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Revolutionizing the treatment of cancer using CAR T Cells and Bispecific Antibodies

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Abstract: Zinc is one of the most crucial trace minerals that is needed for human health and development. This study was conducted to assess zinc concentrations in breast milk samples obtained from Palestinian lactating women. The study also aimed to assess associations between breast milk zinc concentrations, dietary zinc intake, and signs and symptoms of zinc deficiency. Breast milk samples were obtained from 58 lactating women. The demographic variables, dietary zinc intake, and signs and symptoms of zinc deficiency were also collected. Zinc concentrations were assessed using a graphite furnace atomic absorption spectrophotometric method. Of the lactating women, 7 (12.1%) reported loss of appetite, 6 (10.3%) reported sleepiness or lethargy, 11 (19.0%) reported changes in weight, 7 (12.1%) reported increasing hair loss, 8 (13.8%) reported having easily broken nails, 7 (12.1%) reported having immune diseases/issues, and 11 (19.0%) reported dermatologic issues. In this study, 21 (36.2%) of the lactating women reported high consumption of red meats or poultry, 22 (37.9%) reported high consumption of milk or dairy products, 19 (32.8%) reported high consumption of whole grains, 18 (31.0%) reported high consumption of fish or seafood, 12 (20.7%) reported high consumption of eggs, and 9 (15.5%) reported high consumption of zinc-rich drinks. In this study, the median breast milk zinc level was 0.091 [0.063, 0.15] mg/100 mL. Breast milk zinc concentrations were higher among the lactating women who were younger than 30 years, lived in urban areas, were employed, and reported high consumption of zinc-rich drinks. Breast milk zinc concentrations were affected by some demographic variables of the lactating women. These variables included, demographics, living conditions, and consumption of zinc-rich sources. Dieticians, lactation consultants, and other healthcare providers should educate/counsel lactating women on the importance of maintaining adequate breast milk zinc levels and consuming zinc-rich sources. More studies are still needed to assess the impact of zinc supplements on breast milk zinc concentrations.

Keywords: CAR T cell therapy, Bispecific Antibody therapy, Immunotherapy, CD19 CAR T Cells, Immune Check Point Inhibitors, FDA-approved therapies, Advancement in Cancer Therapy.

INTRODUCTION

Recent advancements in cancer therapy have shifted the focus from traditional methods like surgery, chemotherapy, and radiotherapy to immunotherapy, especially CAR T cell therapy. This approach uses genetically modified T cells with Chimeric Antigen Receptors (CARs) to target cancer cells independently of the Major Histocompatibility Complex (MHC) [1]. Proven effective in chemotherapy-resistant B-cell malignancies [2], CAR T cell therapy achieves notable remission rates. Its efficacy is underpinned by Adoptive Cell Transfer (ACT), wherein patients receive immunocompetent cells to target and destroy cancer cells, bypassing the constraints of conventional vaccine-based therapies [3].

In parallel, newer immunotherapies like bispecific T-cell enhancing antibodies and monoclonal antibodies against immune checkpoints CTLA-4 and PD-1 are showing promise across diverse cancer types [4-5]. CAR T cell therapies are particularly potent in blood cancers due to their self-amplifying and persistent nature. However, their effectiveness against solid tumours is still under investigation [3]. Recent trials in multiple myeloma treatment with CAR T cells are encouraging [6-7]. Another innovative approach is the use of Bispecific antibodies (BsAbs), which can target two antigens simultaneously. BsAbs are crucial in liquid tumours, like leukaemia's and lymphomas, enhancing the precision of immunotherapy by linking immune cells to cancer cells [8-9]. They also show potential against solid tumours by disrupting the immunosuppressive tumour microenvironment, improving tumour cell detection and elimination. Yet, optimization of BsAbs is necessary which involves a multifaceted approach encompassing improvements in specificity, binding affinity, immunogenicity, pharmacokinetics, tumour penetration, and resistance prevention for enhanced effectiveness [10]. Their dual-targeting ability marks a significant breakthrough in cancer immunotherapy, potentially reducing the dosage of therapeutic antibodies.

To conclude, CAR T cell therapy and bispecific antibodies have revolutionized cancer treatment [13-14]. CAR T cells are particularly effective against B-cell malignancies but face challenges in solid tumours. Bispecific antibodies, conversely, target both liquid and solid tumours innovatively. These therapies signify a shift towards more personalized, effective cancer treatments, emphasizing the reprogramming of T cells and connecting immune cells to tumour cells. Continuous

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research and development are crucial, but their synergistic potential heralds a new, more targeted era in cancer therapy.

CAR T cell therapy

Origin and Development

Immunotherapy has significantly advanced cancer treatment, offering hope to patients with cancer. The foundation for CAR T cell therapy was laid in 1987 by Dr. Yoshikazu Kurosawa and his team at Japan's Institute for Comprehensive Medical Science. They introduced the concept of a chimeric T cell receptor combining antibody-derived variable regions (VH/VL) with T cell receptor (TCR)-derived constant regions. Their study showed that these receptors, when expressed in murine T-cell lymphoma EL4 cells, could trigger a response to antigens, marking a significant breakthrough in understanding the immune system's role in combating cancer [11]. In 1989, Israeli immunologist Zelig Eshhar proposed reprogramming T cells to recognize antigens independently of the major histocompatibility complex (MHC). This concept led to the development of Chimeric Antigen Receptors (CARs) in the early 2000s. CARs revolutionized cancer immunotherapy by enabling T cells to target specific tumour antigens. This breakthrough has transformed cancer treatment, illustrating the impact of foundational research on medical innovation [12]. They developed a chimeric T-cell receptor (cTCR) fusing the variable regions of an anti-2,4,6-trinitrophenyl (TNP) antibody with TCR constant regions. This innovation allowed T cells to recognize antigens independently of MHC molecules, a crucial step forward. Eshhar's team overcame initial challenges of low co-transduction efficiency by creating a single-chain chimeric receptor, the first-generation CAR, linking the scFv antigen-binding domain to an intracellular signalling domain. This design preserved the specificity and affinity of the original antibody [13].

Initial clinical applications in 2005 for metastatic renal cell carcinoma and ovarian cancer revealed safety concerns and uncertain therapeutic benefits [11]. However, the landscape changed dramatically with the introduction of anti-CD19 CAR T cells, which demonstrated remarkable efficacy in treating lymphomas and leukaemia. These successes at the NCI and the University of Pennsylvania marked a pivotal point in the therapy's evolution [1]. The development of CAR T cell therapy in the USA catalysed its global expansion, underscoring the vital contributions of these early studies to the field of immunotherapy [14]. CAR T cell therapy, a revolutionary cancer treatment, utilizes engineered T-cells with Chimeric Antigen Receptors (CARs). These receptors target tumour cells with high specificity. A CAR comprises an extracellular antigen recognition domain, a transmembrane domain, and an intracellular T cell activation domain, combining precision targeting with effective immune response [15-16].

The extracellular domain begins with a signal peptide, leading the protein into the endoplasmic reticulum, followed by an antigen recognition section. This section includes a single-chain Fragment variant (scFv), formed by linking heavy and light immunoglobulin chains [16-17]. A spacer, typically from the IgG1 hinge region, connects this to the transmembrane domain, which is vital for receptor stability and commonly uses the CD28 transmembrane domain [15-17]. The intracellular domain, primarily comprising the CD3ζ component, is critical for initiating T cell responses upon antigen detection, thus playing a pivotal role in activating the immune response against cancer cells [16]. CAR T cell technology has evolved significantly since the first-generation CARs developed between 1989 and 1993, which had limited efficacy without additional IL-2 [18-19]. Subsequent generations have seen improvements in T-cell antitumor activity and in vivo persistence. Notably, the fourth-generation CARs, known as TRUCKs, have elevated antitumor efficacy and cytokine activity [14]. Research in CAR T cell therapy is continually evolving. Techniques such as CRISPR and the development of smart T cells are being explored to enhance safety and efficacy [20-23]. The optimal mix of costimulatory signals, including CD28 [14], ICOS, OX40, and 4-1BB, is an area of active research, with 4-1BB showing promise in improving CAR T cell persistence [25-27].

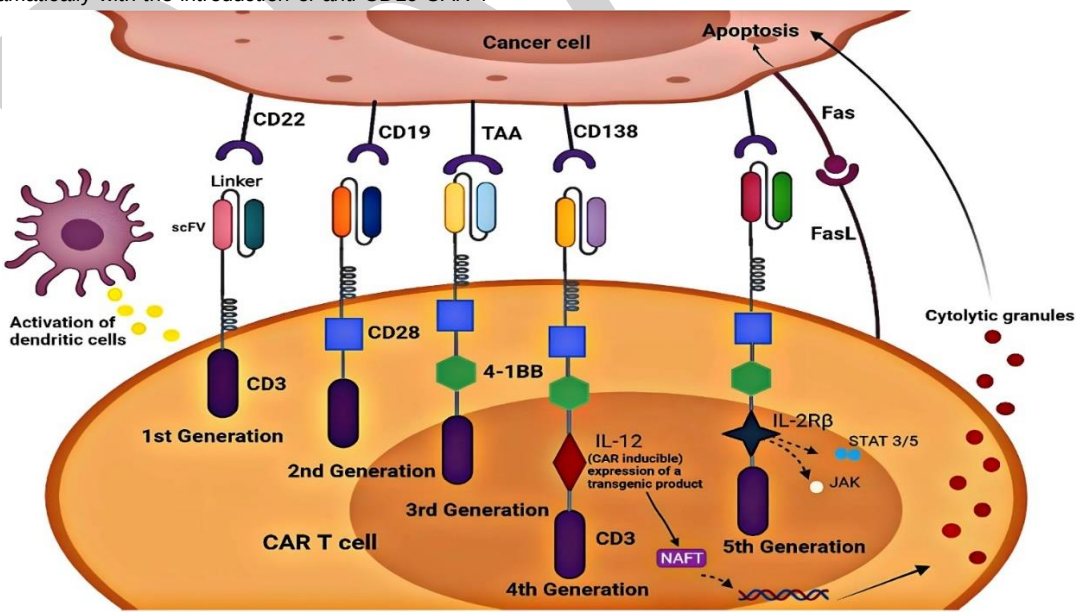
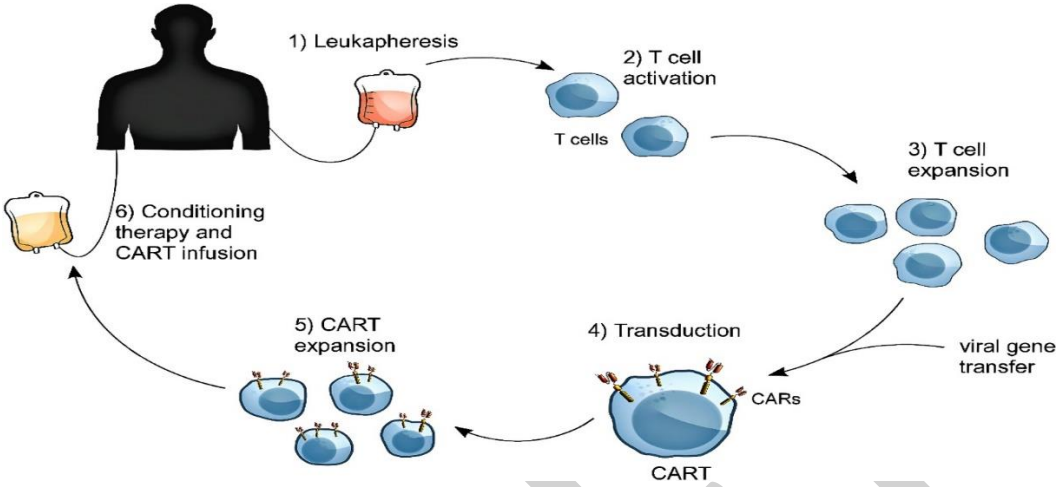


Figure (1): Details the structural progression across five CAR T cell generations and their targets on tumour cells. The first-generation focuses on the CD3ζ component. The second and third generations introduce and combine additional signalling elements like CD28 and 4–1BB. Fourth-generation CARs, or TRUCKs, incorporate genetic modifications for enhanced cytokine secretion. The fifth generation adds a novel intracellular domain, including truncated cytokine receptor domains, to further refine targeting and effectiveness (A Z Mehrabadi et al., Biomedicine& Pharmacotherapy 2022,146) [28].

Engineering CAR T cells, target recognition and tumour cell killing

CAR T cell therapy, a ground-breaking treatment, stands out for its self-replicating and persistent nature in patients. This process, depicted in Figure 2, starts with isolating T cells from the patient or a donor's blood. These cells are then activated and genetically altered to express the CAR construct [14]. After this modification, the CAR T cells undergo expansion outside the body, leading to the formation of the final therapeutic product. The patient typically receives this product via infusion after conditional chemotherapy [14].



As shown in Figure 2, the initial step of CAR T cell generation involves harvesting immune cells through leukapheresis. Post-harvesting, T cells are isolated, activated, expanded, and then undergo gene transfer via a viral vector to express CARs. To increase the quantity of these modified T cells, they are cultivated in a bioreactor. Finally, they are harvested and infused into the patient, usually following lymphodepletion conditioning chemotherapy (KatarzynaS et al., Archivum Immunologiae et Therapiae Experimentalis 2020,68[6])[29].

CAR T cells are classified as autologous, derived from the patient's own blood, or allogeneic, obtained from a healthy donor. Regardless of their source, these cells are engineered to express an artificial T cell receptor, enabling them to target disease-related cells without relying on Major Histocompatibility Complex (MHC) engagement [14]. CARs are synthetic proteins designed to direct T cells toward tumour cell surface molecules, independent of T cell receptor (TCR) - MHC interactions [30-31]. Introduced typically via gene transfer, CARs incorporate a mouse-derived monoclonal antibody-based single-chain variable fragment (scFv) for antigen recognition. These scFvs, connected by an extracellular spacer, bind to specific epitopes and trigger activation signals through intracellular domains [32]. Once introduced to peripheral blood-derived T cells and expanded in culture, these CAR T cells are used to detect and eliminate tumour cells expressing the target antigen [33-34]. Targeting a broad spectrum of tumour cell surface molecules, including proteins, carbohydrates, and glycolipids, is a key feature of CARs. The interaction between CAR and its target creates immune synapses, leading to direct cytotoxicity against tumour cells. The effectiveness of this approach hinges on the selected antigen being abundantly present on the tumour cells [35].

CARs are engineered constructs that bind specific cell surface antigens, using a scFv for recognition [36]. The initial generation of CARs fused a ligand recognition domain with the CD3 zeta (3ζ) chain, comprising an extracellular hinge and a transmembrane domain. This design enables the CD3ζ chain to autonomously signal T cell activation via phosphorylation of ITAMs by the lymphocyte-specific protein tyrosine kinase (Lck). Later generations of CARs incorporated additional signalling endodomains, such as CD28, CD137 (4-1BB), and inducible T cell co-stimulator (ICOS), to mimic antigen-presenting cells' co-stimulatory signals during T cell receptor engagement [37]. Advanced CAR T cells, like the fourth and fifth generations, include cytokine receptor domains and induce inflammatory cytokines, like interleukin-12 (IL-12) or IL-18, enhancing their efficacy against both solid and liquid tumours.

Clinical applications

The evolution of anti-cancer therapy has historically relied on four primary treatments: surgery, radiation, chemotherapy, and immunotherapy. A notable advancement occurred at the University of Pennsylvania and Children's Hospital in Philadelphia, where researchers Carl June, David Porter, and Stephan Grupp pioneered CAR T cell therapy in 2011 and 2012. Initially applied to chronic lymphocytic leukemia and acute lymphoblastic leukemia (ALL), this approach has shown significant success over the past decade, especially in treating B cell ALL and non-Hodgkin lymphoma (NHL) [18, 38-40]. CAR T cells, which are genetically modified autologous T cells equipped with chimeric antigen receptors, excel at recognizing cell surface epitopes without HLA dependence. They are designed to specifically bind to antigens like CD19 and feature optimized T cell activation and co-stimulatory domains [41]. Recent advances in CAR-T therapy signify a new era in cancer treatment, demonstrating substantial progress in hematologic malignancies, including lymphoma and leukemia, and showing promising results in solid tumours like glioblastomas and neuroblastoma [42]. Additionally, adapting chimeric antigen receptors to natural killer (NK) cells is emerging as a potential cellular immunotherapy approach, effective in targeting cancer cells [43].

CAR T cell therapy is under active investigation for solid tumours and various diseases. For instance, mesothelin-specific CAR mRNA-engineered T cells show potential against solid malignancies [44]. Novel applications, such as HLA-A2-specific CARs, are being explored in organ transplants [45] and

preclinical studies for targeting the 5T4 tumour antigen in ovarian cancer [46]. A key advantage of CAR T cell therapy is its rapid administration, typically involving a single infusion and requiring only 2–3 weeks of patient observation. This approach facilitates long-term CAR T cell persistence in the body, combatting cancer relapse effectively [47-48]. FDA-approved therapies like CTL019 (Kymriah), KTE-C19 (Yescarta), and JCAR015, which target CD19, are examples of successful CAR T cell treatments on the market [49-52]. As of April 2023, six approved CAR T cell therapies have shown remarkable efficacy against B-cell malignancies and multiple myeloma [13].

However, applying CAR T cell therapy to solid tumours presents unique challenges, with responses not as robust as those seen with CD19 CAR T cells [53]. Solid tumours create complex obstacles, such as genetic instability, hindered CAR T cell trafficking, and immunosuppressive microenvironments. Additionally, "on-target off-tumour" reactions can cause rapid adverse effects [54]. To overcome these challenges, innovative strategies are being developed, including inhibitory CARs (iCARs) and logic-gated CARs [55]. Enhancing CAR T cell performance can also be achieved by incorporating chemokine receptor genes that match tumour-produced chemokines, like CCR2b in CCL2-secreting neuroblastoma cells, and by arming CAR T cells with enzymes like heparinase to degrade the basement membrane [56]. Combining CAR T cell therapy with immunomodulatory agents such as checkpoint inhibitors, cytokines, and small-molecule antagonists is another approach showing potential for synergistic antitumor responses [57].

Efficacy and safety

Research on CAR T cell therapy, a ground-breaking cancer treatment, started almost twenty years ago. Initially, trials targeted ovarian cancer and renal cell carcinoma. Remarkable results were observed in some patients with neuroblastoma and follicular lymphoma. By 2016, the volume of clinical trials expanded significantly to 220, primarily in the USA and China, with an emphasis on treating blood cancers [14, 58]. A major advancement occurred with the FDA's approval of Cellectis' UCART123 for allogenic CAR T cell trials, which use donor-derived cells [59-60]. In trials for CD19 CAR T cells, which are engineered to attack cancer cells expressing the CD19 protein, 67% of acute lymphoblastic leukemia (ALL) patients and 82% of non-Hodgkin lymphoma (NHL) patients showed a positive response. At 9 months, 40% of ALL patients maintained this response. However, these promising results came with serious side effects like cytokine release syndrome (CRS) and neurotoxicity, which significantly affected patient health [61-62]. CRS leads to an overwhelming release of cytokines, causing symptoms such as high fever and low blood pressure. Treatment strategies for these side effects include the use of tocilizumab and intensive care support. Still, the recurrence rate remains high, with over half of the patients experiencing cancer return, and 30-50% relapsing within a year [62]. The challenges in treating patients without CD19 expression and those with solid tumours highlight the need for new approaches in B cell cancer therapies [63]. CAR T cell therapy can also cause severe CRS, leading to symptoms like fever, chills, and breathing difficulties [64]. With increasing experience, healthcare professionals are improving in both detecting and managing CRS. Neurological issues, including headaches, confusion, seizures, and speech problems — collectively known as immune effector cell–associated neurotoxicity syndrome (ICANS) — are also prevalent, though their exact cause is not yet fully understood [64]. Other side effects of CAR T cell therapy include allergic reactions, changes in blood mineral levels, weakened immunity, increased infection risk, low blood cell counts, fatigue, and bruising [65]. A critical condition, tumour lysis syndrome (TLS), can arise from rapid cancer cell breakdown following therapy or lymphodepleting chemotherapy, potentially causing arrhythmias and renal failure. Preventive measures for TLS in patients with high tumour burdens include adequate hydration and the use of hypouricemic agents [66-70].

Future directions

CAR T therapy, known for its impressive treatment outcomes, faces challenges such as limited response durability, leading to relapse rates as high as 66% [71]. Addressing this, recent advancements in immunology and molecular engineering have led to the development of next-generation CAR T cells. These incorporate diverse mechanisms, including additional costimulatory domains, cytokine secretion induction, and immune checkpoint modulation. These strategies aim to enhance malignant cell elimination [71-73]. Third-generation CAR T cells show variable efficacy, but immune checkpoint modulation, particularly in PD-L1 malignancies, has achieved response rates up to 78% [74-75]. Similarly, TRUCK CAR T cells, which utilize cytokines, have shown promising yet varied response rates, ranging from 0% to 100% [31, 76-78]. Such advancements are pivotal in improving therapies for both solid and liquid tumours, including CAR T-cell and BsAbs treatments.

Bispecific Antibody therapy

Overview and Development

BsAbs represent a significant advancement in cancer therapy. Their dual targeting ability enhances tumour treatment effectiveness. BsAbs exist in various formats such as quadroma, F(ab')2, diabodies, tandem diabodies, and single-chain variable fragments (scFv), detailed in Figure 3. Previously, antibody engineering faced challenges, leading to the development of the Knobs-into-Holes heterodimerization technique for CH3 domains by Carter and colleagues at Genentech in 2016. This method, while innovative, encountered issues like shared light chain usage and glycosylation problems. Advanced recombinant DNA technologies subsequently addressed these challenges, facilitating the production of diverse antibody forms including single-chain tandem Fv bispecific and scFv. According to [79], these forms enhance binding characteristics, improving specificity and affinity, and broadening application scope.

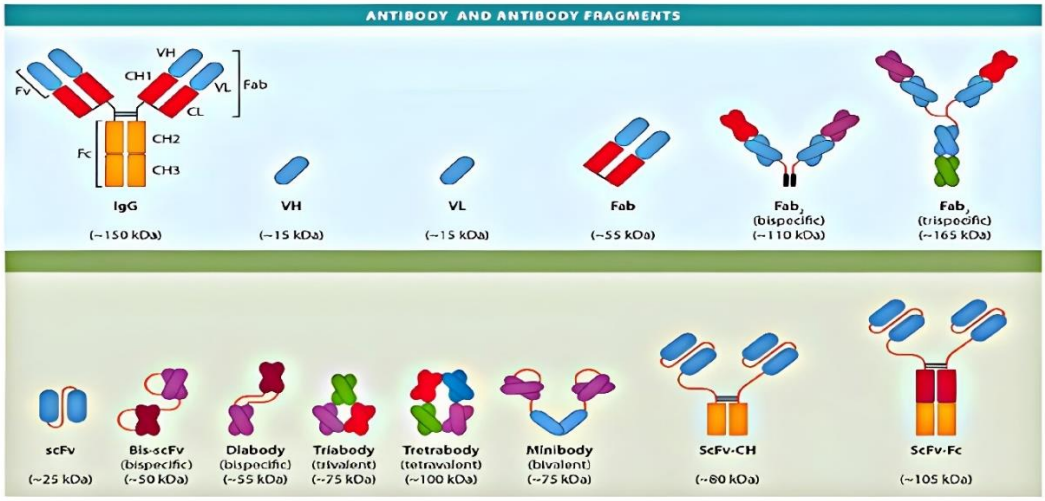


Figure (3): illustrates a conventional antibody, Immunoglobulin G (IgG), and its genetically modified variants (P M Lopez et al.,Cancers 2022,14[17])[80].

IgG, the most common antibody in human serum, has four subclasses [IgG1-4). Its structure, comprising two light and two heavy chains, forms a Y-shaped configuration. This arrangement includes three protein segments connected by a hinge region [81], each segment showing symmetry with two fragment antigen-binding (Fab) regions and one fragment crystallizable (Fc) region [82]. The Fab domain, containing hypervariable regions from heavy and light chains, mediates antigen binding [83]. Understanding antibody architecture and isotypes is vital for bispecific antibody design. Figure 4 showcases antibody isotypes such as IgA, IgG, IgM, IgD, and IgE. Bispecific antibodies are categorized into non-IgG-like, lacking Fc fragments, and IgG-like, incorporating Fc fragments [84].

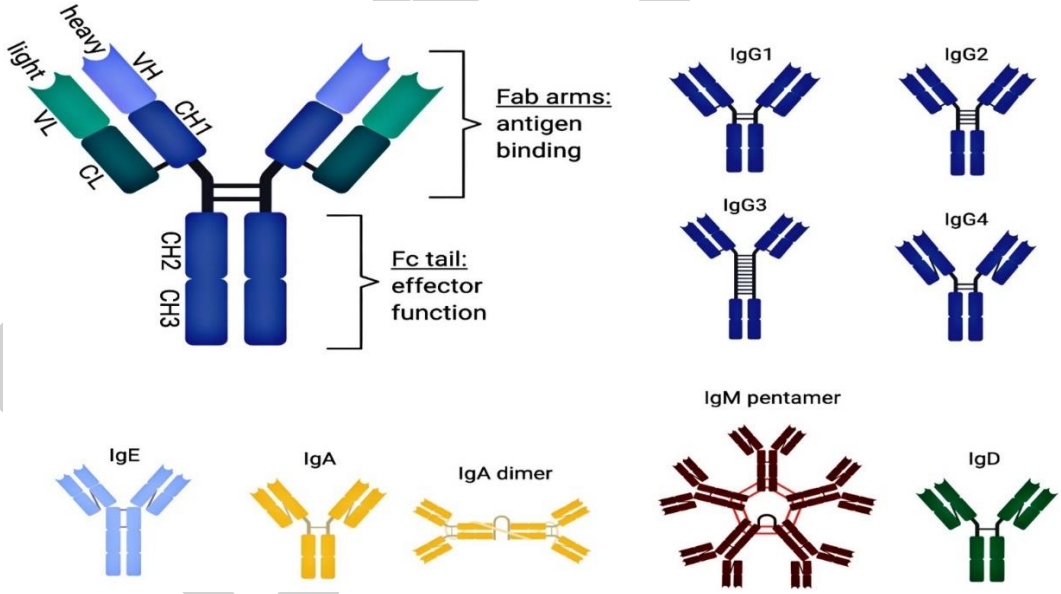


Figure (4): Human antibodies are categorized into five primary isotypes: IgG, IgA, IgM, IgE, and IgD. These isotypes are further divided into subclasses. Despite their diversity, all isotypes share a common structural layout. This layout includes two heavy and two light chains, which are connected by disulphide bonds. The chains comprise a variable domain (VH and VL) and constant domains (CH1, CH2, CH3, and CL). Antibodies function through two subunits: The Fab, which is responsible for specific antigen binding, and the Fc, which activates effector functions (Vukovic N et al., Clinical and Experimental Immunology 2020,203[3])[85].

The concept of BsAbs has evolved over more than five decades, with origins tracing back to the pioneering work of Nisonoff and colleagues [86]. These early researchers provided insights into antibody architecture. Unlike natural antibodies, BsAbs are primarily created using techniques such as recombinant DNA or cell-fusion technology. Initially, their design aimed at applications like redirecting T cells towards cancer targets. They were also used for binding simultaneously to tumour cells and an activating Fcγ receptor. The production methods of BsAbs have seen significant evolution. In their early stages, BsAbs were created using methods like manipulating monoclonal antibody hinge cysteines and through hybridoma fusion. A transformative shift in BsAbs production occurred with the advent of recombinant DNA technology [86]. This technology marked a new era in BsAbs development. Although the concept of BsAbs emerged in the 1960s, it wasn't until the 1980s that the first monoclonal BsAbs were successfully developed [87]. The early 1990s witnessed the documentation of their therapeutic applications. Over the last decade, there has been a surge in publications dedicated to BsAbs, indicating growing interest in

their therapeutic potential [87]. This increased interest in BsAbs has led to significant milestones in their therapeutic application. In 2009, catumaxomab received approval for therapeutic use. It was followed by the approval of blinatumomab in 2014. These approvals were pivotal advancements in the field of bispecific antibody therapy, marking the beginning of a new chapter in medical treatment and research [87].

Mechanism of action

BsAbs are advanced therapeutic proteins used in cancer treatment. Their function hinges on connecting immune cells to cancer cells, thus triggering an immune response against the cancer [88]. BsAbs are uniquely designed with dual binding sites: one targets cancer-specific markers, and the other latches onto immune cells. This dual targeting is crucial for directing the immune attack on cancer cells [89]. The effectiveness of BsAbs lies in creating an 'immunological synapse,' a link between cancer and immune cells [90]. There are two types: bispecific T cell engagers (BiTes) and immune effector cell-engaging bispecific antibodies (ICEs). BiTes connect T cells to cancer cells, while ICEs target various immune cells, like T cells or NK cells, to destroy cancer cells effectively [91].

Function of BiTes and ICEs

BiTes consist of two specific parts: one binds to cancer markers, and the other to the CD3 complex on T cells. This configuration directs T cells to attack cancer cells. Similarly, ICEs are tailored to bind specific immune cells, facilitating a targeted attack on cancer cells (Figure 5).

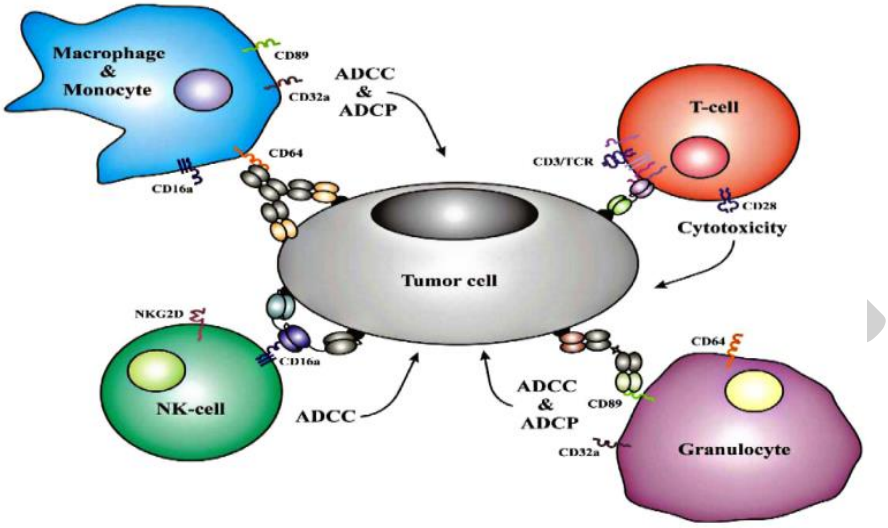


Figure (5): Tumour cell elimination involves using a therapeutic protein derived from antibodies to tag the cells. Effector cells are then recruited for the elimination process, which can occur through various mechanisms like ADCC, ADCP, or cytotoxic T-cell reactions. The agents involved include a monoclonal antibody, a chemically linked bispecific F(ab)2, and a recombinant bispecific tandem single-chain Fv-fragment (bsscFv) (Stein C et al., Antibodies1(1) 2012)[92].

BsAbs also interact with Fc receptors on immune cells and activate checkpoints like CTLA-4 and PD-1/PD-L1 (Figure 6). This interaction enhances the immune cells' ability to induce cancer cell death and inhibit tumour growth, underscoring the potential of BsAbs in cancer therapy [93-94].

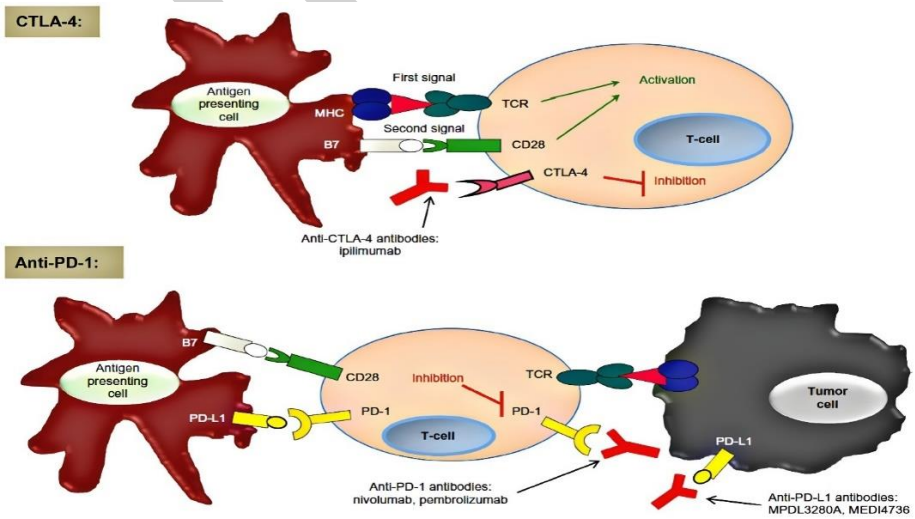


Figure (6): T-cell activation requires two signals. Post-activation, CTLA-4 can inhibit T-cell responses, but anti-CTLA-4 antibodies lift this inhibition, enhancing T-cell activity. Similarly, PD-1 on T-cells, when interacting with PD-L1 and PD-L2, generally suppresses their response. Anti-PD-1 antibodies help overcome this, boosting T-cell function in targeting cancer. This summary focuses on the roles of CTLA-4 and PD-1 in T-cell regulation, vital for understanding cancer immunotherapy (P Momtaz et al., Taylor& Francis 2014)[95].

Clinical applications

Bispecific antibodies (BsAbs) have significantly expanded the therapeutic landscape of cancer immunotherapy, demonstrating remarkable efficacy across various malignancies, including multiple myeloma [96]. Notably, blinatumomab has received FDA and EMA approval for treating refractory or relapsed pre-B cell acute lymphoblastic leukemia (pre-B-ALL) in both adults and children [97-101]. BsAbs also hold promise in targeting specific markers such as HER2 in breast and gastric cancers, PSMA in prostate cancer, and glypican 3 (GPC3) in liver, lung, and other cancers [102].

Immunotherapy has become a pivotal component in cancer treatment, alongside traditional modalities like surgery, radiation therapy, and chemotherapy, offering transformative potential [103]. Combining antibodies with adoptive cellular therapy and vaccination is gaining attention for its synergistic effects in cancer treatment [104-105]. BsAbs, with their ability to engage two distinct epitopes, are advancing cancer diagnostics and therapy, demonstrating enhanced efficacy and cost-effectiveness compared to using twoseparate monoclonal antibodies. This progress is exemplified by the FDA's approval of blinatumomab for B-cell precursor acute lymphoblastic leukemia and amivantamab for non-small cell lung cancer, reflecting the evolution of immunotherapy [106]. Addressing the challenge of treating lymphoid malignancies highlights the importance of integrating personalized therapy with bispecific antibodies and immune checkpoint inhibitors [107]. Particularly in lymphoid neoplasms, bispecific antibody immunotherapy stands out as a potent strategy [108]. Notably, bispecific antibodies with lower CD3 affinity have shown promise in eliminating tumour cells and reducing cytokine release syndrome (CRS) in prostate cancer, signifying significant progress [109]. In the context of glioblastoma multiforme (GBM), targeting EGFRvIII with T-bispecific antibodies is emerging as a promising approach. However, effective systemic delivery across the blood-brain barrier (BBB) remains a challenge [110-111].

Comparative analysis with other therapies

In the realm of bispecific antibody therapies, addressing challenges such as immunogenicity and endogenous biotin interference is crucial. One leading strategy is Pretargeted Radioimmunotherapy (PRIT) using nonimmunogenic human or humanized antibodies, which effectively reduces problems associated with immunogenicity and biotin interference. An example of this approach is the HER2 T-cell-dependent bispecific antibody (TDB), featuring low-affinity HER2 arms that improve tumour targeting and offer better tolerability compared to HER2-targeted CAR-T cell therapies, as supported by clinical data [112]. On the other hand, the SA-biotin method, while effective, faces significant immunogenicity issues due to streptavidin (SA). This pose concerns for repetitive use in therapy cycles. Strategies to mitigate this include developing genetically engineered SA variants with reduced immunogenicity and designing mutant SA molecules. These mutants bind less to endogenous biotin while maintaining high affinity for synthetic radio-biotin ligands, as explored in various studies.Furthermore, bispecific antibodies demonstrate superior selectivity and efficacy compared to monoclonal antibodies, particularly in treatments requiring high specificity like antibody-drug conjugates (ADC) and CAR T cell therapy. By targeting multiple antigens, they enhance effectiveness and minimize toxicity, a significant advantage highlighted in recent research [113].

Efficacy and Safety

Cancer immunotherapy, such as ipilimumab targeting CTLA-4, a protein that regulates immune responses, presents unique challenges compared to conventional treatments [114]. Despite the potential of BsAbs in cancer treatment, they can cause immune-related adverse events (irAEs), including elevated cytokine levels, which are overproductions of immune system proteins [87]. Strategies like premedication and gradual dose increases are proposed to manage these irAEs [115], offering insights into treating immune-mediated diseases [116]. New BsAbs, notably AFM13 targeting CD30/CD16A, show promise in reducing irAEs [116]. This antibody connects to both cancer and immune cells, potentially enhancing cancer cell destruction. Combining T-bispecific antibodies with anti-PD1 monoclonal antibodies—immunotherapies that block PD-1 proteins on T-cells to strengthen immune responses—has shown increased T-cell activity in preclinical studies [117-118], indicating a robust approach in cancer therapy [10]. In a study involving PF-06863135 (PF-3135), a bispecific humanized monoclonal antibody, results from 23 patients indicated one complete response, two minimal responses, and nine cases of stable disease, mostly with manageable side effects. However, six patients experienced grade 3 CRS [119].

Blinatumomab, evaluated in three studies for relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL), a type of lymphatic system cancer, showed specific dosing and response effectiveness [120]. Likewise, REGN5458, a bispecific antibody, displayed potential in treating multiple myeloma, a white blood cell cancer, in preclinical studies [121]. Catumaxomab has been effective against malignant ascites in epithelial cancers. Duligotuzumab, or MEHD7945A, demonstrated encouraging outcomes in treating head and neck squamous cell carcinoma, with a different side effect profile compared to cetuximab [122]. Additionally, combining blinatumomab with a tyrosine kinase inhibitor, a medication blocking enzymes in cancer cells, showed effectiveness in certain leukemia cases [123]. Lastly, FBTA05 showed positive responses in paediatric recurrent or refractory B-cell malignancies, types of cancer affecting specific white blood cells, with documented side effects [124].

Adverse effects

Common Adverse Events (AEs) of Bispecific Antibodies: This study highlights several side effects common in bispecific antibody therapy, a cancer treatment method. Patients often experience lymphopenia, pyrexia, elevated C-reactive protein, fatigue, leukopenia, weight gain, and headaches. Notably, transient blood disorders are common, with febrile neutropenia occurring in 3% of patients [125].

Cytokine Release Syndrome (CRS): A notable adverse effect of T-cell-engaging immunotherapies, including bispecific antibodies and chimeric antigen receptor T-cell therapies, is CRS. This condition, marked by a systemic inflammatory response, can be triggered by infections, drugs, or biological therapies, and manifests in symptoms like fever, nausea, and fatigue [126].

Hematologic Abnormalities: The report emphasizes the importance of monitoring blood-related abnormalities in patients undergoing bispecific antibody treatment. These include thrombocytopenia, lymphopenia, anaemia, and neutropenia, crucial for managing the safety of patients with both solid and liquid tumours [125].

Future directions

BsAbs, particularly effective in treating hematologic malignancies due to their clinical efficacy and manageable toxicity, are facing challenges that require addressing [108]. To optimize their use, there is a need for simplifying BsAbs structures, streamlining production, selecting synergistic target pairs, engineering non-immunogenic BsAbs, and developing strategies to minimize adverse effects. Notably, the potential of BsAbs extends beyond hematologic malignancies, with ongoing research exploring their applications in solid tumours [108]. The insights gained from their use in hematologic malignancies are anticipated to enhance treatments for solid tumour patients. A significant trend in the field is the rapid expansion of BsAbs in the pipeline, with many expected to enter the market in the next 3-5 years [113]. This marks a period of accelerated advancement, poised to transform cancer therapy. Furthermore, the field is evolving towards the development of multispecific antibodies, such as trispecific and tetraspecific antibodies, derived from BsAbs. These innovative antibodies offer enhanced selectivity and efficacy, presenting a promising direction for cancer treatment [113]. In the realm of next-generation cancer therapies, bispecific antibodies stand out, offering new, more effective, and targeted treatment strategies [127]. The continuous research and development of BsAbs are crucial for improving outcomes in both hematologic malignancies and solid tumours [127].

Combination therapies

The Hyper-CVAD chemotherapy regimen, comprising Cyclophosphamide, Vincristine, Doxorubicin, and Dexamethasone, is a cornerstone treatment for newly diagnosed B-cell acute lymphoblastic leukemia (B-ALL) patients [128]. An innovative approach being explored is the combination of Hyper-CVAD with blinatumomab in a phase 2 study for newly diagnosed adult B-ALL patients [129]. This protocol involves four cycles of Hyper-CVAD followed by four cycles of blinatumomab, representing a strategic effort to enhance B-ALL treatment outcomes. This combination leverages Hyper-CVAD's established efficacy and blinatumomab's novel therapeutic potential, underscoring the commitment to advancing treatment options for B-ALL patients [129].

Comparative Analysis

Liquid tumours

CAR T cell therapy has significantly advanced the treatment of hematologic malignancies, especially B cell neoplasms like diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma [130]. These therapies are crucial for cases resistant to or relapsed after standard treatments, including immunochemotherapeutic and transplantation. For instance, CTL019, targeting CD19 in B-cell cancers, achieves high response rates and durable remissions, boosting immune recovery in many patients. However, about 33% of patients experience transient encephalopathy and 20% face severe cytokine-release syndrome [40]. This data, from a study backed by Novartis (ClinicalTrials.gov number, NCT02030834), underlines the efficacy of this therapy in certain hematologic malignancies. In DLBCL, the therapy response rate is 66%, with a 3-year event-free survival rate of about 20% post-rituximab autologous stem-cell transplant. Follicular lymphoma shows a 20% early relapse rate post-rituximab treatment, with a 50% 5-year survival rate. In refractory or relapsed cases, treatments like idelalisib or copanlisib yield median response durations of 10.8 and 12.2 months, respectively [131-132]. CD19-targeted CAR T cells are particularly promising for B-cell cancers [133-136].

CAR T-cell therapy's side effects, including cytokine-release syndrome and neurotoxicity, are notable [40]. Severe cytokine-release syndrome can be managed with tocilizumab [135]. Neurological effects range from mild disturbances to severe encephalopathy. Patients with progressive or unresponsive DLBCL or those relapsing post-transplantation, have a response rate of 20-30% and a median survival of about 6 months [137]. Refractory follicular lymphoma patients treated with idelalisib post-rituximab have a 22% 2-year survival rate [131]. BsAbs like Blinatumomab, are effective in Relapsed/Refractory Multiple Myeloma (RRMM) and B-cell precursor ALL, achieving a 32% complete remission rate in adult ALL treatment [138] and showing promise in minimal residual disease [139]. Daratumumab, another BsAbs, demonstrates anti-myeloma activity with minimal cytokine release [140], though concerns about toxicity remain. BsAbs can be used immediately, unlike CAR T cell therapy, but may be less effective due to the lack of T-cell co-stimulation [97, 141-142]. CAR T cell therapy's Overall Response Rates (ORR) are higher than BsAbs in RRMM and B-ALL [143-146]. Blinatumomab retreatment in B-ALL has a 36% ORR, with ongoing trials examining CAR T cell retreatment feasibility [147]. Current research is exploring BsAbs in early-stage Multiple Myeloma therapy and combating drug resistance, with clinical trials investigating combinations of various immunotherapies.

Solid tumours

Blinatumomab (CD3xCD19), a BsAbs approved by the FDA, effectively treats haematological cancers, especially B-cell malignancies. It achieves over 40% in complete or partial responses, enhancing survival rates in these diseases [97, 148-149]. Flotetuzumab (CD3xCD123 BsAbs) shows a 30% response rate in acute myeloid leukemia [150], while epcoritamab (CD3xCD20 BsAbs) demonstrates high efficacy in early studies, with a 44% complete response in DLBCL or HGBCL and 100% partial response in FL patients [151-153]. However, CD3-BsAbs show limited effectiveness in solid tumours, underscoring the need for more research, particularly in comparing their efficacy to CAR T-cell therapies in these tumours [154].

In ovarian cancer, CAR T-cell therapies targeting antigens like TAG72, MUC16, Her2, Meso, 5T4, and FRα have shown promise. TAG72-specific CAR T cells reduce tumour growth and enhance survival in preclinical mouse models [155]. MUC16-CAR T cells achieve complete regression of ovarian cancer in these models. Additionally, CAR T cells targeting Her2, Meso [156], 5T4 [46], and FRα [157] effectively inhibit ovarian cancer cell growth [154]. In breast cancer, HRG1β-based CAR T cells target HER family receptors to combat resistance [158], and human anti-HER2 CAR T cells destroy HER2-overexpressing cells [159]. Mesothelin-targeting CAR T cells are also being developed for breast cancer. In prostate cancer, PSMA-targeted CAR T cells show significant cytotoxicity [160], with clinical trials confirming their safety and efficacy in advanced cases [161]. Renal cell carcinoma treatments include CAR T cells targeting CA-IX [162-163], effective under hypoxic conditions [164]. In gastric cancer, bi-specific Trop2/PD-L1 CAR T cells exhibit strong efficacy [165], with ongoing research into CAR T cells targeting Claudin18.2, NKG2D, FOLR1, HER2, and ICAM-1 [166-170]. CAR T cells also show potential in pancreatic [171] and liver cancers, targeting antigens like CEA, glypican-3,

mucin-1, and carcinoembryonic antigen [172-173]. However, treating solid tumours with CAR T cell therapy is challenging compared to blood cancers. Solid tumours, often confined to a single organ, have diverse and evolving antigens and are surrounded by immunosuppressive environments that hinder CAR T cell migration, unlike blood cancers [174].

The amalgamation of CAR T cell therapy with additional therapeutic modalities

The integration of CAR T cell therapy with additional treatments represents a promising strategy for enhancing its efficacy against tumours. This novel approach combines CAR T cells with supplementary therapeutics, particularly beneficial in addressing solid tumours [174]. Incorporating CAR T cells with existing drugs opens new therapeutic avenues. Current clinical treatments often do not include adoptive cell therapy (ACT), but combining these methods necessitates understanding drug-immune system interactions. A notable example is lenalidomide, which has shown significant antitumor effects in multiple myeloma. When used in conjunction with CAR T cells, lenalidomide amplifies T cell infiltration and boosts IFNγ production and cytotoxicity. This synergy led to complete remission in treated mice, highlighting the potential of this combined therapy for managing solid tumours.

Overcoming physical barriers to achieve tumour localization

CAR T cells, a type of cancer therapy, face two main challenges in treating solid tumours. First, they must penetrate the tumour's dense structure, primarily made of fibroblasts and myeloid cells. These cells create a fibrous network called the extracellular matrix (ECM), which acts as a barrier. Wang et al. developed FAP-CAR T cells, which target and reduce fibroblasts, easing the way into the tumour and slowing its growth. Second, once inside, CAR T cells encounter the tumour microenvironment (TME), a space that suppresses the immune system. This environment contains elements like regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumour-associated macrophages (TAMs), along with factors like TGF-β and IL-10 that weaken the immune response. Checkpoint inhibitors such as PD-L1 also contribute to this suppression. To counter this, researchers like Caruana et al. have modified CAR T cells to express heparinase (HPSE), an enzyme that breaks down the ECM, facilitating easier T cell infiltration.

The immune-constraining environment within the tumour

Enhancing CAR T cell therapy involves not just getting these cells into the tumour but also ensuring they work effectively once there. Strategies include local antibody secretion to attract different immune cells into the TME [174], and using specialized CAR T cells like EGFRvIII CAR T cells. These cells target a specific protein on tumour cells, offering a focused approach with fewer side effects. Tuned CARs are another innovation, designed to identify and attack less common tumour antigens effectively. Additionally, 'iCARs' specifically target tumour cells, minimizing the impact on healthy cells, and include 'suicide genes' to eliminate the CAR T cells if necessary. Overall, these advancements in CAR T cell therapy highlight a multi-faceted approach to overcome the physical and immunosuppressive barriers presented by solid tumours.

Challenges and considerations

Immunogenicity of CAR T Cells

A major hurdle in CAR T cell therapy is its immunogenicity, specifically due to the CAR constructs [175]. These constructs often include non-human elements that trigger immune responses, leading to early clearance of the infused cells. Studies, including those referenced by [176], have provided strong evidence of such immune responses [175].

Antigen Escape in CAR T Therapy

Additionally, antigen escape poses a significant challenge, as demonstrated in studies at the University of Pennsylvania and the National Cancer Institute (NCI). This phenomenon, particularly in CD19-CAR therapy, is a leading cause of relapse. Similar issues of antigen loss have been documented in CAR therapies targeting multiple myeloma and glioblastoma [177].

Immunogenicity Risk in Bispecific Antibody Therapy

In the realm of bispecific antibody therapy, the risk of immunogenicity is a key concern. Certain antibodies, designed for simultaneous checkpoint inhibition and immune cell activation, present heightened immunogenicity risks. This is particularly evident in combination therapies that involve drugs like nivolumab (anti-PD-1 mAb) and ipilimumab (anti-CTLA-4 mAb), known for their increased antibody-related immunogenicity [178].

Bispecific Antibodies and Tumour Cell Immune Evasion

Recent studies show that certain bispecific antibodies, though effective in activating T cells, may inadvertently encourage tumour cells to adopt immunosuppressive tactics. Such adaptation allows these cells to avoid destruction by antibody actions, posing a significant challenge in effective cancer therapy.

Cost Considerations and Accessibility

The implementation of CAR T cell and bispecific antibody therapies, although promising, is fraught with challenges, primarily due to their complexity and the high incidence of AEs. These therapies are currently limited to specialized tertiary centres equipped for intensive care and monitoring [179], restricting access for many patients. Efforts are underway to facilitate outpatient administration, which could increase accessibility. However, the prevalence of early-onset toxicities remains a significant obstacle to this transition [179].

Financially, these therapies impose a heavy burden on patients and their families due to the prolonged nature of the toxicities and the need for specialized care. It's imperative to have transparent discussions about the financial implications before starting treatment. The lack of global guidelines for evaluating and managing toxicities related to CAR T cell therapy and bispecific antibodies further complicates the situation [179].

These innovative treatments hold great potential in cancer therapy, yet their accessibility is a pressing societal concern. It raises important questions in political discourse about whether such life-saving treatments should be a privilege of the wealthy or a right for all in need [180].

Manufacturing Complexities

The manufacturing process of CAR T cell therapies, typically conducted in distant facilities, adds to the challenges. It involves time, cost, and logistical complexities. Improving this process is essential to extend access to patients, especially those with rapidly progressing diseases, living far from manufacturing sites, or in resource-limited settings [180]. A promising alternative is innovating CAR T cell production to an in vivo approach, where a T cell-targeted transgene and transfer vehicle are introduced directly into the patient. However, this method faces significant technical, safety, and control challenges [180].

Manufacturing BsAbs also requires substantial investment in time and finances. It involves establishing secure and efficient cell lines, meticulous processing, and precise analytical purification methods [12]. Post-production, BsAbs face issues like degradation, aggregation, denaturation, fragmentation, and oxidation. Addressing these challenges is crucial for patients to fully benefit from these advanced therapies [12].

Conclusion

The fusion of CAR T cell and BsAbs therapies is revolutionizing cancer treatment. CAR T cells excel in treating blood cancers but face challenges in solid tumours. Enhancements are needed for wider applicability and is also being explored for the treatment of various pathological conditions such as autoimmune diseases, fibrotic diseases, infectious diseases, etc. Bispecific antibodies bridge immune cells and tumour cells effectively in both blood and solid cancers. This versatility holds promise for more effective treatments. Emerging trends focus on improving CAR T cell therapy through diverse molecular mechanisms and optimizing Bispecific antibody therapy. The rise of multispecific antibodies and advancements in BsAb technology herald a new era of targeted cancer treatments. These immunotherapies are converging to offer personalized treatment options. Ongoing research aims to unlock their full potential against the varied challenges of solid and liquid cancers.

Ethics approval and consent to participate

This manuscript is a review study. Hence, ethics approval and consent to participate are not applicable.

Consent for publication

Not applicable

Availability of data and materials

All data related to this study is included in the manuscript.

Authors contribution

Saritha Medapati: Conceptualization, data curation, validation, visualization, reviewing and editing and supervision. **Haripriya B.V.S.L:** Conceptualization, writing of original draft, data curation and editing. **Priyanka Jyothi Dummari:** conceptualization, writing of original draft, data curation, writing review and editing. **Vinodkumar Mugada:** Data curation, visualization, software, review and editing. **Rooth Vasantha Medapati:** data curation, visualization, validation, writing review and editing. **Srinivas RaoYarguntla:** supervision, administration, resources.

Competing interest

None**.**

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REFERENCES

1] Fesnak, A. D., June, C. H., & Levine, B. L.). Engineered T cells: the promise and challenges of cancer immunotherapy. Nature Reviews Cancer, 2016; 16(9), 566–581. https://doi.org/10.1038/nrc.2016.97

2] Feins, S., Kong, W., Williams, E. F., Milone, M. C., & Fraietta, J. A. An introduction to chimeric antigen receptor (CAR) T-cell immunotherapy for human cancer. American Journal of Hematology, 2019; 94(S1), S3–S9. https://doi.org/10.1002/ajh.25418

3] Knochelmann, H. M., Smith, A., Dwyer, C. J., Wyatt, M., Mehrotra, S., & Paulos, C. M. CAR T Cells in Solid Tumors: Blueprints for Building Effective Therapies. Frontiers in Immunology,2018; 9. https://doi.org/10.3389/fimmu.2018.01740

4] Dahlén, E., Niina Veitonmäki, & Per Norlén. Bispecific antibodies in cancer immunotherapy. Therapeutic Advances in Vaccines and Immunotherapy,2018; 6(1), 3–17. https://doi.org/10.1177/2515135518763280

5] Ribas, A., & Wolchok, J. D. Cancer immunotherapy using checkpoint blockade. Science,2018; 359(6382), 1350–1355. https://doi.org/10.1126/science.aar4060

6] Ramos, C. A., Savoldo, B., Torrano, V., Ballard, B., Zhang, H., Dakhova, O., Liu, E., Carrum, G., Kamble, R. T., Gee, A. P., Mei, Z., Wu, M., Hao Líu, Grilley, B., Rooney, C. M., Brenner, M. K., Heslop, H. E., & Gianpietro Dotti. Clinical responses with T lymphocytes targeting malignancy-associated κ light chains. Journal of Clinical Investigation,2016; 126(7), 2588–2596. https://doi.org/10.1172/jci86000

7] Ormhøj, M., Bedoya, F., Frigault, M. J., & Maus, M. V. CARs in the Lead Against Multiple Myeloma. Current Hematologic Malignancy Reports, 2017;12(2), 119–125. https://doi.org/10.1007/s11899-017-0373-2

8] Andersson, T., Khan, A., Koivula, T., Larsson, T., Svahn, F., & Wahlsten, A. (n.d.). Drugs of the Future -Bispecific Antibodies An investigation of future development needs. https://www.diva-portal.org/smash/get/diva2:1321277/FULLTEXT01.pdf

9] Kubicka, E., Lum, L. G., Huang, M., & Thakur, A. Bispecific antibody-targeted T-cell therapy for acute myeloid leukemia ResearchGate; Frontiers.2022. https://www.researchgate.net/publication/365021165_Bispecific_antibody-targeted_T-cell_therapy_for_acute_myeloid_leukemia

10] Rader, C. Bispecific antibodies in cancer immunotherapy. Current Opinion in Biotechnology, 2020;65, 9–16. https://doi.org/10.1016/j.copbio.2019.11.020

11] Bourbon, E., Hervé Ghesquières, & Bachy, E. CAR-T cells, from principle to clinical applications. Bulletin Du Cancer,2021; 108(10), S4–S17. https://doi.org/10.1016/j.bulcan.2021.02.017

12] Wang, C., Wang, J., Che, S., & Zhao, H. CAR-T cell therapy for hematological malignancies: History, status and promise. Heliyon, 2023; 9(11), e21776–e21776. https://doi.org/10.1016/j.heliyon.2023.e21776

13] Mitra, A., Barua, A., Huang, L., Ganguly, S., Feng, Q., & He, B. From bench to bedside: the history and progress of CAR T cell therapy. Frontiers in Immunology,2023; 14. https://doi.org/10.3389/fimmu.2023.1188049

14] Hartmann, J., Schüßler-Lenz, M., Bondanza, A., & Buchholz, C. J. Clinical development of CAR T cells—challenges and opportunities in translating innovative treatment concepts. Embo Molecular Medicine, 2017;9(9), 1183–1197. https://doi.org/10.15252/emmm.201607485

15] Chimeric antigen receptor (CAR)-engineered lymphocytes for cancer therapy. Expert Opinion on Biological Therapy.2023. https://www.tandfonline.com/doi/full/10.1517/14712598.2011.573476

16] Li, J., Zhong, J., Zhang, X., & Zhang, C. Allogeneic CD19-CAR-T cell infusion after allogeneic hematopoietic stem cell transplantation in B cell malignancies. Journal of Hematology & Oncology, 2017;10(1). https://doi.org/10.1186/s13045-017-0405-3

17] Zhang, C., Li, J., Zhong, J., & Zhang, X. Engineering CAR-T cells. Biomarker Research,2017; 5(1). https://doi.org/10.1186/s40364-017-0102-y

18] Styczyński, J. A brief history of CAR-T cells: from laboratory to the bedside. Acta Haematologica Polonica, 2020;51(1), 2–5. https://doi.org/10.2478/ahp-2020-0002

19] Brocker T. Chimeric Fv-zeta or Fv-epsilon receptors are not sufficient to induce activation or cytokine production in peripheral T cells. Blood, 2023;96(5). https://pubmed.ncbi.nlm.nih.gov/10961908/

20] Zhang, E., & Xu, H. A new insight in chimeric antigen receptor-engineered T cells for cancer immunotherapy. Journal of Hematology & Oncology, 2017;10(1). https://doi.org/10.1186/s13045-016-0379-6

21] Jang Hwan Cho, Collins, J. J., & Wong, W. Universal Chimeric Antigen Receptors for Multiplexed and Logical Control of T Cell Responses. Cell, 2018; 173(6), 1426-1438.e11. https://doi.org/10.1016/j.cell.2018.03.038

22] Sachdeva, M., Busser, B. W., Sonal Temburni, Jahangiri, B., Anne-Sophie Gautron, Maréchal, A., Juillerat, A., Williams, A. F., Stéphane Depil, Philippe Duchâteau, Poirot, L., & Julien Valton. Repurposing endogenous immune pathways to tailor and control chimeric antigen receptor T cell functionality. Nature Communications, 2019;10(1). https://doi.org/10.1038/s41467-019-13088-3

23] Ren, J., & Zhao, Y. Advancing chimeric antigen receptor T cell therapy with CRISPR/Cas9. Protein & Cell, 2017;8(9), 634–643. https://doi.org/10.1007/s13238-017-0410-x

24] AN; Chimeric receptors providing both primary and costimulatory signaling in T cells from a single gene product. Journal of Immunology (Baltimore, Md.:1950), 2023; 161(6). https://pubmed.ncbi.nlm.nih.gov/9743337/

25] De Gang Song, Ye, Q., Carpenito, C., Poussin, M., Li Ping Wang, Ji, C., Mariangela Figini, June, C. H., Coukos, G., & Powell, D. J. In VivoPersistence, Tumor Localization, and Antitumor Activity of CAR-Engineered T Cells Is Enhanced by Costimulatory Signaling through CD137 (4-1BB). Cancer Research, 2011;71(13), 4617–4627. https://doi.org/10.1158/0008-5472.can-11-0422

26] Kawalekar, O. U., O'Connor, R. S., Fraietta, J. A., Guo, L., McGettigan, S. E., Posey, A. D., Patel, P., Guedan, S., Scholler, J., Keith, B., Snyder, N. W., Blair, I. A., Milone, M. C., & June, C. H. Distinct Signaling of Coreceptors Regulates Specific Metabolism Pathways and Impacts Memory Development in CAR T Cells. Immunity,2016; 44(2), 380–390. https://doi.org/10.1016/j.immuni.2016.01.021

27] Guedan, S., Posey, A. D., Shaw, C. E., Wing, A., Da, T., Patel, P., McGettigan, S. E., Casado-Medrano, V., Kawalekar, O. U., Mireia Uribe-Herranz, Song, D., J. Joseph Melenhorst, Lacey, S. F., Scholler, J., Keith, B., Young, R. M., & June, C. H. Enhancing CAR T cell persistence through ICOS and 4-1BB costimulation. JCI Insight, 2018;3(1). https://doi.org/10.1172/jci.insight.96976

28] Ali Zarezadeh Mehrabadi, Ranjbar, R., Mahdieh Farzanehpour, Alireza Shahriary, Ruhollah Dorostkar, Mohammad Ali Hamidinejad, & Hadi. Therapeutic potential of CAR T cell in malignancies: A scoping review. Biomedicine & Pharmacotherapy,2022;146, 112512–112512. https://doi.org/10.1016/j.biopha.2021.112512

29] Katarzyna Skórka, Katarzyna Ostapińska, Aneta Malesa, & Giannopoulos, K. The Application of CAR-T Cells in Haematological Malignancies. Archivum Immunologiae et Therapiae Experimentalis,2020; 68(6). https://doi.org/10.1007/s00005-020-00599-x

30] June, C. H., & Sadelain, M. Chimeric Antigen Receptor Therapy. The New England Journal of Medicine, 2018;379(1), 64–73. https://doi.org/10.1056/nejmra1706169

31] Rafiq, S., Hackett, C. S., & Brentjens, R. J. Engineering strategies to overcome the current roadblocks in CAR T cell therapy. Nature Reviews Clinical Oncology,2019; 17(3), 147–167. https://doi.org/10.1038/s41571-019-0297-y

32] Mohamed-Reda Benmebarek, Karches, C. H., Cadilha, B. L., Lesch, S., Endres, S., & Kobold, S. Killing Mechanisms of Chimeric Antigen Receptor (CAR) T Cells. International Journal of Molecular Sciences, 2019;20(6), 1283–1283. https://doi.org/10.3390/ijms20061283

33] MacKay, M., Ebrahim Afshinnekoo, Rub, J., Hassan, C., Mihir Khunte, Baskaran, N., Owens, B., Liu, L., Roboz, G. J., Guzmán, M. L., Melnick, A., Wu, S., & Mason, C. E. The therapeutic landscape for cells engineered with chimeric antigen receptors. Nature Biotechnology, 2020; 38(2), 233–244. https://doi.org/10.1038/s41587-019-0329-2

34] Magdi Elsallab, Levine, B. L., Wayne, A. S., & Abou-El-Enein, M. CAR T-cell product performance in haematological malignancies before and after marketing authorisation. Lancet Oncology,2020; 21(2), e104–e116. https://doi.org/10.1016/s1470-2045(19)30729-6

35] Xu, J., Wang, Q., Xu, H., Gu, C., Jiang, L., Wang, J., Wang, D., Xu, B., Mao, X., Wang, J., Wang, Z., Xiao, Y., Zhang, Y., Li, C., & Zhou, J. Anti-BCMA CAR-T cells for treatment of plasma cell dyscrasia: case report on POEMS syndrome and multiple myeloma. Journal of Hematology & Oncology, 2018;11(1). https://doi.org/10.1186/s13045-018-0672-7

36] Ajina, A., & Maher, J. Strategies to Address Chimeric Antigen Receptor Tonic Signaling. Molecular Cancer Therapeutics, 2018;17(9), 1795–1815. https://doi.org/10.1158/1535-7163.mct-17-1097

37] Wu, Z., & Xu, J. DNA methyltransferases and their roles in tumorigenesis. Biomarker Research,2017; 5(1). https://doi.org/10.1186/s40364-017-0081-z

38] . Li, D., Lei, C., Jin, Q., & Han, M. Regularization in DQN for Parameter-Varying Control Learning Tasks. Lecture Notes in Computer Science, 2019;35–44. https://doi.org/10.1007/978-3-030-22808-8_4

39] DiNofia, A. M., & Maude, S. L. Chimeric Antigen Receptor T-Cell Therapy Clinical Results in Pediatric and Young Adult B-ALL. HemaSphere, 2019; 3(4), e279–e279. https://doi.org/10.1097/hs9.0000000000000279

40] Schuster, S. J., Svoboda, J., Chong, E. A., Nasta, S., Mato, A. R., Özlem Anak, Brogdon, J. L., Iulian Pruteanu-Malinici, Vijay Bhoj, Landsburg, D. J., Wasik, M. A., Levine, B. L., Lacey, S. F., J. Joseph Melenhorst, Porter, D. L., & June, C. H. Chimeric Antigen Receptor T Cells in Refractory B-Cell Lymphomas. The New England Journal of Medicine, 2017; 377(26), 2545–2554. https://doi.org/10.1056/nejmoa1708566

41] The condition of poverty: a case study of low socioeconomic status on Chinese students' National College Entrance Exam and college enrolment. Asia Pacific Journal of Education.2019; https://www.tandfonline.com/doi/abs/10.1080/02188791.2019.1575794

42] Sha, H., Wang, D., Yan, D., Hu, Y., Yang, S.-J., Liu Siwen, & Feng, J. Chimaeric antigen receptor T-cell therapy for tumour immunotherapy. Bioscience Reports. 2017.https://doi.org/10.1042/bsr20160332

43] Hu, W., Wang, G., Huang, D., Sui, M., & Xu, Y. Cancer Immunotherapy Based on Natural Killer Cells: Current Progress and New Opportunities. Frontiers in Immunology,2019; 10. https://doi.org/10.3389/fimmu.2019.01205

44] Hamid Reza Mirzaei, Rodriguez, A., Jennifer Kelly Shepphird, Brown, C. E., & Badie, B. Chimeric Antigen Receptors T Cell Therapy in Solid Tumor: Challenges and Clinical Applications. Frontiers in Immunology, 2017;8. https://doi.org/10.3389/fimmu.2017.01850

45] Boardman, D. A., Philippeos, C., Fruhwirth, G. O., Ibrahim, M., Hannen, R., Cooper, D., Marelli-Berg, F. M., Watt, F. M., Lechler, R. I., Maher, J., Smyth, L. A., & Lombardi, G. Expression of a Chimeric Antigen Receptor Specific for Donor HLA Class I Enhances the Potency of Human Regulatory T Cells in Preventing Human Skin Transplant Rejection. American Journal of Transplantation,2017; 17(4), 931–943. https://doi.org/10.1111/ajt.14185

46] Owens, G., Sheard, V., Milena Kalaitsidou, Blount, D. G., Lad, Y., Cheadle, E. J., Edmondson, R. J., Kooner, G., Gilham, D. E., & Harrop, R. Preclinical Assessment of CAR T-Cell Therapy Targeting the Tumor Antigen 5T4 in Ovarian Cancer. Journal of Immunotherapy, 2018;41(3), 130–140. https://doi.org/10.1097/cji.0000000000000203

47] CARs on a highway with roadblocks. OncoImmunology.2017. https://www.tandfonline.com/doi/full/10.1080/2162402X.2017.1388486

48] Miguel Angel Perales, Partow Kebriaei, Kean, L. S., & Sadelain, M. Building a Safer and Faster CAR: Seatbelts, Airbags, and CRISPR. Biology of Blood and Marrow Transplantation,2018; 24(1), 27–31. https://doi.org/10.1016/j.bbmt.2017.10.017

49] Bach, P. B., Giralt, S., & Saltz, L. FDA Approval of Tisagenlecleucel. JAMA, 2017;318(19), 1861–1861. https://doi.org/10.1001/jama.2017.15218

50] Fala, L. Yescarta (Axicabtagene Ciloleucel) Second CAR T-Cell Therapy Approved for Patients with Certain Types of Large B-Cell Lymphoma. American Health & Drug Benefits. 2016.

https://www.ahdbonline.com/issues/2018/april-2018-vol-11-ninth-annual-payers-guide/2553-yescarta-axicabtagene-ciloleucel-second-car-t-cell-therapy-approved-for-patients-with-certain-types-of-large-b-cell-lymphoma

51] Spencer Phillips Hey, & Kesselheim, A. S. The FDA, Juno Therapeutics, and the ethical imperative of transparency. BMJ, 2016; i4435–i4435. https://doi.org/10.1136/bmj.i4435

52] Rotolo, A., Caputo, V. S., & Anastasios Karadimitris. The prospects and promise of chimeric antigen receptor immunotherapy in multiple myeloma. British Journal of Haematology, 2016;173(3), 350–364. https://doi.org/10.1111/bjh.13976

53] Juneau, D., Golfam, M., Samir Kumar Hazra, Zuckier, L. S., Shady Nashaat Garas, Redpath, C. J., Bernick, J., Leung, E., Chih, S., Wells, G. A., Beanlands, R., & Benjamin J.W. Chow. Positron Emission Tomography and Single-Photon Emission Computed Tomography Imaging in the Diagnosis of Cardiac Implantable Electronic Device Infection. Circulation-Cardiovascular Imaging, 2017;10(4). https://doi.org/10.1161/circimaging.116.005772

54] Beavis, P. A., Slaney, C. Y., Kershaw, M. H., Gyorki, D. E., Neeson, P. J., & Darcy, P. K. Reprogramming the tumor microenvironment to enhance adoptive cellular therapy. Seminars in Immunology, 2016;28(1), 64–72. https://doi.org/10.1016/j.smim.2015.11.003

55] Davies, D., & Maher, J. Gated chimeric antigen receptor T-cells: the next logical step in reducing toxicity? Translational Cancer Research,2016; 5(S1), S61–S65. https://doi.org/10.21037/tcr.2016.06.04

56] Hamid Reza Mirzaei, Hamed Mirzaei, Lee, S.-Y., Jamshid Hadjati, & Till, B. G. Prospects for chimeric antigen receptor (CAR) γδ T cells: A potential game changer for adoptive T cell cancer immunotherapy. Cancer Letters, 2016;380(2), 413–423. https://doi.org/10.1016/j.canlet.2016.07.001

57] Dai, H., Wang, Y., Lu, X.-C., & Han, W. Chimeric Antigen Receptors Modified T-Cells for Cancer Therapy. Journal of the National Cancer Institute,2016; 108(7). https://doi.org/10.1093/jnci/djv439

58] Pettitt, D., Arshad, Z., Smith, J., Stanic, T., Holländer, G. A., & Brindley, D. CAR-T Cells: A Systematic Review and Mixed Methods Analysis of the Clinical Trial Landscape. Molecular Therapy, 2018;26(2), 342–353. https://doi.org/10.1016/j.ymthe.2017.10.019

59] Kingwell, K. CAR T therapies drive into new terrain. Nature Reviews Drug Discovery,2017; 16(5), 301–304. https://doi.org/10.1038/nrd.2017.84

60] Amy C.Y. Yip, & Webster, R. M. The market for chimeric antigen receptor T cell therapies. Nature Reviews Drug Discovery, 2018;17(3), 161–162. https://doi.org/10.1038/nrd.2017.266

61] Maude, S. L., Laetsch, T. W., Buechner, J., Rives, S., Boyer, M. W., Henrique Bittencourt, Bader, P., Verneris, M. R., Stefanski, H. E., G. Doug Myers, Muna Qayed, Barbara De Moerloose, Hiramatsu, H., Schlis, K., Davis, K. L., Martin, P. L., Nemecek, E. R., Yanik, G. A., Peters, C., & André Baruchel. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. The New England Journal of Medicine, 2018;378(5), 439–448. https://doi.org/10.1056/nejmoa1709866

62] Shah, N. N., & Fry, T. J. Mechanisms of resistance to CAR T cell therapy. Nature Reviews Clinical Oncology.2019. https://doi.org/10.1038/s41571-019-0184-6

63] Wang, V., Gauthier, M., Decot, V., Reppel, L., & Danièle Bensoussan. Systematic Review on CAR-T Cell Clinical Trials Up to 2022: Academic Center Input. Cancers,2023; 15(4), 1003–1003. https://doi.org/10.3390/cancers15041003

64] CAR T Cells: Engineering Immune Cells to Treat Cancer. National Cancer Institute,2022. Cancer.gov. https://www.cancer.gov/about-cancer/treatment/research/car-t-cells

65] CAR T-cell Therapy and Its Side Effects. Cancer.org.2019. https://www.cancer.org/cancer/managing-cancer/treatment-types/immunotherapy/car-t-cell1.html

66] Howard, S. C., Trifilio, S., Gregory, T., Baxter, N., & McBride, A. Tumor lysis syndrome in the era of novel and targeted agents in patients with hematologic malignancies: a systematic review. Annals of Hematology, 2016;95(4), 563–573. https://doi.org/10.1007/s00277-015-2585-7

67] Brudno, J. N., Somerville, R., Shi, V., Rose, J. J., Halverson, D., Fowler, D. H., Gea-Banacloche, J., Pavletić, S. Z., Hickstein, D. D., Lu, T., Feldman, S. A., Iwamoto, A. T., Kurlander, R., Marić, I., Goy, A., Hansen, B., Wilder, J., Bazetta Blacklock-Schuver, Hakim, F. T., & Rosenberg, S. A. Allogeneic T Cells That Express an Anti-CD19 Chimeric Antigen Receptor Induce Remissions of B-Cell Malignancies That Progress After Allogeneic Hematopoietic Stem-Cell Transplantation Without Causing Graft-Versus-Host Disease. Journal of Clinical Oncology,2016; 34(10), 1112–1121. https://doi.org/10.1200/jco.2015.64.5929

68] Varadarajan, I., Kindwall-Keller, T. L., & Lee, D. W. Management of Cytokine Release Syndrome. Elsevier EBooks,2020; 45–64. https://doi.org/10.1016/b978-0-323-66181-2.00005-6

69] Belay, Y., Ketsela Yirdaw, & Bamlaku Enawgaw. Tumor Lysis Syndrome in Patients with Hematological Malignancies. Journal of Oncology, 2017; 1–9. https://doi.org/10.1155/2017/9684909

70] McBride, N. M., Johnco, C., Salloum, A., Lewin, A. B., & Storch, E. A. Prevalence and Clinical Differences of Suicidal Thoughts and Behaviors in a Community Sample of Youth Receiving Cognitive-Behavioral Therapy for Anxiety. Child Psychiatry & Human Development,2016; 48(5), 705–713. https://doi.org/10.1007/s10578-016-0696-6

71] Tomasik, J., Marcin Jasiński, & Basak, G. Next generations of CAR-T cells - new therapeutic opportunities in hematology? Frontiers in Immunology,2022;13. https://doi.org/10.3389/fimmu.2022.1034707

72] Gunilla Enblad, Karlsson, H., Gustav Gammelgård, Wenthe, J., Lövgren, T., Amini, R., Wikström, K., Magnus Essand, Savoldo, B., Heléne Hallböök, Höglund, M., Gianpietro Dotti, Brenner, M. K., Hagberg, H., & Loskog, A. A Phase I/IIa Trial Using CD19-Targeted Third-Generation CAR T Cells for Lymphoma and Leukemia. Clinical Cancer Research,2018; 24(24), 6185–6194. https://doi.org/10.1158/1078-0432.ccr-18-0426

73] Sterner, R. C., & Sterner, R. M. CAR-T cell therapy: current limitations and potential strategies. Blood Cancer Journal,2021; 11(4). https://doi.org/10.1038/s41408-021-00459-7

74] Liu, H., Lei, W., Zhang, C., Yang, C., Wei, J., Guo, Q., Guo, X., Chen, Z., Lu, Y., Young, K. H., Lu, Z., & Qian, W. CD19-specific CAR T Cells that Express a PD-1/CD28 Chimeric Switch-Receptor are Effective in Patients with PD-L1–positive B-Cell Lymphoma. Clinical Cancer Research, 2020;27(2), 473–484. https://doi.org/10.1158/1078-0432.ccr-20-1457

75] Phase 1/2 study of anbalcabtagene autoleucel, novel anti-CD19 CAR-T cell therapy with dual silencing of PD-1 and TIGIT in relapsed or refractory large B-cell lymphoma. | Journal of Clinical Oncology. 2022. https://ascopubs.org/doi/10.1200/JCO.2022.40.16_suppl.7522

76] Qian, W., Zhao, A., Liu, H., Lei, W., Liang, Y., & Yuan, X. Safety and Efficacy of CD19 CAR-T Cells Co-Expressing IL-7 and CCL19 in Combination with Anti-PD-1 Antibody for Refractory/Relapsed DLBCL: Preliminary Data from the Phase Ⅰb Trial (NCT04381741). Blood,2021; 138(Supplement 1), 3843–3843. https://doi.org/10.1182/blood-2021-144523

77] Duan, D., Wang, K., Wei, C., Feng, D., Liu, Y., He, Q., Xu, X., Wang, C., Zhao, S., Leili Lv, Long, J., Lin, D., Zhao, A., Fang, B., Jiang, J., Tang, S., & Gao, J. The BCMA-Targeted Fourth-Generation CAR-T Cells Secreting IL-7 and CCL19 for Therapy of Refractory/Recurrent Multiple Myeloma. Frontiers in Immunology,2021; 12. https://doi.org/10.3389/fimmu.2021.609421

78] Grover, N. S., Ivanova, A., Moore, D. T., Cheng, C., Babinec, C., West, J. A., Cavallo, T., J. Kaitlin Morrison, Faith Brianne Buchanan, Bowers, E. V., Dittus, C., Beaven, A., Gianpietro Dotti, Serody, J. S., & Savoldo, B. CD30-Directed CAR-T Cells Co-Expressing CCR4 in Relapsed/Refractory Hodgkin Lymphoma and CD30+ Cutaneous T Cell Lymphoma. Blood,2021; 138(Supplement 1), 742–742. https://doi.org/10.1182/blood-2021-148102

79] Brinkmann, U., & Kontermann, R. E. The making of bispecific antibodies. MAbs, 2017;9(2), 182–212. https://doi.org/10.1080/19420862.2016.1268307

80] Muñoz-López, P., Rosa María Ribas-Aparicio, Elayne Irene Becerra-Báez, Fraga-Pérez, K., Luis Fernando Flores-Martínez, Armando Alfredo Mateos-Chávez, & Luría-PérezR. Single-Chain Fragment Variable: Recent Progress in Cancer Diagnosis and Therapy. Cancers,2022; 14(17), 4206–4206. https://doi.org/10.3390/cancers14174206

81] Liu, H., Saxena, A., Sidhu, S. S., & Wu, D. Fc Engineering for Developing Therapeutic Bispecific Antibodies and Novel Scaffolds. Frontiers in Immunology,2017;8. https://doi.org/10.3389/fimmu.2017.00038

82] Wang, Q., Chung, C. -S, Chough, S., & Betenbaugh, M. J. Antibody glycoengineering strategies in mammalian cells. Biotechnology and Bioengineering,2018; 115(6), 1378–1393. https://doi.org/10.1002/bit.26567

83] Wang, Q., Chen, Y., Park, J., Xiao, L., Hu, Y., Wang, T., McFarland, K. S., & Betenbaugh, M. J. Design and Production of Bispecific

Antibodies. Antibodies,2019; 8(3), 43–43. https://doi.org/10.3390/antib8030043

84] Suurs, F. V., Hooge, L., G.E, E., & Jan. A review of bispecific antibodies and antibody constructs in oncology and clinical challenges. Pharmacology & Therapeutics,2019; 201, 103–119. https://doi.org/10.1016/j.pharmthera.2019.04.006

85] Vukovic, N., Andrea van Elsas, J. Sjef Verbeek, & Zaiss, D. M. Isotype selection for antibody-based cancer therapy. Clinical and Experimental Immunology,2020; 203(3) , 351–365. https://doi.org/10.1111/cei.13545

86] Krishnamurthy, A., & Jimeno, A. Bispecific antibodies for cancer therapy: A review. Pharmacology & Therapeutics, 2018;185, 122–134. https://doi.org/10.1016/j.pharmthera.2017.12.002

87] Sedykh, S. E., Prinz, V. V., Buneva, V. N., & Nevinsky, G. A. Bispecific antibodies: design, therapy, perspectives. Drug Design Development and Therapy,2018; Volume 12, 195–208. https://doi.org/10.2147/dddt.s151282

88] Wu, Z., & Cheung, N. V. T cell engaging bispecific antibody (T-BsAb): From technology to therapeutics. Pharmacology & Therapeutics,2018; 182, 161–175. https://doi.org/10.1016/j.pharmthera.2017.08.005

89] Dahlén, E. Bispecific antibodies in cancer immunotherapy - Eva Dahlén, Niina Veitonmäki, Per Norlén, 2018. Therapeutic Advances in Vaccines and Immunotherapy. 2018.https://journals.sagepub.com/doi/full/10.1177/2515135518763280

90] Zhu, M., Wu, B., Brandl, C., Johnson, J., Wolf, A., Chow, A., & Doshi, S. Blinatumomab, a Bispecific T-cell Engager (BiTE®) for CD-19 Targeted Cancer Immunotherapy: Clinical Pharmacology and Its Implications. Clinical Pharmacokinectics,2016; 55(10), 1271–1288. https://doi.org/10.1007/s40262-016-0405-4

91] Hong Hanh Nguyen, Kim, T., Sang Yun Song, Park, S., Hyang Hee Cho, Jung, S., Ahn, J., Kim, H.-J., Lee, J., Kim, H., Cho, J.-H., & Yang, D. Naïve CD8+ T cell derived tumor-specific cytotoxic effectors as a potential remedy for overcoming TGF-β immunosuppression in the tumor microenvironment. Scientific Reports,2016; 6(1). https://doi.org/10.1038/srep28208

92] Stein, C., Schubert, I., & Fey, G. H. Natural Killer (NK)- and T-Cell Engaging Antibody-Derived Therapeutics. Antibodies, 2012;1(1), 88–123. https://doi.org/10.3390/antib1010088

93] Novel Small-Molecule PD-L1 Inhibitor Induces PD-L1 Internalization and Optimizes the Immune Microenvironment. Journal of Medicinal Chemistry.2023. https://pubs.acs.org/doi/10.1021/acs.jmedchem.2c01801

94] Ross, S. L., Sherman, M., McElroy, P., Lofgren, J. A., Moody, G., Baeuerle, P. A., Coxon, A., & Arvedson, T. Bispecific T cell engager (BiTE®) antibody constructs can mediate bystander tumor cell killing. PLOS ONE,2017; 12(8), e0183390–e0183390. https://doi.org/10.1371/journal.pone.0183390

95] Momtaz P, Postow MA. Immunologic checkpoints in cancer therapy; focus on the programmed death-1(PD-1) receptor pathway. Pharmgenomics Pers Med. 2014;7:357-65.

96] Caraccio, C., S. Vijaya Krishna, Phillips, D., & Schürch, C. M. Bispecific Antibodies for Multiple Myeloma: A Review of Targets, Drugs, Clinical Trials, and Future Directions. Frontiers in Immunology,2020; 11. https://doi.org/10.3389/fimmu.2020.00501

97] Kantarjian, H. M., Stein, A. S., Gökbuget, N., Fielding, A. K., Schuh, A. C., Ribera, J., Wei, A. H., Hervé Dombret, Foà, R., Bassan, R., Arslan, Ö., Sanz, M. Á., Bergeron, J., Fatih Demırkan, Lech-Maranda, E., Alessandro Rambaldi, Thomas, X., Horst, H., Brüggemann, M., & Klapper, W. Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia. The New England Journal of Medicine, 2017;376(9), 836–847. https://doi.org/10.1056/nejmoa1609783

98] Curran, E., & Stock, W. Taking a “BiTE out of ALL”: blinatumomab approval for MRD-positive ALL. Blood,2019; 133(16), 1715–1719. https://doi.org/10.1182/blood-2018-12-852376

99] Jen, E. Y., Xu, Q., Schetter, A. J., Przepiorka, D., Yuan Li Shen, Roscoe, D., Rajeshwari Sridhara, Deisseroth, A., Philip, R., Farrell, A. T., & Pazdur, R. FDA Approval: Blinatumomab for Patients with B-cell Precursor Acute Lymphoblastic Leukemia in Morphologic Remission with Minimal Residual Disease. Clinical Cancer Research,2019; 25(2), 473–477. https://doi.org/10.1158/1078-0432.ccr-18-2337

100] Dufner, V., Sayehli, C., Chatterjee, M., Hummel, H., Götz Gelbrich, Bargou, R. C., & Goebeler, M.-E. Long-term outcome of patients with relapsed/refractory B-cell non-Hodgkin lymphoma treated with blinatumomab. Blood Advances,2019; 3(16), 2491–2498. https://doi.org/10.1182/bloodadvances.2019000025

101] Labrijn, A. F., Janmaat, M. L., Reichert, J. M., & Paul W.H.I. Parren. Bispecific antibodies: a mechanistic review of the pipeline. Nature Reviews Drug Discovery,2019; 18(8), 585–608. https://doi.org/10.1038/s41573-019-0028-1

102] Ishiguro, T., Sano, Y., Komatsu, S., Kamata-Sakurai, M., Kaneko, A., Kinoshita, Y., Hirotake Shiraiwa, Azuma, Y., Toshiaki Tsunenari, Kayukawa, Y., Sonobe, Y., Ono, N., Sakata, K., Fujii, T., Miyazaki, Y., Noguchi, M., Endô, M., Harada, A., Frings, W., & Fujii, E. An anti–glypican 3/CD3 bispecific T cell–redirecting antibody for treatment of solid tumors. Science Translational Medicine, 2017; 9(410). https://doi.org/10.1126/scitranslmed.aal4291

103] McCune, J. S. Rapid Advances in Immunotherapy to Treat Cancer. Clinical Pharmacology & Therapeutics,2018; 103(4), 540–544. https://doi.org/10.1002/cpt.985

104] Farkona, S., Diamandis, E. P., & Blasutig, I. M. Cancer immunotherapy: the beginning of the end of cancer? BMC Medicine,2016; 14(1). https://doi.org/10.1186/s12916-016-0623-5

105] Corraliza-Gorjón, I., Somovilla-Crespo, B., Silvia Santamaría Santamaría, García-Sanz, J. A., & Kremer, L. New Strategies Using Antibody Combinations to Increase Cancer Treatment Effectiveness. Frontiers in Immunology, 2017;8. https://doi.org/10.3389/fimmu.2017.01804

106] Park, K., Haura, E. B., Leighl, N. B., Mitchell, P., Shu, C. A., Girard, N., Viteri, S., Han, J., Kim, S., Chee Khoon Lee, Sabari, J. K., Spira, A. I., Yang, T., Kim, D.-W., Ki Hyeong Lee, Sanborn, R. E., Trigo, J., Goto, K., Lee, J.-S., & James Chih-Hsin Yang. Amivantamab in EGFR Exon 20 Insertion–Mutated Non–Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results from the CHRYSALIS Phase I Study. Journal of Clinical Oncology,2021; 39(30), 3391–3402. https://doi.org/10.1200/jco.21.00662

107] Klausen, U., Nicolai, Jacob Handlos Grauslund, Morten Orebo Holmström, & Mads Hald Andersen. Cancer immune therapy for lymphoid malignancies: recent advances. Seminars in Immunopathology,2018; 41(1), 111–124. https://doi.org/10.1007/s00281-018-0696-7

108] Thakur, A., Huang, M., & Lum, L. G. Bispecific antibody-based therapeutics: Strengths and challenges. Blood Reviews, 2018;32(4), 339–347. https://doi.org/10.1016/j.blre.2018.02.004

109] Dang, K., Castello, G., Clarke, S., Li, Y., Aarti Balasubramani, Boudreau, A., Davison, L., Harris, K. E., Pham, D., Sankaran, P., Harshad Ugamraj, Deng, R., Kwek, S. S., Starzinski, A., Iyer, S., Wim van Schooten, Schellenberger, U., Sun, W., Trinklein, N. D., & Buelow, R. Attenuating CD3 affinity in a PSMAxCD3 bispecific antibody enables killing of prostate tumor cells with reduced cytokine release. Journal for ImmunoTherapy of Cancer,2021; 9(6), e002488–e002488. https://doi.org/10.1136/jitc-2021-002488

110] Gedeon, P. C., Schaller, T., Chitneni, S. K., Choi, B. D., Kuan, C.-T., Suryadevara, C. M., Snyder, D. J., Schmittling, R. J., Szafranski, S. E., Cui, X., Healy, P., Herndon, J. E., McLendon, R. E., Keir, S. T., Archer, G. E., Reap, E. A., Sánchez-Pérez, L., Bigner, D. D., & Sampson, J. H. A Rationally Designed Fully Human EGFRvIII:CD3-Targeted Bispecific Antibody Redirects Human T Cells to Treat Patient-derived Intracerebral Malignant Glioma. Clinical Cancer Research,2018; 24(15), 3611–3631. https://doi.org/10.1158/1078-0432.ccr-17-0126

111] Pyzik, M., Knudsen, M., Hubbard, J. J., Jan Terje Andersen, Sandlie, I., & Blumberg, R. S. The Neonatal Fc Receptor (FcRn): A Misnomer? Frontiers in Immunology,2019; 10. https://doi.org/10.3389/fimmu.2019.01540

112] Avidity-based binding to HER2 results in selective killing of HER2-overexpressing cells by anti-HER2/CD3. Science Translational Medicine.2018. https://www.science.org/doi/abs/10.1126/scitranslmed.aat5775

113] Sun, Y., Yu, X., Wang, X., Yuan, K., Wang, G., Hu, L., Zhang, G., Pei, W., Wang, L., Sun, C., & Yang, P. Bispecific antibodies in cancer therapy: Target selection and regulatory requirements. Acta Pharmaceutica Sinica B,2023; 13(9), 3583–3597. https://doi.org/10.1016/j.apsb.2023.05.023

114] Chen, S., Li, J., Li, Q., & Wang, Z. Bispecific antibodies in cancer immunotherapy. Human Vaccines & Immunotherapeutics,2016; 12(10), 2491–2500. https://doi.org/10.1080/21645515.2016.1187802

115] Salvaris, R., Ong, J., & Gregory, G. P. Bispecific Antibodies: A Review of Development, Clinical Efficacy and Toxicity in B-Cell Lymphomas. Journal of Personalized Medicine, 2021;11(5), 355–355. https://doi.org/10.3390/jpm11050355

116] Pauken, K. E., Dougan, M., Rose, N. R., Lichtman, A. H., & Sharpe, A. H. Adverse Events Following Cancer Immunotherapy: Obstacles and Opportunities. Trends in Immunology,2019; 40(6), 511–523. https://doi.org/10.1016/j.it.2019.04.002

117] Kobold, S., Stanislav Pantelyushin, Rataj, F., & Johannes vom Berg. Rationale for Combining Bispecific T Cell Activating Antibodies with Checkpoint Blockade for Cancer Therapy. Frontiers in Oncology,2018; 8. https://doi.org/10.3389/fonc.2018.00285

118] Chang, C.-H., Wang, Y., Li, R., Rossi, D. L., Liu, D., Rossi, E. A., Cardillo, T. M., & Goldenberg, D. M. Combination Therapy with Bispecific Antibodies and PD-1 Blockade Enhances the Antitumor Potency of T Cells. Cancer Research,2017; 77(19), 5384 –5394. https://doi.org/10.1158/0008-5472.can-16-3431

119] Raje, N., Andrzej Jakubowiak, Gasparetto, C., Cornell, R. F., Krupka, H. I., Navarro, D., Forgie, A., Chandrasekhar Udata, Basu, C., Chou, J., Abraham C.F. Leung, & Lesokhin, A. M. Safety, Clinical Activity, Pharmacokinetics, and Pharmacodynamics from a Phase I Study of PF-06863135, a B-Cell Maturation Antigen (BCMA)-CD3 Bispecific Antibody, in Patients with Relapsed/Refractory Multiple Myeloma (RRMM). Blood, 134(Supplement_1),2019;1869–1869. https://doi.org/10.1182/blood-2019-121805

120] Goebeler, M.-E., Knop, S., Viardot, A., Kufer, P., Topp, M. S., Einsele, H., Noppeney, R., Hess, G., Kallert, S., Mackensen, A., Rupertus, K., Kanz, L., Libicher, M., Nagorsen, D., Zugmaier, G., Klinger, M., Wolf, A., Dorsch, B., Quednau, B. D., & Schmidt, M. Bispecific T-Cell Engager (BiTE) Antibody Construct Blinatumomab for the Treatment of Patients with Relapsed/Refractory Non-Hodgkin Lymphoma: Final Results from a Phase I Study. Journal of Clinical Oncology, 2016; 34(10), 1104–1111. https://doi.org/10.1200/jco.2014.59.1586

121] DiLillo, D. J., Olson, K. E., Katja Mohrs, T. Craig Meagher, Bray, K., Sineshchekova, O., Startz, T., Retter, M. W., Godin, S., Delfino, F. J., Lin, J., Smith, E., Thurston, O. G., & Kirshner, J. R. REGN5458, a Bispecific BCMAxCD3 T Cell Engaging Antibody, Demonstrates Robust In Vitro and In Vivo Anti-Tumor Efficacy in Multiple Myeloma Models, Comparable to That of BCMA CAR T Cells. Blood, 2018;132(Supplement 1), 1944–1944. https://doi.org/10.1182/blood-2018-99-112500

122] Fayette, J., Wirth, L. J., Oprean, C., Anghel Adrian Udrea, Jimeno, A., Rischin, D., Nutting, C. M., Harari, P. M., Tibor Csőszi, Cernea, D., Paul Edmond O'Brien, Hanley, W. D., Kapp, A. V., Anderson, M., Penuel, E., McCall, B., Pirzkall, A., & Vermorken, J. B. Randomized Phase II Study of Duligotuzumab (MEHD7945A) vs. Cetuximab in Squamous Cell Carcinoma of the Head and Neck (MEHGAN Study). Frontiers in Oncology,2016; 6. https://doi.org/10.3389/fonc.2016.00232

123] Assi, R., Kantarjian, H. M., Short, N. J., Takahashi, K., García-Manero, G., DiNardo, C. D., Burger, J. A., Cortes, J., Jain, N., Wierda, W. G., Chamoun, S., & Konopleva, M. Safety and Efficacy of Blinatumomab in Combination With a Tyrosine Kinase Inhibitor for the Treatment of Relapsed Philadelphia Chromosome-positive Leukemia. Clinical Lymphoma, Myeloma & Leukemia,2017; 17(12), 897–901. https://doi.org/10.1016/j.clml.2017.08.101

124] Fayette, J., Wirth, L. J., Oprean, C., Anghel Adrian Udrea, Jimeno, A., Rischin, D., Nutting, C. M., Harari, P. M., Tibor Csőszi, Cernea, D., Paul Edmond O'Brien, Hanley, W. D., Kapp, A. V., Anderson, M., Penuel, E., McCall, B., Pirzkall, A., & Vermorken, J. B. Randomized Phase II Study of Duligotuzumab (MEHD7945A) vs. Cetuximab in Squamous Cell Carcinoma of the Head and Neck (MEHGAN Study). Frontiers in Oncology,2016; 6. https://doi.org/10.3389/fonc.2016.00232

125] Schuster, S. J. Bispecific antibodies for the treatment of lymphomas: Promises and challenges. Hematological Oncology,2021; 39(S1), 113–116. https://doi.org/10.1002/hon.2858

126] Wang, S., Chen, K., Lei, Q., Ma, P., Yuan, A. Q., Zhao, Y., Jiang, Y., Hong, F., Xing, S., Fang, Y., Jiang, N., Miao, H., Zhang, M., Sun, S., Yu, Z., Tao, W., Zhu, Q., Nie, Y., & Li, N. The state of the art of bispecific antibodies for treating human malignancies. EMBO Molecular Medicine, 2021;13(9). https://doi.org/10.15252/emmm.202114291

127] Carter, P. J., & Lazar, G. A. Next generation antibody drugs: pursuit of the "high-hanging fruit." Nature Reviews Drug Discovery,2017; 17(3), 197–223. https://doi.org/10.1038/nrd.2017.227

128] Seftel, M. D. (2020). Hyper-CVAD: a regimen for all seasons. The Lancet Haematology. https://doi.org/10.1016/s2352-3026(20)30179-4

129] Guillaume Richard-Carpentier, Kantarjian, H. M., Short, N. J., Farhad Ravandi, Ferrajoli, A., Schroeder, H., García-Manero, G., Guillermo Montalbán Bravo, Cortés, J. E., Kwari, M., Loiselle, C., Garris, R., Volter, N., Jain, N., Konopleva, M., Takahashi, K., Sasaki, K., Wierda, W. G., & Jabbour, E. Updated Results from the Phase II Study of Hyper-CVAD in Sequential Combination with Blinatumomab in Newly Diagnosed Adults with B-Cell Acute Lymphoblastic Leukemia (B-ALL). Blood,2019; 134(Supplement_1), 3807–3807. https://doi.org/10.1182/blood-2019-129657

130] Ruella, M., & June, C. H. Chimeric Antigen Receptor T cells for B Cell Neoplasms: Choose the Right CAR for You. Current Hematologic Malignancy Reports, 2016; 11(5), 368–384. https://doi.org/10.1007/s11899-016-0336-z

131] Salles, G., Schuster, S. J., Sven de Vos, Wagner-Johnston, N. D., Viardot, A., Blum, K. A., Flowers, C. R., Jurczak, W., Flinn, I. W., Kahl, B. S., Martin, P., Kim, Y.-H., Sanatan Shreay, Matthias Georg Will, Sorensen, B., Madlaina Breuleux, Pier Luigi Zinzani, & Gopal, A. K. Efficacy and safety of idelalisib in patients with relapsed, rituximab- and alkylating agent-refractory follicular lymphoma: a subgroup analysis of a phase 2 study. Haematologica,2016; 102(4), e156–e159. https://doi.org/10.3324/haematol.2016.151738

132] HIGHLIGHTS OF PRESCRIBING INFORMATION. (n.d.). https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209936s000lbl.pdf

133] Kochenderfer, J. N., Somerville, R., Lu, T., James Chih-Hsin Yang, Sherry, R. M., Feldman, S. A., McIntyre, L., Bot, A., Rossi, J. M., Lam, N., & Rosenberg, S. A. Long-Duration Complete Remissions of Diffuse Large B Cell Lymphoma after Anti-CD19 Chimeric Antigen Receptor T Cell Therapy. Molecular Therapy,2017; 25(10), 2245–2253. https://doi.org/10.1016/j.ymthe.2017.07.004

134] Kochenderfer, J. N., Somerville, R., Lu, T., Shi, V., Bot, A., Rossi, J. M., Xue, A., Goff, S. L., James Chih-Hsin Yang, Sherry, R. M., Klebanoff, C. A., Kammula, U. S., Sherman, M., Perez, A., Yuan, C., Feldman, T., Friedberg, J. W., Roschewski, M., Feldman, S. A., & McIntyre, L. Lymphoma Remissions Caused by Anti-CD19 Chimeric Antigen Receptor T Cells Are Associated With High Serum Interleukin-15 Levels. Journal of Clinical Oncology, 2017;35(16), 1803–1813. https://doi.org/10.1200/jco.2016.71.3024

135] Immunotherapy of non-Hodgkin's lymphoma with a defined ratio of CD8+ and CD4+ CD19-specific chimeric antigen receptor–modified T cells. Science Translational Medicine.2016. https://www.science.org/doi/abs/10.1126/scitranslmed.aaf8621

136] Locke, F. L., Neelapu, S. S., Bartlett, N. L., Siddiqi, T., Chávez, J. C., Chitra Hosing, Armin Ghobadi, Budde, L. E., Bot, A., Rossi, J. M., Jiang, Y., Xue, A., Elias, M., Aycock, J., Wiezorek, J., & Go, W. Y. Phase 1 Results of ZUMA-1: A Multicenter Study of KTE-C19 Anti-CD19 CAR T Cell Therapy in Refractory Aggressive Lymphoma. Molecular Therapy,2017; 25(1), 285–295. https://doi.org/10.1016/j.ymthe.2016.10.020

137] Outcomes in refractory aggressive diffuse large b-cell lymphoma (DLBCL): Results from the internationalSCHOLAR-1study. Journal of Clinical Oncology.2016 https://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.7516

138] HIGHLIGHTS OF PRESCRIBING INFORMATION. (n.d.). https://www.pi.amgen.com/-/media/Project/Amgen/Repository/pi-amgen-com/blincyto/blincyto_pi_hcp_english.pdf

139] Office. FDA expands approval of Blincyto for treatment of a type of leukemia in patients who have a certain risk factor for relapse. U.S. Food and Drug Administration. 2020.https://www.fda.gov/news-events/press-announcements/fda-expands-approval-blincyto-treatment-type-leukemia-patients-who-have-certain-risk-factor-relapse

140] Zuch, C. L., Fajardo, F., Zhong, W., Bernett, M. J., Muchhal, U. S., Moore, G. L., Stevens, J., Case, R., Pearson, J. T., Liu, S., McElroy, P., Canon, J., Desjarlais, J. R., Coxon, A., Mercedesz Balázs, & Olivier Nolan-Stevaux. Targeting Multiple Myeloma with AMG 424, a Novel Anti-CD38/CD3 Bispecific T-cell–recruiting Antibody Optimized for Cytotoxicity and Cytokine Release. Clinical Cancer Research, 2019;25(13), 3921–3933. https://doi.org/10.1158/1078-0432.ccr-18-2752

141] Shah, N., Chari, A., Scott, E. C., Khalid Mezzi, & Usmani, S. Z. B-cell maturation antigen (BCMA) in multiple myeloma: rationale for targeting and current therapeutic approaches. Leukemia,2020; 34(4), 985–1005. https://doi.org/10.1038/s41375-020-0734-z

142] Jacoby, E., Bielorai, B., Avigdor, A., Orit Itzhaki, Hutt, D., Vered Nussboim, Meir, A., Adva Kubi, Levy, M., Dragoslav Zikich, Li at Zeltzer, Brezinger, K., Schachter, J., Nagler, A., Besser, M. J., & Toren, A. Locally produced CD19 CAR T cells leading to clinical remissions in medullary and extramedullary relapsed acute lymphoblastic leukemia. American Journal of Hematology,2018; 93(12), 1485–1492. https://doi.org/10.1002/ajh.25274

143] Anti–B-Cell Maturation Antigen BiTE Molecule AMG 420 Induces Responses in Multiple Myeloma | Journal of Clinical Oncology. 2020. https://ascopubs.org/doi/10.1200/JCO.19.02657

144] Zhao, W., Liu, J., Wang, B., Chen, Y., Cao, X., Yang, Y., Zhang, Y., Wang, F., Zhang, P., Lei, B., Gu, L., Wang, J., Yang, N., Zhang, R., Zhang, H., Shen, Y., Bai, J., Yang, X., Wang, X., & Zhang, R. A phase 1, open-label study of LCAR-B38M, a chimeric antigen receptor T cell therapy directed against B cell maturation antigen, in patients with relapsed or refractory multiple myeloma. Journal of Hematology & Oncology, 2018;11(1). https://doi.org/10.1186/s13045-018-0681-6

145] Raje, N., Berdeja, J. G., Lin, Y., Siegel, D. S., Jagannath, S., Deepu Madduri, Liedtke, M., Rosenblatt, J., Maus, M. V., Turka, A., Lyh Ping Lam, Morgan, R. A., Friedman, K. M., Massaro, M., Wang, J., Russotti, G., Yang, Z., Campbell, T. B., Hege, K., & Fabio Petrocca. Anti-BCMA CAR T-Cell Therapy bb2121 in Relapsed or Refractory Multiple Myeloma. The New England Journal of Medicine, 2019;380(18), 1726–1737. https://doi.org/10.1056/nejmoa1817226

146] Xu, J., Chen, L., Yang, S., Sun, Y., Wu, W., Liu, Y., Xu, J., Zhuang, Y., Wu, Z., Weng, X., Wu, J., Wang, Y., Wang, J., Yan, H., Xu, W., Jiang, H., Du, J., Ding, X., Li, B., & Li, J. Exploratory trial of a biepitopic CAR T-targeting B cell maturation antigen in relapsed/refractory multiple myeloma. Proceedings of the National Academy of Sciences of the United States of America,2019; 116(19), 9543–9551. https://doi.org/10.1073/pnas.1819745116

147] Topp, M. S., Stelljes, M., Gerhard Zugmaier, Barnette, P., Heffner, L. T., Trippett, T. M., Duell, J., Bargou, R. C., Holland, C. P., Benjamin, J., Klinger, M., & Litzow, M. R. Blinatumomab retreatment after relapse in patients with relapsed/refractory B-precursor acute lymphoblastic leukemia. Leukemia, 2017;32(2), 562–565. https://doi.org/10.1038/leu.2017.306

148] Middelburg, J., Kemper, K., Engelberts, P. J., Labrijn, A. F., Schuurman, J., & Thorbald van Hall. Overcoming Challenges for CD3-Bispecific Antibody Therapy in Solid Tumors. Cancers, 2021;13(2), 287–287. https://doi.org/10.3390/cancers13020287

149] Franquiz, M., & Short, N. J. Blinatumomab for the Treatment of Adult B-Cell Acute Lymphoblastic Leukemia: Toward a New Era of Targeted Immunotherapy. Biologics: Targets & Therapy, Volume 2020;14, 23–34. https://doi.org/10.2147/btt.s202746

150] Uy, G. L., Ibrahim Aldoss, Foster, M. C., Sayre, P. H., Wieduwilt, M. J., Advani, A. S., Godwin, J., Arellano, M., Sweet, K., Emadi, A., Farhad Ravandi, Erba, H. P., Byrne, M., Michaelis, L. C., Topp, M. S., Vey, N., Fabio Ciceri, Matteo Giovanni Carrabba, Paolini, S., & Huls, G. Flotetuzumab as salvage immunotherapy for refractory acute myeloid leukemia. Blood,2021; 137(6), 751–762. https://doi.org/10.1182/blood.2020007732

151] Epcoritamab (GEN3013; DuoBody-CD3×CD20) to induce complete response in patients with relapsed/refractory B-cell non-Hodgkin lymphoma (B-NHL): Complete dose escalation data and efficacy results from a phase I/II trial. Journal of Clinical Oncology.2020. https://ascopubs.org/doi/10.1200/JCO.2020.38.15_suppl.8009

152] Rajat Bannerji, Allan, J. N., Arnason, J., Brown, J. R., Advani, R. H., Barnes, J. A., Ansell, S. M., O'Brien, S., Chávez, J. C., Duell, J., David, K. A., Martin, P., Joyce, R., Charnas, R. L., Ambati, S. R., Lieve Adriaens, Ufkin, M., Zhu, M., Li, J., & Gasparini, P. Clinical Activity of REGN1979, a Bispecific Human, Anti-CD20 x Anti-CD3 Antibody, in Patients with Relapsed/Refractory (R/R) B-Cell Non-Hodgkin Lymphoma (B-NHL). Blood,2019; 134(Supplement_1), 762–762. https://doi.org/10.1182/blood-2019-122451

153] Schuster, S. J., Bartlett, N. L., Sarit Assouline, Sung Soo Yoon, Bosch, F., Sehn, L. H., Cheah, C. Y., Shadman, M., Gregory, G. P., Ku, M., Wei, M. C., Yin, S., Kwan, A., Yousefi, K., Hernandez, G., Chi Chung Li, O'Hear, C., & Budde, L. E. Mosunetuzumab Induces Complete Remissions in Poor Prognosis Non-Hodgkin Lymphoma Patients, Including Those Who Are Resistant to or Relapsing After Chimeric Antigen Receptor T-Cell (CAR-T) Therapies, and Is Active in Treatment through Multiple Lines. Blood, 2019;134(Supplement_1), 6–6. https://doi.org/10.1182/blood-2019-123742

154] Faroogh Marofi, Roza Motavalli, Сафонов, В. А., Lakshmi Thangavelu, Alexei Valerievich Yumashev, Марков, А. В., Navid Shomali, Max Stanley Chartrand, Pathak, Y., Mostafa Jarahian, Izadi, S., Hassanzadeh, A., Naghmeh Shirafkan, Safa Tahmasebi, & Farhad Motavalli Khiavi. CAR T cells in solid tumors: challenges and opportunities. Stem Cell Research & Therapy, 2021;12(1). https://doi.org/10.1186/s13287-020-02128-1

155] Murad, J. P., Kozłowska, A., Hee Jun Lee, Ramamurthy, M., Chang, W.-C., Yazaki, P. J., Colcher, D., Shively, J. E., Cristea, M., Forman, S. J., & Priceman, S. J. Effective Targeting of TAG72+ Peritoneal Ovarian Tumors via Regional Delivery of CAR-Engineered T Cells. Frontiers in Immunology, 2018;9. https://doi.org/10.3389/fimmu.2018.02268

156] Chien Fu Hung, Xu, X., Li, L., Ma, Y., Qiu, J., Viley, A., Allen, C., Natarajan, P., Rama Shivakumar, Peshwa, M. V., & Emens, L. A. Development of Anti-Human Mesothelin-Targeted Chimeric Antigen Receptor Messenger RNA–Transfected Peripheral Blood Lymphocytes for Ovarian Cancer Therapy. Human Gene Therapy,2018; 29(5), 614–625. https://doi.org/10.1089/hum.2017.080

157] Zuo, S., Wen, Y., Hean Panha, Dai, G., Wang, L., Ren, X., & Fu, K. Modification of cytokine-induced killer cells with folate receptor alpha (FRα)-specific chimeric antigen receptors enhances their antitumor immunity toward FRα-positive ovarian cancers. Molecular Immunology,2017; 85, 293–304. https://doi.org/10.1016/j.molimm.2017.03.017

158] Zuo, B., Yan, B., Zheng, G., Xi, W., Zhang, X., Yang, A., & Jia, L. Targeting and suppression of HER3-positive breast cancer by T lymphocytes expressing a heregulin chimeric antigen receptor. Cancer Immunology, Immunotherapy, 2017;67(3), 393–401. https://doi.org/10.1007/s00262-017-2089-5

159] Rusheni Munisvaradass, Kumar, S., Chandramohan Govindasamy, Al-Numair, K. S., & Pooi Ling Mok. Human CD3+ T-Cells with the Anti-ERBB2 Chimeric Antigen Receptor Exhibit Efficient Targeting and Induce Apoptosis in ERBB2 Overexpressing Breast Cancer Cells. International Journal of Molecular Sciences, 2017;18(9), 1797–1797. https://doi.org/10.3390/ijms18091797

160] Shao, W., Asimujiang Abula, Ding Qianghong, & Wang, W. Chimeric cytokine receptor enhancing PSMA-CAR-T cell-mediated prostate cancer regression. Cancer Biology & Therapy,2020; 21(6), 570–580. https://doi.org/10.1080/15384047.2020.1739952

161] Junghans, R. P., Ma, Q., Rathore, R., Gomes, E. M., Bais, A. J., Lo, A. S., Abedi, M., Davies, R., Cabral, H., A. Samer Al-Homsi, & Cohen, S. Phase I Trial of Anti-PSMA Designer CAR-T Cells in Prostate Cancer: Possible Role for Interacting Interleukin 2-T Cell Pharmacodynamics as a Determinant of Clinical Response. The Prostate,2016; 76(14), 1257–1270. https://doi.org/10.1002/pros.23214

162] Bagley, S., & O'Rourke, D. M. Clinical investigation of CAR T cells for solid tumors: Lessons learned and future directions. Pharmacology & Therapeutics,2020; 205, 107419–107419. https://doi.org/10.1016/j.pharmthera.2019.107419

163] Bui. Carbonic anhydrase IX is an independent predictor of survival in advanced renal clear cell carcinoma: implications for prognosis and therapy. Clinical Cancer Research: An Official Journal of the American Association for Cancer Research,2023; 9(2). https://pubmed.ncbi.nlm.nih.gov/12576453/

164] Li, J., Li, W., Huang, K., Zhang, Y., Kupfer, G. M., & Zhao, Q. Chimeric antigen receptor T cell (CAR-T) immunotherapy for solid tumors: lessons learned and strategies for moving forward. Journal of Hematology & Oncology,2018; 11(1). https://doi.org/10.1186/s13045-018-0568-6

165] Zhao, W., Jia, L., Zhang, M., Huang, X., Qian, P., Tang, Q., Zhu, J., & Feng, Z. The killing effect of novel bi-specific Trop2/PD-L1 CAR-T cell targeted gastric cancer. American Journal of Cancer Research, 2019;9(8), 1846–1856. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6726977/

166] Jiang, H., Shi, Z., Wang, P., Wang, C., Yang, L., Du, G., Zhang, H., Shi, B., Jia, J., Li, Q.-X., Wang, H., & Li, Z. Claudin18.2-Specific Chimeric Antigen Receptor Engineered T Cells for the Treatment of Gastric Cancer. Journal of the National Cancer Institute,2018; 111(4), 409–418. https://doi.org/10.1093/jnci/djy134

167] Tao, K., He, M., Feng, T., Xu, G., Ye, M., Zheng, Y., & Li, Y. Development of NKG2D-based chimeric antigen receptor-T cells for gastric cancer treatment. Cancer Chemotherapy and Pharmacology,2018; 82(5), 815–827. https://doi.org/10.1007/s00280-018-3670-0

168] Deok Soo Ahn, Lee, H., Hwang, J., Han, H., Kim, B., & Shim, B.-S. Lambertianic Acid Sensitizes Non-Small Cell Lung Cancers to TRAIL-Induced Apoptosis via Inhibition of XIAP/NF-κB and Activation of Caspases and Death Receptor 4. International Journal of Molecular Sciences,2018; 19(5), 1476–1476. https://doi.org/10.3390/ijms19051476

169] Song, Y., Tong, C., Wang, Y., Gao, Y., Dai, H., Guo, Y., Zhao, X., Wang, Y., Wang, Z., Han, W., & Chen, L. Effective and persistent antitumor activity of HER2-directed CAR-T cells against gastric cancer cells in vitro and xenotransplanted tumors in vivo. Protein & Cell, 2017;9(10), 867–878. https://doi.org/10.1007/s13238-017-0384-8

170] Jung, M., Yang, Y., McCloskey, J. E., Zaman, M., Yogindra Vedvyas, Zhang, X., Dessislava Stefanova, Gray, K. D., Min, I. M., Reza Zarnegar, Yoon Young Choi, Cheong, J., Sung Hoon Noh, Sun Young Rha, Hyun Cheol Chung, & Jin, M. M. Chimeric Antigen Receptor T Cell Therapy Targeting ICAM-1 in Gastric Cancer. Molecular Therapy - Oncolytics,2020; 18, 587–601. https://doi.org/10.1016/j.omto.2020.08.009

171] Whilding, L. M., Halim, L., Draper, B., Parente-Pereira, A. C., Zabinski, T., Davies, D., & Maher, J. CAR T-Cells Targeting the Integrin αvβ6 and Co-Expressing the Chemokine Receptor CXCR2 Demonstrate Enhanced Homing and Efficacy against Several Solid Malignancies. Cancers, 2019;11(5), 674–674. https://doi.org/10.3390/cancers11050674

172] Chen, C., Li, K., Jiang, H., Song, F., Gao, H., Pan, X., Shi, B., Bi, Y., Wang, H., Wang, H., & Li, Z. Development of T cells carrying two complementary chimeric antigen receptors against glypican-3 and asialoglycoprotein receptor 1 for the treatment of hepatocellular carcinoma. Cancer Immunology, Immunotherapy,2016; 66(4), 475–489. https://doi.org/10.1007/s00262-016-1949-8

173] Yang, C., E Changyong, Gong, Z., Shui, L., Wang, Z., Yang, Y., & Zhang, X. Chimeric antigen receptor-engineered T-cell therapy for liver cancer. Hepatobiliary & Pancreatic Diseases International,2018; 17(4), 301–309. https://doi.org/10.1016/j.hbpd.2018.05.005

174] Xia, A., Wang, X., Lu, Y., Lu, X., & Sun, B. Chimeric-antigen receptor T (CAR-T) cell therapy for solid tumors: challenges and opportunities. Oncotarget,2017; 8(52), 90521–90531. https://doi.org/10.18632/oncotarget.19361

175] Khan, A., Chowdhury, A., Atharva Karulkar, Ankesh Kumar Jaiswal, Banik, A., Sweety Asija, & Rahul Purwar. Immunogenicity of CAR-T Cell Therapeutics: Evidence, Mechanism and Mitigation. Frontiers in Immunology,2022; 13. https://doi.org/10.3389/fimmu.2022.886546

176] Hege, K., Bergsland, E. K., Fisher, G. A., Nemunaitis, J., Warren, R. S., McArthur, J. G., Lin, A., Schlom, J., June, C. H., & Sherwin, S. A. Safety, tumor trafficking and immunogenicity of chimeric antigen receptor (CAR)-T cells specific for TAG-72 in colorectal cancer. Journal for ImmunoTherapy of Cancer,2017; 5(1). https://doi.org/10.1186/s40425-017-0222-9

177] Wang, Z., Wu, Z., Liu, Y., & Han, W. New development in CAR-T cell therapy. Journal of Hematology & Oncology,2017; 10(1). https://doi.org/10.1186/s13045-017-0423-1

178] Zhou, Y., Hweixian Leong Penny, Kroenke, M. A., Bautista, B. L., Hainline, K., Chea, L. S., Parnes, J. R., & Mytych, D. T. Immunogenicity assessment of bispecific antibody-based immunotherapy in oncology. Journal for ImmunoTherapy of Cancer, 2022;10(4), e004225–e004225. https://doi.org/10.1136/jitc-2021-004225

179] Markouli, M., Ullah, F., Serhan Ünlü, Omar, N., Nerea Lopetegui-Lia, Duco, M., Anwer, F., Raza, S., & Dima, D. Toxicity Profile of Chimeric Antigen Receptor T-Cell and Bispecific Antibody Therapies in Multiple Myeloma: Pathogenesis, Prevention and Management. Current Oncology,2023; 30(7), 6330–6352. https://doi.org/10.3390/curroncol30070467

180] Charrot, S., & Hallam, S. CAR-T Cells: Future Perspectives. HemaSphere, 3(2), e188–e188. https://doi.org/10.1097/hs9.0000000000000188Underwood, D., Bettencourt, J., & Jawad, Z. (2022). The manufacturing considerations of bispecific antibodies. Expert Opinion on Biological Therapy,2019; 22(8), 1043–1065. https://doi.org/10.1080/14712598.2022.2095900