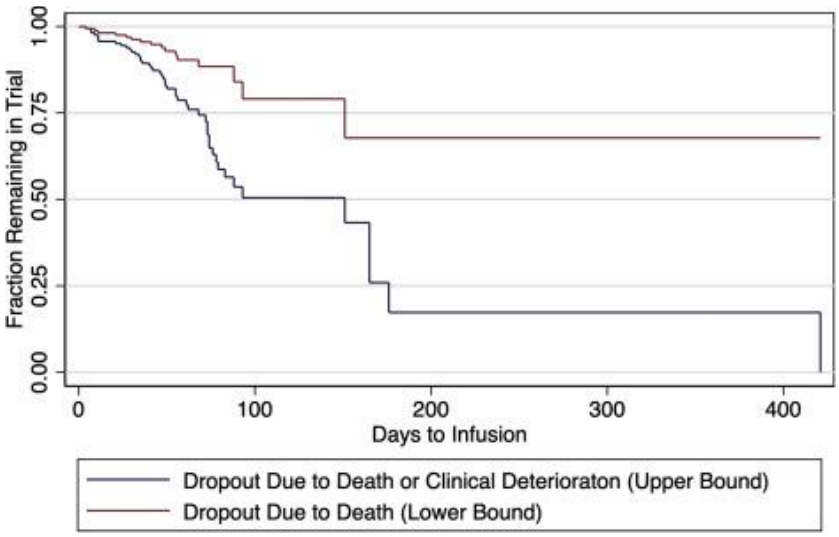

Figure 4: Proportion of patients remaining eligible for CAR T-cell infusion over time (JULIET trial). Kaplan-Meier estimates show eligibility for infusion; the lower bound accounts for ineligibility due to death, and the upper bound includes death or non-mortality dropout. Reproduced with permission from Chen et al., *Value in Health.* 2022. doi:10.1016/j.jval.2022.02.007.

Role of Bispecific Antibodies as Bridging Therapy Prior to CAR T-cell Therapy:

Bridging therapy refers to systemic or local treatment administered after leukapheresis and before CAR T-cell infusion[50]. The primary goal of bridging therapy is to decrease disease burden and prevent rapid progression during the CAR T-cell manufacturing interval, as high tumor volume at the time of infusion has been associated with increased rates of CRS, ICANS, and inferior survival outcomes[50]. Historically, bridging therapy has typically involved chemotherapy, radiation, or corticosteroids, but these strategies often yield limited disease control, induce cytopenias, and may hinder lymphocyte fitness[50]. Adequate disease control is imperative before CAR T-cell administration, as some authors report that nonresponse to bridging, regardless of the modality, was strongly associated with relapse within 12 months[51].

Bispecific antibodies have emerged as a novel bridging option due to their off-the-shelf availability and cytoreductive potential

independent of human leukocyte antigen (HLA) compatibility[52]. Early observational studies suggest that BsAbs can safely and effectively bridge the interval between apheresis and CAR T-cell infusion[53]. In multiple myeloma, talquetamab, a GPRC5D-targeting BsAb, demonstrated a 71% response rate as bridging therapy, with most patients successfully proceeding to BCMA-directed CAR T-cell therapy and achieving high response rates post-infusion[53]. Another study comparing various treatment modalities as bridging therapy before BCMA-directed CAR T-cell therapy showed that the BsAb group had the greatest reduction in disease burden (measured by soluble BCMA (sBCMA) levels) among all bridging therapy options[54].

In LBCL, emerging real-world evidence from an abstract presented at the 2025 American Society of Hematology (ASH) annual meeting evaluated the safety and efficacy of sequencing CAR T-cell and BsAb therapy[55]. Among 15 patients who received bispecific antibodies as bridging therapy prior to CAR T-cell infusion, the ORR to CAR T-cell therapy was 73% with a CR rate of 47%[55]. Patients who achieved disease control with BsAb therapy and proceeded to CAR T-cell therapy without progression had even higher response rates (83% overall response rate and complete response rate)[55]. In relapsed/refractory FL, prospective data on treatment outcomes for bispecific antibodies used as bridging therapy prior to CAR T-cell therapy is limited. Ongoing studies are needed to define the optimal sequencing and combination of BsAbs and CAR T-cell therapy, as well as elucidate the long-term impact of BsAb bridging on CAR T-cell expansion, persistence, and durability of response.

One concern that has been raised regarding using BsAbs as bridging therapy is whether targeting the same antigen with both BsAbs and CAR T-cells affects treatment outcomes. Preclinical and early clinical data suggest that targeting the same antigen with both BsAbs and CAR T-cells may lead to antigen loss or downregulation, potentially reducing the efficacy of subsequent CAR T-cell therapy[56]. In a retrospective analysis by Crochet et al., the authors evaluated the safety and efficacy of CD19-directed CAR T-cell therapy in patients with R/R LBCL who had already received CD22 and CD20-targeted BsAb therapy[57]. Notably, these authors found that exposure to prior bispecific antibodies does not affect the efficacy of subsequent CAR T-cell therapy. However, patients exposed to CD19-directed BsAbs were excluded from the study. Larger data sets are needed to definitively confirm that BsAb treatment does not reduce the efficacy of subsequent CAR T-cell therapy, but currently available evidence suggests it does not. Of note, this is currently less of an issue with the most of the current CD20-targeting BsAbs used in lymphoma, as currently approved CAR T-cell therapies target a separate antigen (CD19).

Mechanisms of Resistance to BsAb Therapy:

Clinical responses to BsAbs are not universal, and resistance often emerges while on active treatment. Mechanisms conferring resistance to bispecific antibodies in hematologic malignancies are multifactorial and include both tumor-intrinsic and immune-mediated factors[58]. Tumor-related factors include antigen escape through mutations or deletions of target genes, extramedullary disease, shedding of target antigens, and high tumor burden[59]. Immune-mediated resistance primarily involves T-cell dysfunction and the immune microenvironment[60]. Understanding and overcoming these challenges will ultimately allow for the design of optimal BsAb therapy.

Antigen Loss and Modulation

While BsAb therapy has dramatically improved patient outcomes, not all patients respond to treatment, and resistance can develop even after a single dose[61]. Loss or downregulation of the target antigen is a well-established mechanism of resistance. In a study by Schuster et al., the authors noted that CD20 loss occurred in 34% of patients with R/R NHL after treatment with mosunetuzumab, a CD20/CD3 BsAb[62]. This was attributed to the acquisition of truncating mutations and decreased CD20 transcription[62]. Duell et al. reported similar findings and identified truncating mutations in the CD20 gene in 80% of patients who relapsed after treatment with CD20 BsAbs[63]. In relapsed/refractory MM, resistance to teclistamab, a B-cell maturation antigen (BCMA)-CD3 BsAb, has been attributed to deletions in *TNFRSF17*, the gene that codes for BCMA[64]. A study by Lee et al. reported biallelic or monoallelic

deletions in 42.8% of relapsed patients after receiving teclistamab therapy[65]. Other studies note monoallelic *TNFRSF17* deletions in patients with newly diagnosed MM, which may predispose them to biallelic loss after further treatment[66].

Soluble Antigen Decoys

Another well-documented escape mechanism in MM is BCMA shedding. In MM cells, a gamma-secretase complex cleaves BCMA from the tumor cell surface, creating soluble BCMA in the bloodstream[64]. Certain studies use soluble BCMA levels as a marker of disease activity and correlate them with disease burden, prognosis, and response to therapy in active MM[67]. Yet, high levels of sBCMA create a decoy molecule for BCMA-targeted therapy, ultimately decreasing therapy effectiveness and impeding T-cell engagement, particularly in BsAbs such as teclistamab and elranatamab[68]. Unfortunately, the clinical development of Alnuctamab, a unique BsAb featuring a 2:1 binding configuration that makes it less affected by BCMA shedding due to bivalent binding, was discontinued in the spring of 2024[64]. Figure 5 illustrates the mechanisms of resistance to BCMA-targeted therapy that have emerged.

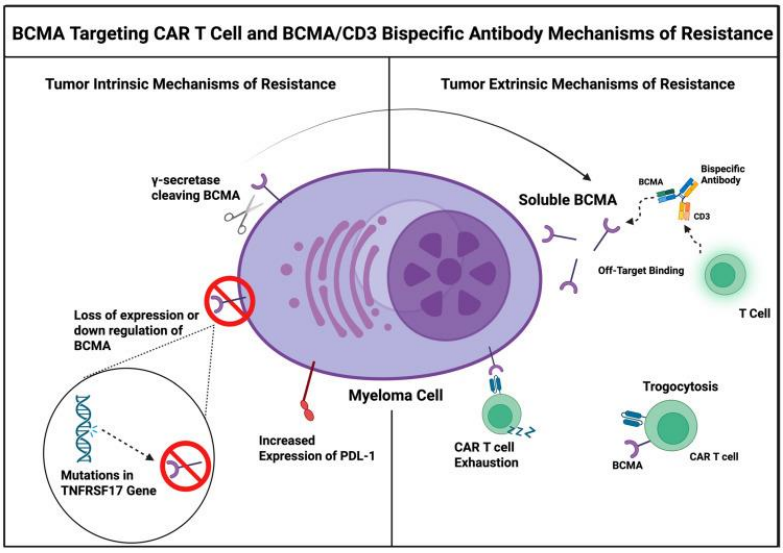

Figure 5: Mechanisms of resistance to BCMA-targeted therapy. Tumor-intrinsic mechanisms (left) include γ-secretase–mediated BCMA cleavage, BCMA downregulation or loss, and increased PDL-1 expression. Tumor-extrinsic mechanisms (right) include soluble BCMA–mediated decoy binding, CAR T-cell exhaustion, and trogocytosis with antigen transfer. Reproduced with permission from Tedder B. (2025) BioRender.com/a2ezh17.

High Disease Burden and Extramedullary Relapse

Other more common reasons for relapse and resistance to BsAb therapy are high tumor burden and extramedullary relapse. When the number of malignant cells is high, the ratio of effector T cells to targets becomes unfavorable, reducing cytotoxic capacity and yielding lower response rates[69]. High tumor load also increases the risk of treatment-limiting inflammatory toxicity (i.e., CRS and ICANS), which may necessitate dose interruptions, thereby reducing efficacy[70]. Extramedullary relapse presents additional obstacles as well. Relapse in the central nervous system (CNS) is particularly problematic, as biologic and anatomic barriers limit antibody penetration and T-cell access[71]. CNS involvement, therefore, often requires CNS-directed strategies (intrathecal therapy, radiation, or agents with CNS activity) in addition to systemic BsAb therapy[72].

Immune-Mediated Mechanisms:

T-CELL EXHAUSTION

When T cells are habitually exposed to an antigen, they can enter a state of "exhaustion" through expression of inhibitory molecules such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1)[73]. This ultimately leads to reduced T-cell proliferative capacity and impaired cytokine secretion, placing patients at high risk of relapse or nonresponse[74].

Features of T-cell exhaustion include upregulation of inhibitory checkpoint molecules such as PD-1 and reduced IL-2 and interferon-gamma production[75]. Comprehensive phenotyping of bone marrow samples from R/R MM patients treated with BsAbs showed high levels of PD-1+, CTLA-4+, and CD38+ immune-suppressor T cells, and this correlated with primary resistance[76]. In DLBCL patients receiving glofitamab, disease

progression correlated with exhausted T cells, characterized by increased PD-1 expression[77].

While BsAbs can recruit T-cells, sustained T-cell activation induced by persistent antigen stimulation can ultimately worsen outcomes[78]. In vitro studies have shown that continuous exposure to BsAbs can impair T-cell-mediated lysis of tumor cells[59]. In a phase 1-2 trial of talquetamab in patients with R/R MM, every-other-week dosing resulted in superior progression-free survival (PFS) compared to weekly dosing (median PFS 11.2 vs. 7.5 months), suggesting that less frequent dosing may help preserve T-cell function, although the study did not directly evaluate this mechanism[79]. Immune profiling revealed that T-cell exhaustion was delayed with talquetamab administered every other week compared to once per week dosing, emphasizing the importance of treatment-free intervals[59]. Yet, this decline in T-cell function is not permanent. Preclinical models have shown that treatment-free intervals can yield transcriptional reprogramming and reinvigoration of T cells[78].

TUMOR MICROENVIRONMENT

The tumor microenvironment (TME) in hematologic malignancies also contributes to resistance to BsAb therapy. The TME is comprised of immunosuppressive cells (regulatory T-cells (T-regs), myeloid-derived suppressor cells) and inhibitory ligands (PD-L1, CD38), which dampen T-cell activation and cytotoxicity[80]. Certain studies note that the strong presence of T-regs in the TME modulates the therapeutic response to BsAbs[81]. Duell et al. found that patients who responded to blinatumomab demonstrated an average of 4.82% Tregs (CI: 1.79-8.34%) in the peripheral blood, whereas non-responders had 10.25% Tregs (CI: 3.36-65.9%)[85]. In addition, prior therapies, advanced age, and disease-related immunosuppression can further compromise T-cell function[82].

STRATEGIES TO OVERCOME RESISTANCE

Overcoming resistance to BsAb therapy requires a multifaceted approach. Current research has focused on TME alteration, dual/multi-specific targeting, and immune modulation. In R/R MM, certain authors have reported that the addition of cyclophosphamide to the BCMA BsAb can restructure the TME, removing regulatory T cells and exhausted T cells, bringing fresh T cells to the tumor[83]. Other authors have focused on simultaneous targeting of multiple antigens, such as combinations of various BsAbs or trispecific antibodies (TsABs) in order to mitigate antigen escape[59]. For instance, early-phase clinical trials utilizing CD19/CD22/CD3 TsABs in B-cell malignancies or CD38/CD28/CD3 in MM have shown compelling results[3]. Other research has focused on antigen sequential strategies (i.e., targeting CD79b once CD19 is lost in B-cell lymphomas) to circumvent resistance[84].

Another emerging design involves combining checkpoint blockade with tumor antigen targeting to reverse inhibitory signaling. As PD-1, CTLA-4, and other checkpoint pathways are upregulated in chronic T-cell stimulation, blocking these pathways can restore T-cell effector function[85]. This ultimately enhances T-cell activation within the tumor microenvironment while simultaneously blocking immune checkpoints, overcoming resistance mechanisms[86]. Early-phase studies have shown improved antitumor responses and T-cell activation with these techniques, albeit with a higher risk of immune-related adverse events[87]. Combination strategies such as these can reverse the immunosuppressive effects of the tumor microenvironment, ultimately improving the efficacy and durability of BsAb treatments.

Conclusion:

Bispecific antibodies have rapidly become an integral part of treatment strategies for hematologic malignancies, both as a bridge to CAR T-cell therapy and as independent therapeutic options. Their rapid availability, ability to reduce disease burden, and manageable toxicity make them especially valuable for patients who might otherwise progress while waiting for CAR T-cell manufacturing or who are not eligible for cellular therapy. At the same time, their increasing use has brought attention to important questions about how best to sequence these therapies, manage overlapping toxicities, and address emerging resistance. Moving forward, clinical integration will depend on precise patient selection, antigen targeting strategies, and continued innovation in construct design. Rather than replacing one another, BsAbs and CAR T-cells are likely to work in coordination to improve access, reduce treatment delays, and extend meaningful remission to more patients.

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