BLOOD RESEARCH
VOLUME 58 · NUMBER 4
December 2023
REVIEW ARTICLE

Recent advances in cellular immunotherapy for lymphoid malignancies

Haerim Chung, Hyunsoo Cho

Division of Hematology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

p-ISSN 2287-979X / e-ISSN 2288-0011
https://doi.org/10.5045/br.2023.2023177
Blood Res 2023;58:166-172.

Received on September 21, 2023
Revised on October 27, 2023
Accepted on November 1, 2023

*This study was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (RS-2023-00208390) and the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Korea (HI22C1217 and HI22C1826).

Correspondence to
Hyunsoo Cho, M.D., Ph.D.
Division of Hematology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
E-mail: hyunsoocho@yuhs.ac

Abstract

Cellular immunotherapy with chimeric antigen receptor (CAR) T-cells has revolutionized the treatment of lymphoid malignancies. This review addresses the need for CAR expression in our endogenous T-cells to kill tumor cells with a focus on the basic principles of T-cell receptor recognition of major histocompatibility complex-peptide complexes. We review the factors associated with CAR T-cell outcomes and recent efforts to employ CAR T-cells in earlier lines of therapy. We also discuss the value of bispecific T-cell engagers as off-the-shelf products with better toxicity profiles. Finally, natural killer cells are discussed as an important cellular immunotherapy platform with the potential to broaden immunotherapeutic applications beyond lymphoid malignancies.

Key Words Cellular immunotherapy, Chimeric antigen receptor T cells, Lymphoma, Multiple myeloma

INTRODUCTION

Lymphoid malignancies comprise a heterogeneous group of leukemias and lymphomas originating from the lymphoid organs, which form a major part of the immune system. Primary lymphoid organs consist of the bone marrow (BM) and thymus, while secondary lymphoid organs include the lymph nodes (LNs) and spleen. Lymphoid cancers are grouped into five main categories: Hodgkin lymphoma, non-Hodgkin lymphoma (NHL), multiple myeloma (MM), and acute and chronic leukemias. However, recent advances in our understanding of the genetic drivers of lymphoid cancers have resulted in a better subclassification of these tumors that differ widely in their phenotype, biology, and clinical behavior [1, 2]. For instance, approximately 20–30% of patients with diffuse large B-cell lymphoma (DLBCL), which is the commonest subtype of NHL, are unable to achieve complete remission with the standard chemoimmunotherapy regimen of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) [3]. Furthermore, patients with high-grade B-cell lymphoma (HGBL) with concurrent *MYC* plus *BCL2* and/or *BCL6* rearrangements, the so-called double-hit or triple-hit lymphomas, constitute an additional high-risk group with a complete remission (CR) rate of less than 60% with the conventional R-CHOP therapy [4].

IMPORTANCE OF IMMUNOTHERAPY FOR LYMPHOID MALIGNANCIES

The success of the anti-CD20 monoclonal antibody ritux-

imab, which was approved by the Food and Drug Administration (FDA) in 1997 for B-cell lymphoma, highlights the importance of immunotherapy for B-cell malignancies. Rituximab was one of the first form of immunotherapy for cancer treatment, and its mechanisms of action included direct induction of apoptosis, complement-dependent cytotoxicity (CDC), and antibody-dependent cell-mediated cytotoxicity (ADCC) [5], although their relative contributions to its overall effects remain unclear. These effects are mainly mediated by cytotoxic lymphocytes, including $CD8^+$ cytotoxic T-cells and natural killer (NK) cells, which play major roles in adaptive and innate immune responses, respectively [6]. T cells can recognize neoantigens generated by cancer-causing mutations or tumor-associated antigens (TAAs), which are highly expressed in tumors but can also be expressed in healthy tissues. Despite the presence of endogenous T-cells in the tumor microenvironment, most tumors progress through the hyporesponsive state of $CD8^+$ cytotoxic T-cells or NK cells owing to self-tolerance, which is the host immune mechanism for preventing autoimmunity [7].

MHC-RESTRICTED ENDOGENOUS T-CELL ACTIVATION AND RECOGNITION OF VARIOUS TARGETS BY B-CELL RECEPTORS

$CD8^+$ cytotoxic T-cells can detect and directly eradicate tumor cells in an antigen-specific manner. T-cell activation requires three signals: stimulatory signals mainly mediated by T-cell receptor (TCR) complexes (signal 1); co-stimulatory signals controlled by antigen-presenting cells (APCs), such as dendritic cells (signal 2); and cytokines (signal 3). To initiate an immune response, antigens must be captured and presented on T-cells by APCs. Subsequently, the TCR on T-cells recognizes neoantigens or TAA on major histocompatibility complex (MHC) molecules in collaboration with CD8 or CD4 co-receptors. Class I MHC molecules are expressed on all nucleated cells, whereas class II MHC molecules are primarily expressed on APCs and a few other cell types, including thymic epithelial and endothelial cells [8]. MHC molecules require the formation of a complex with peptides for their stable expression on the cell surface as an MHC-peptide complex; Class I MHCs can accommodate 8–11 peptides, while Class II MHCs can accommodate 10–30 or more peptides [9]. Therefore, neoantigens or TAAs must be processed for MHC. However, before their presentation to T-cells, endogenous antigens, such as TAAs are processed by proteasomes for class I MHC molecules, whereas extracellular antigens are ingested and degraded in lysosomes to form complexes with class II MHC molecules [9]. Additionally, TCRs recognize only two or three amino acid residues of a peptide within the MHC-peptide complex as antigenic determinants [9]. TCRs bind only to specific peptide-MHC complexes and not to other molecules; therefore, TCR binding is MHC-restricted. Indeed, T-cells can only recognize cell-associated antigens but not soluble or cell-free antigens.

Overall, characteristics of TCR binding to an MHC-peptide complex includes low affinity, slow kinetics, and high cross-reactivity. This is different from the antigen binding of immunoglobulins of the B-cell receptor (BCR), which can bind to linear and conformational determinants of various target macromolecules, such as proteins, lipids, polysaccharides, and even small chemicals [10]. Additionally, BCR can recognize soluble antigens and bind to antigens with high affinity at a rapid on-rate, unlike TCRs which cannot undergo affinity maturation [10].

BCR CHARACTERISTICS IN CHIMERIC ANTIGEN RECEPTOR T-CELLS

CARs are synthetic fusion receptors that redirect T-cells to TAAs, such as CD19 on B-cell lineage tumors or B-cell maturation antigen (BCMA) on MM cells [11]. Most CAR

Table 1. FDA approved CAR T cells for lymphoid malignancies as of Sep 2023.

Target	Generic name	Trade name (manufacturer)	FDA approval	Indications
CD19	Tisagenlecleucel	Kymriah (Norvatis)	2017 2018 2022	• Relapsed or refractory (R/R) B-cell acute lymphoblastic leukemia (ALL) (third line) • R/R large B-cell lymphoma (LBCL) (third line) • R/R follicular lymphoma (FL) (third line)
	Brexucabtagene autoleucel	Tecartus (Kite Pharma)	2020 2021	• R/R mantle cell lymphoma • R/R B-ALL
	Axicabtagene ciloleucel	Yescarta (Kite Pharma)	2017 2021 2022	• R/R LBCL (third line) • R/R FL (third line) • R/R LBCL (second line)
	Lisocabtagene maraleucel	Breyanzi (Juno Therapeutics, Bristol-Myers Squibb)	2021 2022	• R/R LBCL (third line) • R/R LBCL (second line)
BCMA	Idecabtagene vicleucel	Abecma (Celgene, Bristol-Myers Squibb)	2021	• R/R multiple myeloma (fifth line)
	Ciltacabtagene autoleucel	Carvykti (Janssen Biotech)	2022	

T-cells have features of BCRs in the form of a single-chain variable fragment from the antibody as an antigen recognition domain, which is linked to the intracellular costimulatory domain, such as CD28 or CD137 (4-1BB) [11]. However, the antigen-binding domain of ciltacabtagene autoleucel, a BCMA targeting CAR T-cells for MM, comprises only heavy-chain variable domain without the light chain (nanobody), which may reduce the immunogenicity associated with the linker region [12]. CAR T-cells can recognize TAA independently without the MHC-TCR complex (signal 1), and they have their own co-stimulatory domain (signal 2) that are attached to the activating domain, typically the zeta chain of the CD3 complex, which form the backbone of the current second-generation CAR T-cells [13]. Ever since CAR T-cells were approved for B-cell malignancies in 2017, their unprecedented success in clinical trials in highly refractory patients with lymphoid cancers has resulted in FDA approval of six CAR T-cells against relapsed or refractory subsets of B-cell lymphoma/leukemia and MM (Table 1).

FUNCTIONAL CONSEQUENCES ACCORDING TO THE CO-STIMULATORY DOMAIN

Axicabtagene ciloleucel (axi-cel) and brexucabtagene autoleucel (brexu-cel) have a CD28 costimulatory domain, whereas other FDA-approved CAR T-cells are based on the 4-1BB costimulatory domain. Mechanistically, CD28-based CAR T-cells can elicit a robust proliferative response and yield effector memory T-cells, whereas 4-1BB can lead to a progressive response with enhanced persistence and central memory differentiation [14]. Indeed, 4-1BB CAR T-cells have demonstrated distinct exhaustion features driven by the transcription factor FOXO3 [15] that differ from the classic exhaustion features that can occur in CD28-based CAR T-cells. It is clinically challenging to compare the efficacies of different types of CAR T-cells. However, the French DESCAR-T registry study demonstrated better outcomes with axi-cel than with tisagenlecleucel in terms of response rate and survival [16]. In contrast, real-world studies from the US and Germany have demonstrated no statistically significant differences in the response rates and survival between the two CAR T-cell products [17, 18]. Collectively, it would be valuable to further investigate the issue of selecting CAR T-cells based on different co-stimulation and exhaustion mechanisms to improve CAR T-cell function.

DISEASE-RELATED FACTORS AND CAR T-CELL OUTCOMES

Recent long-term follow-up data suggest that patients with B-cell lymphoma have a lower CR rate than patients with MM following CAR T-cell treatment, although a direct comparison is difficult [19]. Patients with B-cell lymphoma tend to have more durable responses once CR is achieved [19]. Patients with MM demonstrated a higher CR rate than those with B-cell lymphoma; however, they encountered less sustained remission, even after achieving CR, although patients with deeper initial remission are likely to have sustained responses [19]. Indeed, patients with a low tumor burden and less extramedullary disease are more likely to have better responses to CAR T-cell treatment [20]. Moreover, target antigen escape plays an important role in the durability of response and relapse following CAR T-cell therapy, although its relative contributions have been reported to vary significantly across disease subtypes [21]. In this regard, targeting dual antigens simultaneously with CAR T-cells is being explored in pre-clinical and clinical settings [22-24].

CAR T-CELL DIFFERENTIATION AND OUTCOMES

Preclinical and clinical studies have demonstrated that CAR T-cells derived from less-differentiated T-cell subsets, such as stem cell memory T-cells (T_{SCM}) and central memory T-cells, are associated with better CAR cell expansion and clinical response [25]. T_{SCM} has been demonstrated to contribute to circulating CAR T-cell pools during long-term persistence, with predominant clonal burst immediately after infusion [26]. Of note, single-cell multi-omics analysis has revealed that decade-persisting CD19 CAR T-cells are $CD4^+$ CAR T-cells that express cytotoxic molecules with direct cytotoxic functions upon stimulation with CD19-expressing cells *ex vivo* [27]. Notably, a higher CD4-to-CD8 ratio in leukapheresis products was associated with better *in vivo* expansion and durable clinical response of BCMA CAR T-cells [28, 29]. Specifically, a higher percentage of naïve and early memory $CD4^+$ T-cells was associated with long-term response in patients who received decabtagene vicleucel [30]. In line with these findings, CAR T-cell expansion with a balanced ratio of $CD4^+$ naïve and $CD8^+$ T_{SCM} cells reduced the number of infusion products required to achieve clinical responses, which is now commercially available as lisocabtagene maraleucel [31, 32].

CAR T-CELLS AS EARLIER TREATMENT

Efforts to improve CAR T-cell outcomes based on T-cell-related factors have led to the development of CAR T-cells as an early line of therapy. Data from the ZUMA-7 trial demonstrated the overall survival benefit of second-line axi-cel in patients with early relapse or refractory large B-cell lymphoma (LBCL) who were eligible for autologous stem cell transplantation (ASCT) [33]. This was the first randomized trial in nearly 30 years to demonstrate a survival benefit with second-line treatment for patients with aggressive lymphoma. Indeed, the second line axi-cel was efficacious in patients with relapsed or refractory LBCL who were not eligible for ASCT [34], which accounts for roughly half of the patients with relapsed or refractory LBCL in real-world clinical practice. Furthermore, axi-cel demonstrated efficacy

even in the front-line setting for patients with LBCL with high-risk features, including those with positive PET results after two cycles of standard first-line chemoimmunotherapy, either double- or triple-hit, or with high-intermediate- and high-risk International Prognostic Index (IPI) scores [35]. However, no phase 3 trial has compared CAR T-cells with the standard of care in a first-line setting. In this regard, results of the ZUMA-23 trial, which is assessing first-line axi-cel versus chemoimmunotherapy after one cycle of chemoimmunotherapy in high-risk LBCL are awaited, which could delineate the role of front-line CAR T-cell therapy in LBCL. The KarMMa-3 and CARTITUDE-4 trials demonstrated superior progression-free survival with CAR-T cells compared with standard-of-care combinations in earlier lines of MM treatment [36, 37]. Whether CAR T-cell therapy will replace ASCT may be answered by the CARTITUDE-6 trial in which ciltacabtagene autoleucel is compared with ASCT as a consolidation treatment.

COMPLEMENTARY ROLES OF CAR T-CELLS AND BISPECIFIC T-CELL ENGAGERS

One of the major limitations of CAR T-cell therapy is the manufacturing time, which takes at least several weeks [38]. Common adverse events, such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) also remain significant issues with CAR T-cell therapy [39]. Furthermore, increasing the number of CAR T-cell deliveries also led to a limited slot for CAR T-cell generation, which may impair timely CAR T-cell treatment for patients with rapid disease progression [40]. Allogenic CAR T-cells have been actively investigated to overcome these issues but their persistence remains poor [41]. In this regard, bispecific T-cell engagers (BiTE) can act as off-the-shelf platforms for T-cell redirection strategies [42]. BiTE links tumor cells and T-cells by binding to both TAA and CD3, which are components of TCR. They have better safety profiles in terms of precise dose titration and they can be discontinued at any time. This can be advantages over CAR T-cells, which are administered as a single infusion with varying doses as a dividing drug. Both CAR T-cells and BiTEs activate T-cells independently of MHC expression on target cells, but their immunologic synapses are quite different. BiTEs form well-organized immunological synapses between T cells and target cells, similar to conventional T cells for the delivery of lytic granules. However, the immunological synapses of CAR T-cells are disorganized, which may paradoxically promote CAR T-cell degranulation [43].

BISPECIFIC ANTIBODIES AS AN OFF-THE-SHELF OPTION

CAR T-cells have better efficacy when derived from less differentiated T-cell subsets; however, bispecific antibodies mediate T-cell effector functions mainly by redirecting more differentiated effector memory T-cells [44]. Blinatumomab was the first BiTE targeting CD19 and CD3 and is now approved for B-cell acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) ≥0.1% based on a BLAST trial [45]. The outcomes from the MajesTEC-1 and MagnetisMM-3 trials, which evaluated BCMA-targeting bispecific antibodies, teclistamab and elranatamb, respectively, led to the approval of these bispecific antibodies by the FDA for relapsed or refractory MM in the fifth-line setting [46, 47]. Additionally, the MonumenTAL-1 trial demonstrated the efficacy and safety of the bispecific antibody talquetamab, which targets GPRC5D [48], thus leading to its approval as the fifth-line treatment for relapsed or refractory MM. CD20 and CD3 bispecific antibodies—mosunetuzumab, epcoritamab, and

Table 2. FDA approved bispecific T-cell engager for lymphoid malignancies as of Sep 2023.

Target	Generic name	Trade name (manufacturer)	FDA approval	Indications
CD19×CD3	Blinatumomab	Blincyto (Amgen)	2014 2017 2018	• Philadelphia chromosome (Ph)-negative relapsed or refractory (R/R) B cell acute lymphoblastic leukemia (ALL) • Ph-positive R/R B-ALL • CD19-positive B-ALL in first or second complete remission with minimal residual disease of at least 0.1%
BCMA×CD3	Teclistamab-cqyv	Tecvayli (Janssen Biotech)	2022	• R/R multiple myeloma (MM) (fifth line)
	Elranatamab-bcmm	Elrexfio (Pfizer)	2023	
CD20×CD3	Mosunetuzumab-axgb	Lunsumio (Genentech-Roche)	2022	• R/R follicular lymphoma (FL) (third line)
	Epcoritamab-bysp	Epkinly (Genmab-AbbVie)	2023	• R/R diffuse large B cell lymphoma (DLBCL), high-grade B cell lymphoma (third line)
	Glofitamab-gxbm	Columvi (Genentech-Roche)	2023	• R/R DLBCL, large B cell lymphoma arising from FL (third line)
GPRC5D×CD3	Talquetamab-tgvs	Talvey (Janssen Biotech)	2023	• R/R MM (fifth line)

glofitamab—have also recently been approved for the treatment of both subtypes of aggressive and indolent B-cell lymphoma [49-51]. Mosunetuzumab, epcoritamab, and glofitamab have demonstrated efficacy in relapsed or refractory DLBCL, follicular lymphoma (FL), transformed FL, primary mediastinal large B-cell lymphoma, mantle cell lymphoma, and Richter's transformation [49-51]. Notably, glofitamab demonstrated favorable efficacy in terms of duration or response in relapsed or refractory DLBCL as 70% of patients continue to be in CR after 18 months [51]. Therefore, bispecific antibodies represent effective approaches for subsets of relapsed or refractory lymphoid malignancies (Table 2), and bispecific combination approaches targeting various antigens are currently active areas of investigation [52].

NK CELLS AS AN OFF-THE-SHELF CELLULAR IMMUNOTHERAPY PLATFORM

Natural killer (NK) cells are innate lymphoid cells that recognize target T-cells in a manner that is not restricted by the MHC-peptide complex [53]. Their effector functions are regulated by a balance of signals of various inhibitory and activating receptors [54]. CARs can also be expressed on NK cells, which are similar to the CAR design for T-cells that including a single-chain variable fragment, a co-stimulatory domain, and CD3 zeta. However, recent studies have attempted to design CAR NK cells by employing activating signals associated with NK cell functions. For example, CD3 zeta may be replaced by DNAX-activation protein 10 (DAP10), which induces NK cytotoxicity via signalling through the activating receptor NKG2D–DAP10 complex [55]. NKG2D is one of the major activating receptors on NK cells that recognizes NKG2D ligands, which are stress-induced and are normally not expressed in healthy cells [56]. Indeed, NKG2D CAR NK cells have demonstrated better efficacy than NKG2D CAR T cells in preclinical models of MM [57]. CAR NK cells have the advantage of being an off-the-shelf platform with various gene editing options to enhance efficacy and they have better safety profile compared with CAR T. However, NKG2D ligands are shed from leukemic cells or MM cells to form soluble NKG2D ligands during progression, which can downregulate NKG2D and impair NK cytotoxicity [58]. Consequently, approaches targeting soluble NKG2D ligands have been developed in solid tumor models and in MM to promote NK cell effector functions [59, 60]. In addition to NKG2D-mediated effector functions, ADCC is an important mechanism of NK cell-mediated tumor killing. Our group and others have demonstrated that a subset of NK cells, known as adaptive NK cells, mediate superior ADCC compared to conventional NK cells against MM cells [61, 62]. Therefore, promoting conventional NK cells with CAR and harnessing the superior ADCC of adaptive NK cells with monoclonal antibodies, while clearing soluble NKG2D ligands, may be an effective combination strategy for promoting NK cell-based immunotherapy outcomes [63].

CONCLUSION

Cellular immunotherapy using CAR T-cells and BiTEs has emerged as a transformative approach for treating lymphoid malignancies. The remarkable progress made in recent years, in addition to ongoing innovative strategies for harnessing NK cells, will provide new hope for patients with these aggressive diseases. A better understanding of both disease biology and the basic principles of the resistance mechanisms of cytotoxic lymphocytes will enable us to improve the efficacy and safety of cellular immunotherapy associated with improved patient survival. Therefore, collaborations between basic and translational researchers, clinicians, and healthcare providers are pivotal to harnessing the full potential of cellular immunotherapy in lymphoid malignancies.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

REFERENCES

1. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of haematolymphoid tumours: lymphoid neoplasms. Leukemia 2022;36:1720-48.
2. Campo E, Jaffe ES, Cook JR, et al. The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee. Blood 2022;140:1229-53.
3. Yi JH, Jeong SH, Kim SJ, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from two prospective Korean cohorts. Cancer Res Treat 2023;55:325-33.
4. Dunleavy K. Double-hit lymphoma: optimizing therapy. Hematology Am Soc Hematol Educ Program 2021;2021:157-63.
5. Weiner GJ. Rituximab: mechanism of action. Semin Hematol 2010;47:115-23.
6. Kim KH, Kim CG, Shin EC. Peripheral blood immune cell-based biomarkers in anti-PD-1/PD-L1 therapy. Immune Netw 2020;20:e8.
7. Philip M, Schietinger A. $CD8^+$ T cell differentiation and dysfunction in cancer. Nat Rev Immunol 2022;22:209-23.
8. Neefjes J, Jongsma ML, Paul P, Bakke O. Towards a systems understanding of MHC class I and MHC class II antigen presentation. Nat Rev Immunol 2011;11:823-36.
9. Rock KL, Reits E, Neefjes J. Present yourself! By MHC class I and MHC class II molecules. Trends Immunol 2016;37:724-37.
10. Burger JA, Wiestner A. Targeting B cell receptor signalling in cancer: preclinical and clinical advances. Nat Rev Cancer 2018;18:148-67.
11. Labanieh L, Mackall CL. CAR immune cells: design principles, resistance and the next generation. Nature 2023;614:635-48.
12. Holliger P, Hudson PJ. Engineered antibody fragments and the rise of single domains. Nat Biotechnol 2005;23:1126-36.

13. Larson RC, Maus MV. Recent advances and discoveries in the mechanisms and functions of CAR T cells. Nat Rev Cancer 2021;21:145-61.
14. Kawalekar OU, O' Connor RS, Fraietta JA, et al. Distinct signaling of coreceptors regulates specific metabolism pathways and impacts memory development in CAR T cells. Immunity 2016;44:712.
15. Selli ME, Landmann JH, Terekhova M, et al. Costimulatory domains direct distinct fates of CAR-driven T cell dysfunction. Blood 2023;141:3153-65.
16. Bachy E, Le Gouill S, Di Blasi R, et al. A real-world comparison of tisagenlecleucel and axicabtagene ciloleucel CAR T cells in relapsed or refractory diffuse large B cell lymphoma. Nat Med 2022;28:2145-54.
17. Bethge WA, Martus P, Schmitt M, et al. GLA/DRST real-world outcome analysis of CAR T-cell therapies for large B-cell lymphoma in Germany. Blood 2022;140:349-58.
18. Gauthier J, Gazeau N, Hirayama AV, et al. Impact of CD19 CAR T-cell product type on outcomes in relapsed or refractory aggressive B-NHL. Blood 2022;139:3722-31.
19. Cappell KM, Kochenderfer JN. Long-term outcomes following CAR T cell therapy: what we know so far. Nat Rev Clin Oncol 2023; 20:359-71.
20. Locke FL, Rossi JM, Neelapu SS, et al. Tumor burden, inflammation, and product attributes determine outcomes of axicabtagene ciloleucel in large B-cell lymphoma. Blood Adv 2020;4:4898-911.
21. Majzner RG, Mackall CL. Tumor antigen escape from CAR T-cell therapy. Cancer Discov 2018;8:1219-26.
22. Spiegel JY, Patel S, Muffly L, et al. CAR T cells with dual targeting of CD19 and CD22 in adult patients with recurrent or refractory B cell malignancies: a phase 1 trial. Nat Med 2021;27:1419-31.
23. Cordoba S, Onuoha S, Thomas S, et al. CAR T cells with dual targeting of CD19 and CD22 in pediatric and young adult patients with relapsed or refractory B cell acute lymphoblastic leukemia: a phase 1 trial. Nat Med 2021;27:1797-805.
24. Roddie C, Lekakis LJ, Marzolini MAV, et al. Dual targeting of CD19 and CD22 with bicistronic CAR-T cells in patients with relapsed/refractory large B-cell lymphoma. Blood 2023;141:2470-82.
25. Tantalo DG, Oliver AJ, von Scheidt B, et al. Understanding T cell phenotype for the design of effective chimeric antigen receptor T cell therapies. J Immunother Cancer 2021;9:e002555.
26. Biasco L, Izotova N, Rivat C, et al. Clonal expansion of T memory stem cells determines early anti-leukemic responses and long-term CAR T cell persistence in patients. Nat Cancer 2021;2: 629-42.
27. Melenhorst JJ, Chen GM, Wang M, et al. Decade-long leukaemia remissions with persistence of $CD4^+$ CAR T cells. Nature 2022;602:503-9.
28. Cohen AD, Garfall AL, Stadtmauer EA, et al. B cell maturation antigen-specific CAR T cells are clinically active in multiple myeloma. J Clin Invest 2019;129:2210-21.
29. Garfall AL, Dancy EK, Cohen AD, et al. T-cell phenotypes associated with effective CAR T-cell therapy in postinduction vs relapsed multiple myeloma. Blood Adv 2019;3:2812-5.
30. Lin Y, Raje NS, Berdeja JG, et al. Idecabtagene vicleucel for relapsed and refractory multiple myeloma: post hoc 18-month follow-up of a phase 1 trial. Nat Med 2023;29:2286-94.
31. Turtle CJ, Hanafi LA, Berger C, et al. CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. J Clin Invest 2016;126:2123-38.
32. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet 2020;396:839-52.
33. Westin JR, Oluwole OO, Kersten MJ, et al. Survival with axicabtagene ciloleucel in large B-cell lymphoma. N Engl J Med 2023;389:148-57.
34. Houot R, Bachy E, Cartron G, et al. Axicabtagene ciloleucel as second-line therapy in large B cell lymphoma ineligible for autologous stem cell transplantation: a phase 2 trial. Nat Med 2023;29:2593-601.
35. Neelapu SS, Dickinson M, Munoz J, et al. Axicabtagene ciloleucel as first-line therapy in high-risk large B-cell lymphoma: the phase 2 ZUMA-12 trial. Nat Med 2022;28:735-42.
36. Rodriguez-Otero P, Ailawadhi S, Arnulf B, et al. Ide-cel or standard regimens in relapsed and refractory multiple myeloma. N Engl J Med 2023;388:1002-14.
37. San-Miguel J, Dhakal B, Yong K, et al. Cilta-cel or standard care in lenalidomide-refractory multiple myeloma. N Engl J Med 2023;389:335-47.
38. Byun JM. Practical issues in CAR T-cell therapy. Blood Res 2023;58(S1):S11-2.
39. Jain MD, Smith M, Shah NN. How I treat refractory CRS and ICANS after CAR T-cell therapy. Blood 2023;141:2430-42.
40. Mikhael J, Fowler J, Shah N. Chimeric antigen receptor T-cell therapies: barriers and solutions to access. JCO Oncol Pract 2022;18:800-7.
41. Song F, Hu Y, Zhang Y, et al. Safety and efficacy of autologous and allogeneic humanized CD19-targeted CAR-T cell therapy for patients with relapsed/refractory B-ALL. J Immunother Cancer 2023;11:e005701.
42. Moon D, Tae N, Park Y, Lee SW, Kim DH. Development of bispecific antibody for cancer immunotherapy: focus on T cell engaging antibody. Immune Netw 2022;22:e4.
43. Lindner SE, Johnson SM, Brown CE, Wang LD. Chimeric antigen receptor signaling: functional consequences and design implications. Sci Adv 2020;6:eaaz3223.
44. Goebeler ME, Bargou RC. T cell-engaging therapies - BiTEs and beyond. Nat Rev Clin Oncol 2020;17:418-34.
45. Jen EY, Xu Q, Schetter A, et al. FDA approval: blinatumomab for patients with B-cell precursor acute lymphoblastic leukemia in morphologic remission with minimal residual disease. Clin Cancer Res 2019;25:473-7.
46. Moreau P, Garfall AL, van de Donk NWCJ, et al. Teclistamab in relapsed or refractory multiple myeloma. N Engl J Med 2022; 387:495-505.
47. Lesokhin AM, Tomasson MH, Arnulf B, et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. Nat Med 2023;29:2259-67.
48. Chari A, Minnema MC, Berdeja JG, et al. Talquetamab, a T-cell-redirecting GPRC5D bispecific antibody for multiple myeloma. N Engl J Med 2022;387:2232-44.
49. Budde LE, Sehn LH, Matasar M, et al. Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre,

phase 2 study. Lancet Oncol 2022;23:1055-65.
50. Hutchings M, Mous R, Clausen MR, et al. Dose escalation of subcutaneous epcoritamab in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: an open-label, phase 1/2 study. Lancet 2021;398:1157-69.
51. Dickinson MJ, Carlo-Stella C, Morschhauser F, et al. Glofitamab for relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med 2022;387:2220-31.
52. Zhu WM, Middleton MR. Combination therapies for the optimisation of bispecific T-cell engagers in cancer treatment. Immunother Adv 2023;3:ltad013.
53. Laskowski TJ, Biederstädt A, Rezvani K. Natural killer cells in antitumour adoptive cell immunotherapy. Nat Rev Cancer 2022;22:557-75.
54. Wolf NK, Kissiov DU, Raulet DH. Roles of natural killer cells in immunity to cancer, and applications to immunotherapy. Nat Rev Immunol 2023;23:90-105.
55. Gong Y, Klein Wolterink RGJ, Wang J, Bos GMJ, Germeraad WTV. Chimeric antigen receptor natural killer (CAR-NK) cell design and engineering for cancer therapy. J Hematol Oncol 2021;14:73.
56. Duan S, Guo W, Xu Z, et al. Natural killer group 2D receptor and its ligands in cancer immune escape. Mol Cancer 2019;18:29.
57. Leivas A, Valeri A, Córdoba L, et al. NKG2D-CAR-transduced natural killer cells efficiently target multiple myeloma. Blood Cancer J 2021;11:146.
58. Chiossone L, Dumas PY, Vienne M, Vivier E. Natural killer cells and other innate lymphoid cells in cancer. Nat Rev Immunol 2018;18:671-88.
59. Du C, Bevers J 3rd, Cook R, et al. MICA immune complex formed with alpha 3 domain-specific antibody activates human NK cells in a Fc-dependent manner. J Immunother Cancer 2019;7:207.
60. Dhar P, Wu JD. NKG2D and its ligands in cancer. Curr Opin Immunol 2018;51:55-61.
61. Cho H, Kim KH, Lee H, et al. Adaptive natural killer cells facilitate effector functions of daratumumab in multiple myeloma. Clin Cancer Res 2021;27:2947-58.
62. Bigley AB, Spade S, Agha NH, et al. FcεRIγ-negative NK cells persist in vivo and enhance efficacy of therapeutic monoclonal antibodies in multiple myeloma. Blood Adv 2021;5:3021-31.
63. Maddineni S, Silberstein JL, Sunwoo JB. Emerging NK cell therapies for cancer and the promise of next generation engineering of iPSC-derived NK cells. J Immunother Cancer 2022;10:e004693.