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Abstract

Chimeric antigen receptors (CARs) are synthetic engineered receptors with an antigen recognition domain derived from a high-specificity monoclonal antibody that can target surface molecules on tumor cells. T cells are genetically engineered to express CARs, thereby harnessing the antigen-recognition ability of antibodies and effector function of T cells. Target surface molecule selection is crucial for manufacturing CARs. Ideally, a target surface molecule should be restricted to tumor cells and minimally expressed or absent on normal tissues. Different CD19-targeted CAR-T cell therapies have been approved for the treatment of B-cell lymphoid malignancies that are refractory to other therapies, including indolent and aggressive B-cell non-Hodgkin lymphomas (NHL) and B-cell acute lymphoblastic leukemia (B-ALL). Despite impressive results, many patients with aggressive and refractory B-cell malignancies do not respond to or relapse after CD19 CAR-T cell therapies. Thus, several additional strategies are currently being evaluated to overcome these limitations. This review discusses studies on other promising CAR-T cell targets, including CD20, CD22, BAFF-R, ROR1, CD70, BCR complex, kappa/lambda light chains, multitargeted CAR-T cells, and combinations of CAR-T cell therapy with different drugs.

Keywords: Chimeric antigen receptor T-cell therapy, CD19, Targets beyond CD19

1. Introduction

The 5-year relative survival outcomes for B-cell malignancies have improved over the past 60 years, although such improvements depend on the subtype [1]. During that time, the field expanded owing to better targeted therapies and an improved understanding of the inherent functions of the immune system. This knowledge revolution introduced a wide array of new clinical therapies, including oncolytic viruses, immune modulators, monoclonal antibodies (mAbs), immune checkpoint inhibitors (ICIs), and chimeric antigen receptor T-cell therapy (CAR-T cell).

Chimeric antigen receptors (CARs) are synthetic engineered receptors with an antigen recognition

domain derived from a high-specificity monoclonal antibody that can target surface molecules on tumor cells [2]. T cells are genetically engineered to express CARs, thereby harnessing the antigen-recognition ability of antibodies and effector function of T cells [3]. The interaction between CAR-T cells and their targets leads to the formation of immune synapses that induce contact-dependent cytotoxicity [4].

Target surface molecule selection is a crucial determinant for the development of CARs. Ideally, a target surface molecule should be restricted to tumor cells at sufficient concentrations to induce an antigen-specific activation of T cells, minimally expressed or absent on normal tissues, and expressed at the stage of the B-cell lifecycle in a specific B-cell malignancy [5]. Several surface

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markers have been identified, including CD19, CD20, and CD22, among which CD19 has the broadest surface expression, followed by CD20 and CD22.

2. CD19

CD19 is a 95 kDa transmembrane glycoprotein encoded by the *cd19* gene located on the short arm of chromosome 16 [6]. The surface expression of CD19 is initially observed in the early B-cell progenitor fraction around the same time as immunoglobulin rearrangement occurs [7]. It is highly regulated and expressed throughout B-cell development and maturation until its expression is lost at the plasma cell differentiation stage [7]. CD19 is a co-receptor protein that functions to augment signals by the pre-BCR/BCR (B-cell receptor), and as a result, it can modulate B-cell fate at multiple stages of development [7]. It is one of the most reliable diagnostic surface markers for B-cell malignancies, and it is ubiquitously expressed on nearly all malignancies of B-cell origin, including 80% of B-cell precursor acute lymphoblastic leukemia (B-ALL) and 88% of B-cell lymphomas [8]. These properties make it a unique surface molecular target for treating B-cell malignancies. Nonetheless, CD19 is also expressed on non-malignant B lymphocytes. Hence, CD19-targeted therapy can result in B-cell aplasia, which may require immunoglobulin support and antimicrobial prophylaxis [5].

Several studies assessed the use of CD19 CAR-T cell for the treatment of B-cell malignancies, including indolent and aggressive B-cell non-Hodgkin lymphoma (NHL) and B-ALL.

2.1. CD19-targeted CAR T-cell for the treatment of indolent and aggressive B-cell NHL

As of mid-2022, four CD19 CAR T-cell products have been approved for the treatment of indolent and/or aggressive B-cell NHL: axicabtagene ciloleucel (Axi-cel), tisagenlecleucel (Tisa-cel), brexucabtagene autoleucel (Brexu-cel), and lisocabtagene maraleucel (Liso-cel). Axi-cel is currently approved for the treatment of relapsed/refractory (R/R) large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL), high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (FL) after two or more lines of systemic therapy based on the results of the ZUMA-1 trial; primary refractory or LBCL relapsing within 12 months of first-line therapy based on the results of the ZUMA-7 trial; and R/R

FL after two or more lines of systemic therapy based on the results of the ZUMA-5 trial [9–13].

Tisa-cel was approved for the treatment of LBCL in May 2018 based on the JULIET trial and in May 2022 for the treatment of R/R FL based on results of the phase 2 ELARA trial [14–16]. In July 2020, Brexu-cel was approved for the treatment of adult patients with R/R mantle cell lymphoma (MCL) who had been previously treated with a Bruton kinase inhibitor (BTK) based on the ZUMA-2 study [17]. Additionally, lisocabtagene maraleucel was approved in February 2021 for the treatment of adult patients with R/R LBCL after two or more lines of systemic therapy based on the results of the TRANSCEND NHL001 study [18].

2.2. CD19-targeted CAR T-cell for the treatment of R/R B-ALL

In 2017, Tisa-cel was approved for the treatment of pediatric and young adults (up to 25 years of age) with R/R B-ALL based on the results of the ELIANA trial [19]. In 2021, Brexu-cel was also approved for adult patients with R/R B-ALL based on the results of the ZUMA-3 study [12,20].

Despite impressive results from these breakthrough studies, many patients with aggressive and refractory lymphomas still do not respond to aforementioned CD19 CAR-T therapies. This is also the case for patients with B-ALL [20,21]. These therapies introduced a unique class-specific toxicities, including cytokine release syndrome (CRS) and neurotoxicity. Therefore, understanding the mechanism(s) or resistance to various therapies and determining how to manage expected toxicities are essential for developing new treatment strategies. The foremost challenges for CAR T-cell therapy include identifying effective target antigens, determining the impact of the tumor microenvironment, reconciling the lack of tumor-killing ability, and improving CAR-T persistence [22]. One strategy for addressing resistance has been the identification of targets beyond CD19 [5].

3. CD20

CD20 is a 33–37 kDa non-glycosylated phosphoprotein expressed on the surface of mature undifferentiated B-cells [23]. It is encoded by *MS4A1* gene located within a cluster on chromosome 11 [24]. Expression of CD20 begins at the pre-B-cell stage and persists until terminal differentiation into plasma cells [23]. In B-cell malignancies, the level of CD20 expression is variable depending on specific lymphoma subtypes, with the lowest CD20

expression observed in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and the highest expression observed in patients with DLBCL and hairy cell leukemia (HCL) [25]. Anti-CD20 mAbs are integral components of treatment algorithms of several B-cell malignancies, namely rituximab, obinutuzumab, and ofatumumab.

In 2011, *Till et al.* conducted a pilot study with CD20-targeted CAR-T in patients with relapsed indolent B-cell and MCL [26]. In total, 4 patients were enrolled: 3 with R/R MCL and 1 with R/R FL. All patients had received at least two prior lines of therapy, and 2 had a prior autologous hematopoietic stem cell transplantation (auto-HCT). Two patients remained progression-free for 12 and 24 months. The third patient had a partial response (PR) and relapsed 12 months after infusion [26]. In 2014, *Wang et al.* reported outcomes of CD20-targeted CAR-T in patients with chemotherapy-refractory advanced DLBCL [27]. In total, 7 patients were enrolled: 5 had an objective response that lasted over 6 months. In terms of the side effect profile, 1 patient died and 2 had grade 4 gastrointestinal (GI) hemorrhage [27]. In 2016, *Zhang et al.* conducted an early phase II trial with CD20 CAR-T for patients with R/R NHL [28]. Eleven patients were enrolled, and treatment with prior cytotoxic or biologic therapies had to be administered at least 4 weeks before enrollment. The overall response rate (ORR) was 81.8%, with a complete response (CR) rate of 54.5%, and the median progression free survival (PFS) was 6 months. No grade 4 toxicities were observed in this study, although one patient was diagnosed with CRS affecting the lungs [28].

These initial trials evaluated CD20 as a possible target in CAR T-cell therapy. The main limitation of using CD20 as a target is the prior use of anti-CD20 immunotherapy in many B-cell malignancies. A major concern is the downregulation of CD20 after anti-CD20 therapy, which in principle may limit CAR-T efficacy. In 2016, *Rufener et al.* evaluated the activity of CD20 CAR-T in the presence of various concentrations of rituximab *in vivo* and *in vitro* [29]. The study demonstrated that CAR binding sites on CD20+ tumor cells were blocked by rituximab in a dose-dependent manner and showed reduced cytokine secretion and cytotoxicity. In murine models, rituximab did not seem to impair CAR-T activity [29]. The possible effect of other anti-CD20 mAbs on the efficacy of CAR T cells is presently unknown. Interestingly, CD20 has adopted the role of a safety switch in CAR development to capitalize on clearance of the CAR-T with rituximab through complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity [30].

Several ongoing trials are assessing CD20 CAR T-cell therapy in R/R NHL (Table 1). Based on previous investigations, CD20 remains an appealing target antigen for CAR-T therapy. Nonetheless, sustained responses to therapy continue to be limited, and the side effect profile remains a significant concern.

4. CD22

CD22 is a 140 kDa cell surface glycoprotein encoded by *hcd22* gene located on the long arm of chromosome 19 at q13.1 [31]. CD22 is a B-lymphocyte-specific marker that can be seen on pre-B cells. During maturation, CD22 levels increase, with the highest levels described in mature B lymphocytes and a loss of CD22 occurring during terminal differentiation prior to the plasma cell stage [32]. Functional studies in CD22-deficient mice have demonstrated that it is important in downregulating BCR mediated signaling, hypothesized to prevent overstimulation of B cells [33]. It is also involved in signaling through CD40, a critical receptor in B-cell activation, proliferation, and class switching [33]. In a study by *Huang et al.*, up to 70% of the evaluated B-cell lymphoproliferative disorders showed aberrant expression of CD22 [34]. CD22 has been validated as a successful target for B-cell leukemias and lymphomas through recombinant immunotoxin and anti-CD22 therapies [35].

CD22-targeted CAR-T cells have been evaluated for their antileukemic effect against B-ALL *in vitro* and *in vivo* in murine models [36]. In 2018, *Fry et al.* reported the first clinical experience using a CD22 CAR as therapy for B-ALL. In this study, treatment was administered to 21 patients with R/R B-ALL who had all undergone a prior allogeneic hematopoietic stem cell transplantation (allo-HSCT); moreover, 71% had received prior CD19-directed CAR-T [37]. The patients were evaluated at 3-, 6- and 9-months post-infusion. Twelve (57%) patients achieved CR, with three of these patients achieving lasting remission (21 months). Out of 10 patients who had previously received CD19-targeted immunotherapy, 9 achieved a CR, although 8 relapsed within 1.5–12 months following infusion [37]. Relapse was associated with diminished CD22 surface expression. In terms of the side effect profile, 76% had CRS (any grade), although the majority were mild, with only 2 patients experiencing grade 3 CRS [37].

In 2019, *Pan et al.* presented results of CD22 CAR-T in R/R B-ALL [38]. This study included 34 patients, among which 31 (91%) had failed a prior CD19 CAR-T and 13 (38%) patients had a prior allo-HSCT.

Table 1. Ongoing CD20-targeted CAR-T cell therapy trials for B-cell malignancies.

Study type	Indication	CAR-T product	Status	Identifier	Center
Phase I/II	R/R NHL, CLL/SLL	CD20 CAR-T cells	Recruiting	NCT03277729	Fred Hutch/University of Washington Cancer Consortium
Phase I	R/R B-cell Lymphoma	CD20 CAR-T cells	Recruiting	NCT04169932	First Affiliated Hospital with Nanjing Medical University
Phase I	R/R B-cell lymphoma treated with prior CD19 CAR-T therapy	C-CAR066	Unknown	NCT04036019	Shanghai Tongji Hospital, Tongji University School of Medicine
Phase I	R/R DLBCL treated with prior CD19 CAR-T therapy	C-CAR066	Unknown	NCT04316624	Institute of Hematology & Blood Diseases Hospital
Phase I	R/R CD20+ B-cell lymphomas and NHL	MB-CART20.1	Active, not recruiting	NCT03664635	University Hospital of Cologne Universitätsklinikum Leipzig
Phase I	R/R B-cell Lymphomas	CD20 CAR-T cells	Recruiting	NCT03576807	Affiliated Hospital of Xuzhou Medical University
Phase I/II	R/R CD-20 expressing B-cell malignancies after at least one standard chemotherapy and one salvage regimen	CD20 CAR-T cells	Unknown	NCT02710149	Southwest Hospital of Third Military Medical University

Abbreviations: R/R – relapsed or refractory NHL - non-Hodgkin lymphoma, B-ALL – B-cell acute lymphoblastic leukemia, DLBCL – diffuse large B-cell lymphoma, CLL/SLL – Chronic lymphocytic leukemia/small lymphocytic lymphoma.

CD22 expression was measured by flow cytometry, with 30 of 34 patients having CD22+ blasts and 2 having CD22+ extramedullary disease. Thirty patients survived for 30 days or longer, and the CR rate was 70.5% at day 30. Only 11 patients were followed for a longer duration, and they were bridged to allo-HSCT. Of the 11 CR patients, 2 died of transplant-related mortality at 1.5 and 6 months, 1 had a relapse at 1.1 months, and 8 remained in remission at 4.6–13.3 months after allo-HSCT. CRS was reported in 31/34 (96%) patients, with only 2 having grade 3–4 CRS. Grade 2 neurotoxicity was observed in 1 case. Four patients died: 2 died from severe infection, 1 died from severe CRS, and 1 died from veno-occlusive disease [38].

CD22-targeted CAR-T cells are currently being evaluated for the treatment of other R/R B-cell malignancies (Table 2). Preliminary data from phase I/Ib clinical trial (NCT04088890) recruiting patients with R/R LBCL or transformed lymphomas after CD19-targeted CAR-T cell therapy indicate good tolerance and CR in their first 3 patients after a mean follow-up of 7.8 months (range, 6–9.3 months) [39].

Although data are still emerging, similar mechanisms of resistance may occur between CD19-

targeted CAR-T therapy and CD22-targeted CAR T-cell therapy. While the mechanisms(s) remain poorly understood, downregulation of surface antigens after targeted therapy continues to be an area of interest. Some studies have suggested that CD22 protein downregulation after CD22 CAR T-cell therapy may occur at the post-translational level, with different CD22 splice forms being found [40]. Understanding these mechanisms may help elucidate possible combination therapies with CAR-T to reduce the rate of relapse and overcome resistance.

5. Other targets

Although the aforementioned targets have potential usefulness, few antigens truly fulfill the requirements of an effective target surface molecule [22]. One of the major challenges is ensuring safety and limiting “off target” effects. The second major challenge is decreasing early relapse through antigen escape mechanisms. Currently, many other B-cell targets are being evaluated for the treatment of B-cell malignancies [41]. To clarify these findings, we sorted these targets into different subgroups: a. targets for B-cell survival and b. targets for B-cell receptor signaling. B-cell survival targets include B-

Table 2. Ongoing CD22-targeted CAR-T cell therapy trials for B-cell malignancies.

Study type	Indication	CAR-T product	Status	Identifier	Center
Phase I	R/R B-ALL	CD22 CAR-T cells	Recruiting	NCT04546906	Hebei yanda Ludaopei Hospital Beijing Ludaopei Hospital
Phase I	R/R B-ALL	CD22 CAR-T cells	Recruiting	NCT03999697	Anhui Provincial Hospital
Phase I	R/R B-ALL	CD22 CAR-T cells	Recruiting	NCT03825731	Hebei Yanda Ludaopei Hospital
Phase I	R/R B-ALL	CD22 CAR-T cells	Terminated	NCT02588456	Abramson Cancer Center of the University of Pennsylvania
Phase I	CD22+ R/R B-ALL and B-cell malignancies	CD22 CAR-T cells	Recruiting	NCT03262298	Affiliated Hospital to Academy of Military Medical Sciences
Phase I	R/R CD22+ pediatric B-ALL or B-cell lymphoma	CD22 CAR-T cell	Active, not recruiting	NCT03244306	Seattle Children's Hospital
Phase Ib	Pediatric and young adult R/R CD22+ B-cell ALL or lymphoma	CD22 CAR-T cells	Enrolling by invitation	NCT04088864	Stanford University
Phase I/II	Pediatric and Young Adult CD 22+ leukemia or lymphoma	SCRI-CAR22v2	Recruiting	NCT04571138	Children's Hospital Los Angeles Children's National Hospital Riley Hospital for Children Texas Children's Hospital Seattle Children's Hospital
Phase II	R/R pediatric B-ALL	Autologous humanized anti-CD22 chimeric antigen receptor T-cells	Recruiting	NCT04340167	Beijing Boren Hospital
Phase I/II	R/R B-ALL, CLL and NHL	Anti-CD22-CAR-T cells	Not yet recruiting	NCT04163575	Hebei Yanda Ludaopei Hospital
Phase I/Ib	R/R CD22+ B-ALL, aggressive B-cell NHL	CD22 CAR-T cells	Recruiting	NCT04088890	Stanford University
Phase I	R/R B-ALL and R/R B-cell Lymphomas	Third-generation anti-CD22 CAR-T cells	Recruiting	NCT04007978	Union Hospital, Tongji Medical College, Huazhong University of Science and Technology
Phase I/II	R/R CD22+ B-ALL and B-cell lymphomas	CD22-targeted CAR-T cells	Recruiting	NCT02935153	Southwest Hospital of Third Military Medical University
Phase I/II	R/R B-cell malignancies	CD22 CAR-T cells	Recruiting	NCT02794961	Affiliated hospital of Xuzhou medical college
Phase I	R/R NHL after CD19 CAR-T cell therapy	Retroviral vector-transduced CD22 CAR-T cells	Recruiting	NCT02721407	Xinqiao Hospital of Chongqing Xuzhou Medical University
Phase I	R/R CD22+ B-cell Malignancies	CD22 CAR-T cells	Recruiting	NCT02315612	National Institutes of Health Clinical Center

Abbreviations: R/R – relapsed or refractory; NHL - non-Hodgkin lymphoma; B-ALL – B-cell acute lymphoblastic leukemia, DLBCL – diffuse large B-cell lymphoma.

cell activating factor receptor or BAFF-R (B lymphocyte stimulator, BLyS, CD257, TALL-1, or TNFRSF13C); ROR1 (receptor tyrosine kinase-like orphan receptor or neurotrophic tyrosine kinase, receptor-related 1 (NTRKR1)); and CD70 (tumor necrosis factor ligand 8A, CD27L). B-cell receptor signaling candidates include CD79b (Ig-beta, B-cell antigen receptor complex-associated protein beta chain) and Immunoglobulin kappa (κ) light chain.

5.1. B-cell survival targets

5.1.1. BAFF-R-targeted CAR T-cell therapy

BAFF-R is a B-cell marker selectively expressed in mature B cells. BAFF and its receptor BAFF-R modulate signaling cascades critical for B-cell development and survival [42]. Without BAFF-R, a profound reduction in circulating mature B cells occurs. Therefore, it is an attractive surface target since it is more selectively expressed in mature B cells and present on the surface of several different B-cell neoplasms, including FL, DLBCL, MCL, Burkitt lymphoma and CLL [43]. *In vitro* and xenograft studies using BAFF-R-targeted CAR-T in CD19-negative B-ALL and lymphoma cell lines have shown cytotoxicity *in vitro* and tumor eradication *in vivo* [44–46]. Other pre-clinical studies have also evaluated targeting soluble BAFF ligand. BAFF is a soluble protein that binds to 3 receptors on B cells: BAFF-R, B-cell maturation antigen (BCMA), and transmembrane activator and CAML interactor (TACI) [47]. Wong et al. developed a ligand-based CAR and generated BAFF CAR-T cells. Their study demonstrated cytotoxicity of BAFF CAR T cells against MCL, ALL, and multiple myeloma (MM) cells *in vitro* and *in vivo* in xenograft models [47]. Early clinical studies evaluating BAFFR-CAR-T for the treatment of R/R B-ALL are currently underway (NCT04690595).

5.1.2. ROR1-targeted CAR-T cell therapy

ROR1 is a tyrosine kinase that plays a major role in embryonic and cancer development [48]. ROR1 is expressed at high levels in MCL and CLL, and results have indicated that higher ROR1 levels occur with accelerated disease progression and adverse survival prognosis in CLL [49,50]. Jiang et al. showed that increased levels of ROR1 expression occurred in patients with relapsed MCL after CD19 CAR-T cell therapy and effective therapy with anti-ROR1 antibody VLS-101 [50].

ROR1 targeting CAR T cells displayed promising anti-tumor effects in pre-clinical studies against CLL and MCL [51]. However, several other normal tissues also express ROR1, such as B-cell precursors

in the bone marrow, parathyroid cells, pancreatic islet cells, adipocytes, and several areas of the GI tract, albeit at lower levels than in cancer cells [52]. Thus, ROR1-specific CAR T cells may negatively impact the B-cell compartment and have significant on-target off-tumor toxicity. Early clinical studies evaluating ROR-1 CAR-T for treatment of CLL, MCL, ALL, stage IV non-small cell lung cancer (NSCLC), or triple-negative breast cancer (TNBC) (NCT04690595) are underway.

5.2. CD70-targeted CAR-T cell therapy

CD70 is the membrane ligand of CD27, which belongs to the tumor necrosis factor (TNF) family and is essential in regulating lymphocyte growth and differentiation [53]. Expression of CD70 has been reported for DLBCL, MCL, FL, Hodgkin's lymphoma, Waldenström macroglobulinemia, and MM, but rarely for normal B cells or T cells [54]. Dysregulation of the CD70:CD27 axis, specifically the frequent co-expression of CD70 and CD27 in malignancy, identifies it as an attractive new target [55]. In 2021, Deng et al. reported the development of novel CAR T cells against CD70 and their potential anti-tumor effect in CD19-positive and CD19-negative murine models [54]. However, CD70 expression in tumor cells varies amongst tumor types; thus, dual targeting of CD19 and CD70 represents a logical future therapeutic strategy.

5.3. B-cell signaling targets

5.3.1. BCR complex associated proteins

BCR is a transmembrane protein complex that controls B-cell fate and guides cell maturation, survival, anergy, and production of antibodies in plasma B cells [56]. BCR functions in a complex with CD79a and CD79b, and the knockdown of any of these BCR components causes apoptosis in B cells [56]. BCR-associated proteins are an attractive target for CAR-T therapy. In fact, their expression is restricted to the B-cell lineage and is maintained in most subtypes of NHL, including MCL, DLBCL, Burkitt's, and FL [57]. CD79a has been investigated as a prognostic tool in minimal residual disease (MRD) detection in patients with R/R B-ALL who received CD19 CAR T-cell therapy as bridging therapy to allo-HSCT. In this study, 8 patients were found to be MRD-positive by the presence of CD79a. The MRD-positive group had worse post-transplant prognosis compared to the MRD-negative group [58]. Currently, no additional pre-clinical studies have been published describing CD79a CAR-T cell therapy use.

However, targeting CD79b has been explored in patients with R/R NHL and CLL by the antibody–drug conjugate polatuzumab [59]. *Palanca-Wessels* et al. demonstrated an objective response in 14 of 25 patients, of which 12 had primary refractory DLBCL [59]. In 2019, *Ormhøj* et al. developed a novel CAR construct directed against CD79b and demonstrated antigen recognition and cytotoxicity in a MCL cell line and patient-derived xenograft models [57]. There is an ongoing clinical trial (NCT04609241) evaluating the safety of CD79b CAR-T cells in patients with R/R ALL and NHL.

5.3.2. Kappa/lambda light chains

Mature B-cell malignancies arise from post-isotype selected cells expressing one type of light chain. In contrast, non-malignant cells remain polyclonal. Another method to reduce the risk of B-cell aplasia while targeting B-cell receptors is by targeting only the light chain isotype expressed by the clonal malignancy. CAR-T targeting light chains dates back to 2006 when *Vera* et al. described kappa-targeted CAR T cells against kappa positive tumor cell lines [60]. This same group showed the results of phase I clinical trial using kappa-directed CAR T cells in 16 patients with R/R neoplasias (9 with NHL and 7 with MM).

Interestingly, they used limited or no lymphodepleting chemotherapy (12.5 mg/kg cyclophosphamide). Clinical responses were reported in 4 of 9 NHL patients: 2 with CR, 1 with PR, and 1 with stable disease (SD). In terms of the side effect profile, infusion was well tolerated except in 1 patient with MM who developed grade 3 lymphopenia. None of the patients had severe CRS [61]. There is a trial in progress evaluating kappa-targeted CAR-T in various subtypes of NHL (NCT04223765).

Lambda-targeted CAR-T cells were described by *Ranganathan* et al. in 2021 in a pre-clinical setting. They assessed the efficacy of lambda CAR-T cells *in vitro* against patient-derived CLL cells and *in vivo* with a patient-derived xenograft model of MCL. This study reported anti-tumor effects against Ig lambda positive lymphoma cells *in vitro* and *in vivo* while sparing the reciprocal light chain carrying B cells [58]. No current clinical trials are evaluating the safety or efficacy of Ig lambda-directed CAR T cells in B-cell lymphomas.

6. Multitargeted CAR-T

Although single-target CAR-T methods seeking the “optimal” target continue to be developed, antigen escape remains one of the major limitations of these constructs. There are many mechanisms of

CAR T-cell evasion, including receptor genetic mutations, cell lineage changes, epitope masking, or antigen downregulation. As a possible solution, dual and triple targeting strategies have been developed to mitigate immune escape. There are several approaches to creating a multitargeted therapy: generating two or more CAR-T cell populations targeting different antigens and administering them concurrently or sequentially; using a bicistronic vector that encodes two different CARs on the same cell; and encoding two CARs on the same chimeric protein (bi-specific) [62].

In 2013, *Hegde* et al. observed that targeting HER2 in glioblastoma cell lines would result in the emergence of HER2-null tumor cells [63]. They designed a mathematical model that predicted that combinatorial targeting of tumor-associated antigens could overcome this resistance mechanism. Thus, they generated bispecific CARs expressing HER2/IL-13R α 2, which induced an enhanced effector activity *in vitro* and in murine models [63]. Interestingly, their model did not predict an added advantage by targeting a third antigen in the tumor cohort.

Applying this concept to B-cell malignancies, *Zah* et al. designed a bispecific CAR-T targeting CD19 and CD20, demonstrated that bispecific CAR-T was efficacious, and showed that bispecificity did not affect CAR-T cell growth, differentiation, exhaustion profile, or lytic capability *in vitro* [64]. *Tong* et al. in 2020 reported the results of a phase I/IIa trial using bispecific CD19/CD20 CAR-T cells in 28 patients with R/R NHL, including DLBCL, tFL, FL, MCL, CLL/SLL [65]. All patients were CD20+, and 79% had CD19+ tumors by immunohistochemistry (IHC). Most patients had received 3–5 lines of therapy. The ORR was 79%, with 71% achieving CR and 7% a PR. Out of 4 patients with CD19-disease, 2 achieved CR. In the intention-to-treat group, the ORR was 67%, with an estimated 12-month PFS of 59%. In terms of the adverse events, 100% of patients had adverse events, with 50% being grade 3 or 4. Also, 50% of the patients presented with greater than grade 3 neutropenia. Neurologic events occurred in 6 patients, the majority being grade 1 or 2 [65].

Zhou et al. in 2020 reported a phase II trial co-administering CD19 and CD20 CAR T cells with a median of 1.0×10^6 cells/kg for each type of CAR-T cell. Twenty-one patients with R/R DLBCL received CD19 and CD20 CAR-T cell infusion. The ORR was 81%, with 52.4% of the patients achieving a CR. Median PFS and overall survival (OS) were 5 months and 8.1 months, respectively. CRS occurred in 100% of patients, with 6% being grade 3–4. Encephalopathy was observed in 23.8% of patients.

Another possible combination for multitargeted CAR-T is using CD19/CD22 CAR T cells. In 2018, *Qin et al.* hypothesized that simultaneous targeting of CD19 and CD22 may reduce the likelihood of antigen loss, and considering that pan-B antigen expression may be heterogenous from patient to patient, they concluded that dual targeting would overcome interpatient variability in antigen expression. They compared multiple bi-specific targeting strategies in xenograft models, including co-infusion of 2 different CAR T-cell products, co-transduction of 2 viral CAR vectors into a single T cell, and a single-CAR construct with two different antigen-binding specificities (bivalent CAR) to simultaneously target CD19 and CD22. The latter showed comparable efficacy for CD19 and/or CD22 CAR-T cells. In 2021, *Spiegel et al.* completed a phase I trial using CD19/CD22 bispecific CAR-T in adults with R/R B-ALL and LBCL [66]. Thirty-nine patients were enrolled in the study, with 17 exhibiting B-ALL and 22 exhibiting LBCL, and 38 received CD19/CD22 CAR-T. All the patients in the LBCL group were CAR-T naïve. ORR was 40%, with 33% of patients achieving CR in the LBCL group. At a median follow-up of 10 months, the median OS and PFS were 22.5 months and 3.2 months, respectively. In the B-ALL group, the ORR was 100%, with 82% achieving CR. The median follow-up was 9.3 months, and the median OS and PFS were 11.8 months and 5.8 months, respectively. In terms of toxicity, CRS occurred in 76% of patients, of which 5% experienced grade >3 CRS. Neurotoxicity occurred in 37% of patients, with 4 experiencing grade >3 neurotoxicity. CD19 + CD22+ relapse were associated with resistance to the bispecific CAR, which likely reflected the intrinsic limitations of CAR-T cells [66]. Several ongoing trials are evaluating the efficacy of CD19/CD22 CAR-T cells in B-cell malignancies.

Other possible targets have been also explored. *Ruella et al.* evaluated the dual targeting of CD19 and CD123 in B-ALL [67]. The argument supporting the use of CD123 as a CAR-T target antigen was based on its surface expression in hematopoietic progenitor cells that exhibited resistance to chemotherapy, its ubiquitous expression, and prior studies of therapy directed against CD123. In their cohort of 42 patient samples, they found that CD123 was robustly and homogeneously expressed on the surface of most ALL blasts. They also noted that a particular blast subpopulation of CD19 negative but CD123 positive cells could be responsible for relapse and resistance to CD19 CAR T cell in B-ALL patients. Hence, targeting CD19 and CD123 could prevent CD19- CD123+ relapses. Having shown

that CD123-targeted CAR-T cells were effective against CD19 negative B-ALL *in vitro* and in murine models, they evaluated the efficacy of CD19/CD123 CAR-T cells against CD19+/CD123+ B-ALL in a murine model. This combination showed sustained clearance of the disease [67].

Taking a different approach, trivalent CAR-T cells have also been developed. *Fousek et al.* described CD19/CD20/CD22-targeting CAR-T cells by co-expressing individual CAR molecules on a single T cell using one tricistronic transgene encoding the three CAR molecules joined in tandem. These cells exhibited antigen-specific anti-tumor activity in both B-ALL cell lines and murine models, even in CD19-negative models [68].

The field of multitargeted CAR T-cell design is expanding. Thus, T cells have been created against specific targets to limit antigen escape, and other types of domains are being added to CARs to optimize CAR T-cell efficacy and safety. In addition, as our understanding of CAR T cells and B-cell malignancies deepens, new strategies may be developed to optimize efficacy of CAR T-cell therapy.

7. Combining CAR-T cells with other drugs

Unfortunately, the duration of remission with the aforementioned products are short-lived owing to poor CAR T-cell expansion and limited persistence [69]. Several hypotheses have been postulated to understand the causes of relapse, including intrinsic T-cell defects affecting CAR T-cell manufacturing and exhaustion [70–72]. T cells derived from patients with CLL exhibit a dysfunctional phenotype demonstrated by the upregulation of inhibitory receptors, particularly programmed cell death (PD-1), triggered by the disease itself, the tumor microenvironment, and/or as the result of antineoplastic treatment(s). This leads to decreased T-cell proliferation and impaired function [73]. It has been hypothesized that CAR T-cell manufacturing is affected in patients with CLL based on the limited ability of T cells to expand.

Ibrutinib is an irreversible BTK inhibitor that is approved for the treatment of CLL. Ibrutinib may improve T-cell function, enhance anti-tumor effect, and decrease CAR-T-related adverse effects [71,74]. Based on these observations, the combination of ibrutinib with CAR T-cell therapy has been studied to improve CAR T-cell manufacturing and expansion, which may ultimately lead to improved CAR T-cell function. Pre-clinical data showed that T cells derived from patients with CLL treated with ibrutinib for 5 or more cycles exhibit an enhanced proliferation capability and significantly reduced

inhibitory receptor expression when cultured *in vitro*. These findings were also seen *in vivo* in a murine xenograft MCL model, where a combination of ibrutinib and CAR T cells led to prolonged tumor responses [75].

In a phase 2 study, Gill et al. evaluated CD19 CAR T-cell therapy in patients with CLL that had progressed after at least 6 months of ibrutinib therapy [76]. Patients continued to receive ibrutinib during CAR T-cell therapy. A total of 19 patients were included. CRS was seen in 18 of 19 patients, although only 2 patients required administration of tocilizumab. Neurotoxicity was diagnosed in 5 patients. One patient died of severe grade 4 CRS and ICANS. One death due to infection was observed at 31 months while the patient was still receiving ibrutinib. Pertaining to efficacy, 7 of 16 evaluable patients achieved a CR (43.8%) at 3 months. MRD negativity was seen in 13 of 18 patients at 12 months, with continued remission at 48 months. PFS at 48 months was 70% [76]. The median OS and PFS were not reached. Seventeen and eight patients had detectable and quantifiable CAR T cells at 12 months, respectively. Also, at 12 months, 13 of 18 patients had B-cell aplasia, which is a purportedly proxy marker for persistent CAR T-cell function.

In another pilot study, ibrutinib was started 2 weeks before T-cell collection and continued through CAR T-cell therapy until at least 3 months after treatment, and the outcomes were compared to that of another cohort of CAR T-cell monotherapy [77]. The ORR values and MRD-negativity rates at four weeks were 83% and 61%, respectively. The 1-year OS was 83% and 1-year PFS were 59% and 38%, with or without ibrutinib therapy ($P = .91$), respectively. CRS and neurotoxicity severity appeared to be lower with the ibrutinib plus CAR T-cell combination relative to CAR T-cell therapy alone. Of note, one death was reported in each arm due to cardiac arrhythmia with ibrutinib and CRS and neurotoxicity without ibrutinib [77]. Overall, these studies show that the addition of ibrutinib to CAR T-cell therapy appears safe, is associated with low incidence of severe CRS, and could lead to higher and more prolonged responses. The TRANSCEND CLL 004 study is ongoing and includes different cohorts of CD19 CAR T-cell monotherapy or other combinatorial approaches using a non-randomized strategy (NCT03331198).

Another hypothesis to explain the short-term responses after CAR T-cell therapy is CAR T-cell exhaustion, which was demonstrated by comparing CAR T-cell antigen expression in responders and non-responders following CAR T-cell therapy in

patients with CLL. Reports have shown that in non-responders, CAR T cells upregulate exhaustion markers, particularly PD-1, TIM-3, and LAG-3 receptors [78]. Moreover, tumor cells effectively elude the immune system by the tumor escape mechanism through inhibitory ligands (PD-L1), thus leading to decreased CAR-T lytic function and cytokine production and limiting the anti-tumor efficacy [79].

CPI, including anti-PD1 and anti-PDL1 (ligand for PD-1), showed promising results in the treatment of several malignancies [79]. Based on these data, it has been hypothesized that adding CPI to CAR T-cell therapy could salvage CAR T-cell exhaustion, enhance the therapeutic function, and potentially reduce the risk of toxicity [79]. Chong et al. showed that pembrolizumab therapy in patients with R/R B-cell lymphoma that progressed after CD19 CAR T-cell therapy is safe and leads to re-expansion of CAR T cells, potentially resulting in better clinical responses [80]. In another phase I dose-escalation trial, durvalumab, an anti-PD-L1 monoclonal antibody, was combined with CD19 CAR T-cell therapy (JCAR014) for R/R aggressive B-cell lymphoma [81]. A total of 15 patients were included. Patients received durvalumab after (21–28 days) or before (1 day) CAR-T infusion for up to 10 cycles until disease progression or toxicity. The ORR was 50%, with 5 patients achieving CR. Four of six patients who were initially non-responding achieved response after 5 cycles of durvalumab. For adverse events, five and one patients developed CRS and neurotoxicity, respectively, with only one grade 4 CRS. In responding patients, CAR T cells were detectable after a median of five months after infusion (range, 1.7–9.1 months) (NCT02706405) [81]. Further studies evaluated the addition of other anti-PD-1, e.g., pembrolizumab and nivolumab, and an anti-PD-L1, e.g., durvalumab, mAbs to CD19 CAR T cells in ALL and NHL [81–83]. On the other hand, the combination of tisa-cel and pembrolizumab in the phase Ib PORTIA trial failed to show an improved efficacy with this combination [84]. The authors attributed this failure to the fact that patients included in PORTIA had more refractory and advanced disease compared to the JULIET study which was a phase 2 trial which evaluated tisa-cel monotherapy in R/R NHL [84,85]. Indeed, it showed lower frequency (and severity) of CRS with the combination. Studies with a larger cohort of patients and longer follow-up times are awaited to help identify the optimal schedule and assess the effect of these combinations on CAR T cells expansion and toxicity.

8. Discussion and future directions

The development of CD19 CAR T-cell therapy has thus far revolutionized the treatment of various subtypes of B-cell lymphomas, B-ALL, and MM. For LBCL, survival has improved significantly, with a reported five-year OS of 42.6% [86]. This compares favorably with SCHOLAR-1, which showed a two-year OS of less than 20% using non-CAR T-cell conventional chemoimmunotherapies [1].

Unfortunately, CD19 CAR T-cell therapies are not universally effective, and a proportion of patients will experience disease relapse or progress with a CD-19 negative phenotype or through other escape mechanisms. To address these challenges, future CAR T-cell constructs are evaluating other potential targets alone or in combination as part of a multi-targeted approach. This will likely have a beneficial effect on improving efficacy and reducing the risk of recurrence, such as preventing a CD19-negative phenotype relapse after anti-CD19 CAR-T cell treatment. An ideal target should also have increased specificity in order to reduce the possible off-target effect(s), which is a limitation of commercially available CD19 CAR T-cell therapies as normal (or non-malignant) B cells are also eliminated along with the anti-tumor effect of CD19 CAR T cells.

Another approach evaluated to optimize the efficacy of CD19 CAR T cells combines ibrutinib or ICL. Although the combination of ibrutinib with CD19 CAR T cells against CLL is feasible and may be applied in patients with MCL, future studies will likely evaluate the feasibility of this combination in other B-cell malignancies. This is also the case for CPI, which has been shown to reverse CAR T-cell exhaustion. Both combinations potentially enhance CAR T-cell persistence and decrease toxicity. Larger phase III trials are definitely needed to confirm these findings and evaluate other combinatorial approaches.

Finally, the success of future non-CD19 CAR T-cell products, particularly autologous products, is dependent on overcoming challenges related to delayed and/or failed manufacturing. Pursuing an allogeneic strategy might be a solution to increasing patients' access to these living therapies and hopefully reducing costs.

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YMV, RM, MEG, YL, MA, HQ and MAK-D declare that they have no relevant financial conflicts of interest in relation to this manuscript.

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