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Review article

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Long-term outcomes following CAR T cell therapy: what we know so far

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Abstract

Chimeric antigen receptors (CAR) are engineered fusion proteins designed to target T cells to antigens expressed on cancer cells. CAR T cells are now an established treatment for patients with relapsed and/or refractory B cell lymphomas, B cell acute lymphoblastic leukaemia and multiple myeloma. At the time of this writing, over a decade of follow-up data are available from the initial patients who received CD19-targeted CAR T cells for B cell malignancies. Data on the outcomes of patients who received B cell maturation antigen (BCMA)-targeted CAR T cells for multiple myeloma are more limited owing to the more recent development of these constructs. In this Review, we summarize long-term follow-up data on efficacy and toxicities from patients treated with CAR T cells targeting CD19 or BCMA. Overall, the data demonstrate that CD19-targeted CAR T cells can induce prolonged remissions in patients with B cell malignancies, often with minimal long-term toxicities, and are probably curative for a subset of patients. By contrast, remissions induced by BCMA-targeted CAR T cells are typically more short-lived but also generally have only limited long-term toxicities. We discuss factors associated with long-term remissions, including the depth of initial response, malignancy characteristics predictive of response, peak circulating CAR levels and the role of lymphodepleting chemotherapy. We also discuss ongoing investigational strategies designed to improve the length of remission following CAR T cell therapy.

Sections

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Key points

- Among haematological malignancies, the indications for use of chimeric antigen receptor (CAR) T cells are rapidly expanding. CD19-targeted CAR T cells are now approved for relapsed and/or refractory B cell lymphoma and B cell acute lymphoblastic leukaemia, and B cell maturation antigen-targeted CAR T cells are approved for relapsed and/or refractory multiple myeloma.
- Long-term follow-up data indicate that CD19-targeted CAR T cells are likely to be curative for a subset of patients with B cell lymphomas. These CAR T cells might need to be combined with consolidative allogeneic haematopoietic stem cell transplantation to enable long-term remissions for patients with B cell acute lymphoblastic leukaemia.
- B cell maturation antigen-targeted CAR T cells can induce prolonged remissions in patients with relapsed and/or refractory multiple myeloma, although whether any of these responses are curative remains unclear.
- Factors associated with durable remission after CAR T cell therapy include a deep initial response, lower baseline tumour volume, an absence of extramedullary disease, higher peak circulating CAR T cell levels and receipt of lymphodepleting chemotherapy.
- The most prominent long-term toxicities after CAR T cell therapy include cytopenias and hypogammaglobulinaemia. The incidence of severe infections >1 month after CAR T cell therapy is low compared to infections seen in the acute period immediately after cell infusion.
- Ongoing research efforts are attempting to improve the durability of responses after CAR T cell therapy, for example, through improved patient selection, novel CAR designs, including those targeting multiple antigens, and modifications to the manufacturing process.

Introduction

Chimeric antigen receptor (CAR) T cells are engineered fusion proteins that target T cells to a specific antigen present on tumour cells to generate an antitumour immune response[1–3]. CAR T cells targeting CD19, which is expressed on malignant B cells, were found to have potent activity in early phase clinical trials involving patients with relapsed and/or refractory (R/R) B cell malignancies over a decade ago[4–8]. In the multicentre trials that followed, complete response (CR) rates of 40–54%, 67% and 69–74% were observed in patients with R/R aggressive B cell lymphomas[9–11], in patients with mantle cell lymphoma[12] and in those with indolent B cell lymphomas[13,14], respectively. These outstanding CR rates heralded a paradigm shift in the treatment of patients with R/R B cell lymphomas, who historically had dismal outcomes following salvage chemoimmunotherapy[15]. As discussed later in this Review, some of the responses were highly durable, suggesting that CD19-targeted CAR T cells are able to cure certain patients with B cell lymphomas[16]. CD19-targeted CAR T cells are now approved by the FDA for the treatment of R/R aggressive B cell lymphomas[9–11], mantle cell lymphomas[12] and indolent B cell lymphomas[13,14]. These CAR T cells have also generated CR rates of 71–81% in multicentre clinical trials involving patients with R/R B cell acute lymphoblastic leukaemia (B-ALL), who have limited treatment options[17,18]. Hence, CD19-targeted CAR T cells are now also approved by the FDA for patients with R/R B-ALL and provide an important standalone treatment or bridge to allogeneic haematopoietic stem cell transplantation (HSCT)[19]. More recently, CAR T cells targeting B cell maturation antigen (BCMA) have had remarkable successes in patients with R/R multiple myeloma (RRMM), with trials showing overall response rates (ORRs) of 73–98%[20–22]. BCMA-targeted CAR T cells are now approved by the FDA for patients with RRMM and are effective in those with disease progression on many other targeted agents. Overall, CAR T cell therapies have become an important component of the treatment landscape for a range of haematological malignancies, and the indications for these therapies continue to expand to earlier lines of treatment.

The CD19-targeted CAR T cell products currently approved by the FDA include axicabtagene ciloleucel[9,14,23], tisagenlecleucel[11,13,17], lisocabtagene maraleucel[10,24] and brexucabtagene autoleucel[12,18]. The BCMA-targeted CAR T cell products idecabtagene vicleucel[22] and ciltacabtagene autoleucel[21] are also approved by the FDA (Fig. 1). All these products are generated by viral transduction of autologous (patient-derived) T cells to express the CAR construct[2]. The currently approved CAR T cell products use second-generation constructs that include an antigen-binding domain, hinge and transmembrane domains, a co-stimulatory domain (derived from either CD28 or 4-1BB), and a T cell activation domain derived from CD3ζ[25,26]. The products differ in some of the specific domains included in the CAR, the viral vector used for CAR transgene delivery and certain aspects of the manufacturing process[25–27]. Lymphodepleting chemotherapy is given in the week prior to CAR T cell infusion to support CAR T cell proliferation and possibly activation following infusion[28]. Thus far, all approved CAR T cell products share, to varying degrees, the class-specific adverse effects of cytokine-release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome, hypogammaglobulinaemia and cytopenias, particularly B cell aplasia[29].

The remarkable successes and rapid FDA approvals of new CAR T cell products are exciting and reflect an expanding role for such agents in the treatment of patients with haematological malignancies. However, as the manufacturing and administering CAR T cells is labour intensive and expensive, an examination of the long-term outcomes of patients who received these novel therapies is essential[30]. In this Review, we provide a summary of the long-term outcomes of patients with B cell malignancies or RRMM following CAR T cell therapy.

Long-term outcomes

CD19-targeted CAR T cell therapy for B cell lymphoma and CLL

Most data on long-term outcomes following infusion with CAR T cell therapies are from patients with R/R B cell lymphoma or chronic lymphocytic leukaemia (CLL) who received CD19-targeted CAR T cell therapies in the early trials (Table 1). A total of 10 studies have provided ≥24 months of follow-up data (range 24–123 months)[16,23,31–38]. These data indicate ORRs of 44–91% and CR rates of 28–68%[16,23,31–38]. All studies reported the existence of a subset of patients with ongoing responses at ≥2 years after infusion without any consolidative treatment[16,23,31–38]. These long-term durable remissions were reported for all malignancies treated, including aggressive B cell lymphomas, follicular lymphomas, mantle cell lymphomas and CLL, and with all currently approved CD19-targeted CAR T cell products[16,23,31–38].

We conducted one of the longest follow-up studies to provide data on CD19-targeted CAR T cells; this study was designed to assess the outcomes of patients receiving a CAR T cell therapy that was developed

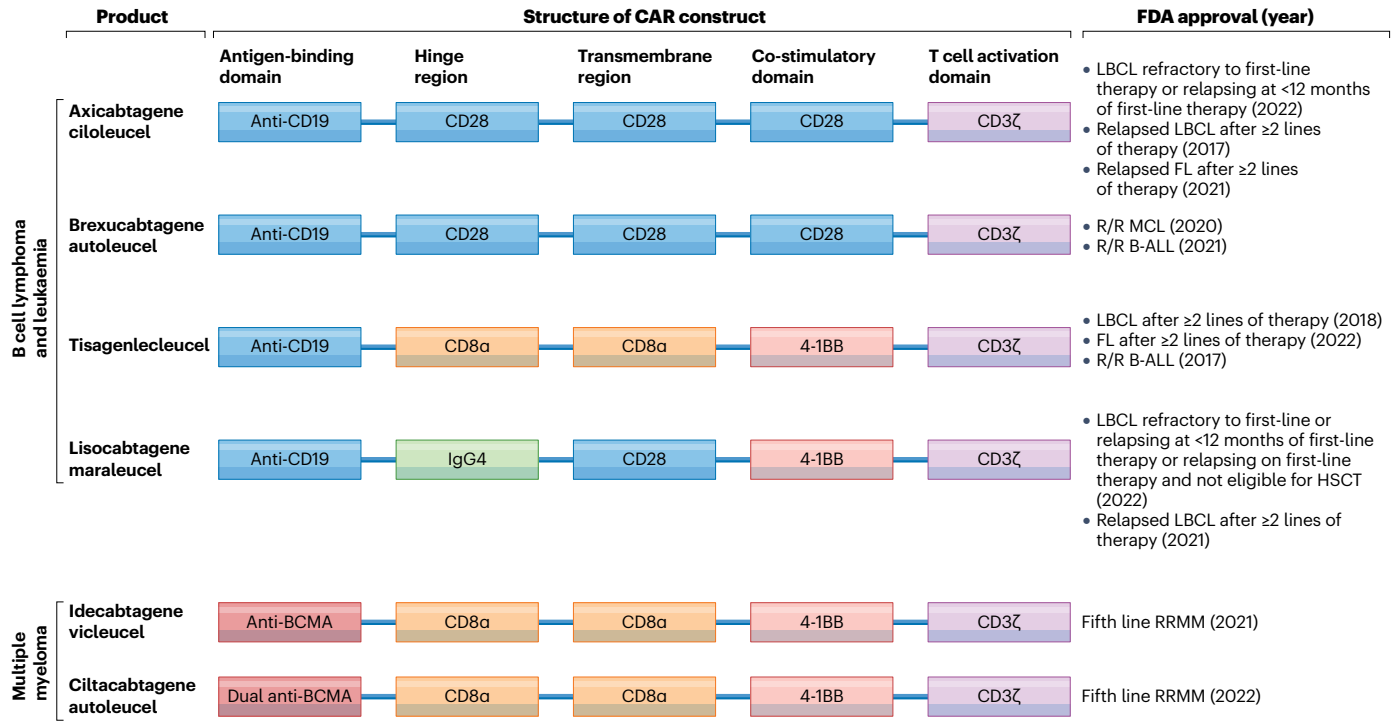

Fig. 1 | FDA-approved CAR T cell therapies. A total of six chimeric antigen receptor (CAR) products are currently available commercially, including four for patients with B cell lymphomas, two for patients with B cell acute lymphoblastic leukaemia (B-ALL) and two for those with multiple myeloma (MM). All approved products have a second-generation CAR construct, consisting of an antigen-binding domain, a hinge region, a transmembrane region, a co-stimulatory domain and a T cell activation domain. All CD19-targeted CARs contain the same antigen-binding domain, which is a single-chain variable fragment derived from the mouse FMC63 monoclonal antibody. Axicabtagene ciloleucel and brexucabtagene autoleucel use the same CAR but differ in their manufacturing processes, with production of brexucabtagene autoleucel including an additional step designed to remove malignant cells from the leukapheresis product. Tisagenlecleucel differs from these products in that it contains different hinge and transmembrane domains and includes a 4-1BB domain instead of a CD28 domain for co-stimulation. Lisocabtagene maraleucel is delivered at a defined $CD4^+$:$CD8^+$ T cell composition. The CAR gene for axicabtagene ciloleucel and brexucabtagene autoleucel is delivered using a gammaretrovirus, whereas those for tisagenlecleucel and lisocabtagene maraleucel are delivered using lentiviruses. Idecabtagene vicleucel includes a mouse 11D5-3 single-chain variable fragment targeting B cell maturation antigen (BCMA). Ciltacabtagene autoleucel has a binding domain consisting of two linked camelid heavy-chain-only variable (VHH) antigen-binding domains targeting BCMA. In both products, the CAR gene is delivered using a lentivirus. FL, follicular lymphoma; HSCT, haematopoietic stem cell transplantation; LBCL, large B cell lymphoma; MCL, mantle cell lymphoma; R/R, relapsed and/or refractory.

at the National Cancer Institute and later commercialized as axicabtagene ciloleucel[16]. In our study involving 43 patients with R/R B cell lymphoma or CLL, 58% of treated patients had a CR and 76% of those with a CR remained in long-term remission[16]. At the latest follow-up, the duration of these CRs ranged from 43 to 113 months[16]. Long-term remissions were also observed in a study involving patients who received tisagenlecleucel in the initial single-centre clinical trial of tisagenlecleucel for lymphoma[31]. This study demonstrated a CR rate of 55%, and 60% of these patients remained in remission at 5 years[31]. Overall, these results demonstrate that some patients with R/R B cell lymphoma who receive CD19-targeted CAR T cell therapy are probably cured of their disease without a need for further intervention. This finding stands in contrast to the available chemoimmunotherapy approaches for R/R large B cell lymphoma (LBCL), which are usually used as a bridge to potentially curative autologous HSCT[39]. Moreover, the long-term remission rates of patients receiving salvage chemoimmunotherapy plus autologous HSCT have decreased since the adoption of rituximab as part of first-line therapy[40,41].

CD19-targeted CAR T cell therapy for B-ALL

Data are now available from multiple long-term follow-up studies of the efficacy of CD19-targeted CAR T cell therapy in patients with B-ALL[18,42–53]. A total of 12 studies provide data on the outcomes of patients with a minimum median follow-up duration of 1 year (range 1–4.8 years)[18,42–53] (Table 2). Data from these studies confirm the excellent initial CR rates ranging from 62% to 86%, with the majority of these being deep minimal residual disease (MRD)-negative remissions[18,42–53]. Median event-free survival (EFS) durations varied between studies, which probably reflects the fact that most studies included a substantial and variable fraction of patients (13–88%) who received consolidative allogeneic HSCT while in remission[18,42–53]. This approach obscures the interpretation of the ability of CAR T cells alone to elicit a curative response. Long-term data are available for both commercially available CAR T cell products used in adults with B-ALL, namely tisagenlecleucel and brexucabtagene autoleucel. Data from the initial study of tisagenlecleucel indicate a CR rate of 69% with a median EFS of 5.6 months at a median follow-up duration of 13 months[48]. Similarly, follow-up data from the initial

Table 1 | Long-term outcomes of patients with B cell lymphoma and/or CLL/SLL receiving CD19-targeted CAR T cells

Study (year of publication)	CAR product and trial phase	Cancer types (*n*)	Median follow-up (range)	ORR and CRR	PFS or EFS	DOR in responding patients
Chong et al. (2021)[31]	Tisagenlecleucel, single-centre case series	DLBCL (24); FL (14)	61 months	ORR: 66%; CRR: 55%	31% PFS at 5 years for DLBCL; 43% PFS at 5 years for FL	60% remained in response at 5 years
Jacobson et al. (2021)[32]	Axicabtagene ciloleucel, multicentre phase I/II	DLBCL (77); PMBCL (8); tFL (16)[9]	51 months	ORR: 74%; CRR: 54%[67]	Median EFS: 5.7 months, with 24-month EFS of 38%	NR
Cappell et al. (2020)[16]	FMC63-28Z[a], single-centre phase I	DLBCL/PMBCL (28); indL (8); CLL/SLL (7)	42 months (1–123 months)	ORR: 81%; CRR: 58%	Median EFS: 55 months	76% of patients with a CR remained in response at last follow-up with a DOR ranging from 43 to 113 months
Schuster et al. (2021)[33]	Tisagenlecleucel, multicentre phase II	DLBCL, HGBCL or tFL (115)	40 months (IQR 38–44 months)	ORR: 53%; CRR: 39%	Median PFS: 2.9 months; median EFS: 2.8 months	Median DOR: not estimable
Hirayama et al. (2019)[34]	Lisocabtagene maraleucel, single-centre phase I/II	tFL (13) and FL (8)	38 months for patients with tFL and 24 months for those with FL	ORR: NR for FL and 46% for tFL; CRR: 88% for FL and 46% for tFL	Median PFS: 1.4 months in tFL cohort; NR for FL cohort	All patients with FL with a CR remained in remission at a median follow-up duration of 24 months (range 5–37 months)
Wang et al. (2023)[35]	Brexucabtagene autoleucel, multicentre phase II	MCL (68)	36 months (26–56 months)	ORR: 91%; CRR: 68%	Median PFS: 26 months	Median DOR: 47 months in patients with a CR
Frey et al. (2020)[36]	CART-19, single-centre phase II	CLL (38)	32 months (2–75 months)	ORR: 44%; CRR: 28%	Median PFS: 1 month in all patients; 40 months in those with CR	4/9 (44%) of patients with a CR had disease relapse
Abramson et al. (2021)[37]	Lisocabtagene maraleucel, multicentre phase I	LBCL (270)	All patients had ≥24 months of follow-up data; median NR	ORR: 73%; CRR: 53%	Median PFS: 6.8 months	Median DOR: 26 months in those with a CR
Locke et al. (2022)[23 b]	Axicabtagene ciloleucel, multicentre phase III	DLBCL (126); HGBCL (31); NR (18); other (5)	25 months	ORR: 83%; CRR: 65%	Median PFS: 15 months	Median DOR: 27 months
Siddiqi et al. (2022)[38]	Lisocabtagene maraleucel, multicentre phase I	CLL/SLL (23)	24 months	ORR: 82%; CRR: 45%	Median PFS: 18 months	Median DOR: not reached

Studies meeting the following criteria were included in this table: ≥2 years of follow-up and >20 patients on study plus availability of the majority of the above data. Studies are listed in order of longest duration of follow-up. Studies of chimeric antigen receptor (CAR) T cells targeting CD19 in addition to other antigens and retrospective or real-world studies were not included. All studies involved adult patients. CLL, chronic lymphocytic leukaemia; CR, complete response; CRR, complete response rate; DLBCL, diffuse large B cell lymphoma; DOR, duration of response; EFS, event-free survival; FL, follicular lymphoma; HGBCL, high-grade B cell lymphoma; IQR, interquartile range; indL, indolent lymphoma; LBCL, large B cell lymphoma; MCL, mantle cell lymphoma; NR, not reported; ORR, overall response rate; PFS, progression-free survival; PMBCL, primary mediastinal B cell lymphoma; SLL, small lymphocytic lymphoma; tFL, transformed follicular lymphoma. [a]The CAR used in this trial was later commercially developed into axicabtagene ciloleucel. [b]The trial included randomization of patients to axicabtagene ciloleucel versus standard of care. Data presented are from patients who received axicabtagene ciloleucel only.

study of brexucabtagene autoleucel also show a CR rate of 69%, with a median relapse-free survival duration of 7 months at a median follow-up duration of 22 months[45]. These data suggest similar efficacy of both products, albeit with short durations of remission in most adults with B-ALL relative to those with other B cell malignancies. By contrast, only tisagenlecleucel is currently approved for paediatric patients (defined as those ≤25 years of age) with B-ALL. Long-term follow-up of such patients (median 11 years of age, range 3–24) who received tisagenlecleucel in the ELIANA study indicate a complete remission rate of 82% and a median EFS duration of 24 months[51]. Comparably high EFS rates have also been noted in retrospective studies involving patients of a similar age[54,55]. These data clearly demonstrate that younger (paediatric and young adult) patients receiving CD19-targeted CAR T cell therapies have markedly superior survival outcomes compared with those of the adult population.

The need for consolidative allogeneic HSCT for durable remissions after CAR T cell therapy in patients with B-ALL is currently debatable[19]. The markedly different long-term outcomes in paediatric and adult patients warrant separate discussions of the role of consolidative HSCT in these populations. In the paediatric population, a substantial proportion of patients have long-term remissions after tisagenlecleucel alone without consolidative allogeneic HSCT[51]. For example, in the ELIANA study, 17/79 (22%) patients underwent allogeneic HSCT, including 11 who were in tisagenlecleucel-mediated remission at the time of transplantation[51]; the 3-year relapse-free survival was 52% with censoring for allogeneic HSCT or other therapies and 48% without censoring[51]. Overall, these data suggest that a cure is possible without consolidative allogeneic HSCT in some paediatric patients treated with tisagenlecleucel. Data from four studies have detailed the outcomes of paediatric patients who received other CD19-targeted CAR

Table 2 | Long-term outcomes of patients with B-ALL receiving CD19-targeted CAR T cells

Study (year of publication)	CAR design, name[a] and trial phase	Trial population (*n*)	Median follow-up (range)	CR/CRi	Survival outcomes	Proportion of patients in CR receiving consolidative alloHSCT	Outcomes of patients in CR not receiving consolidative alloHSCT
Shah et al. (2021)[42]	Mouse scFv, CD28 H/T, CD28 co-stimulatory domains[b,153]; CD19.28ζ; single-centre phase I	Children and adults aged 4–30 years (50)	4.8 years (3.5–7.2 years)	31/50 (62%)	Median EFS: 3.1 months	21/28 (75%) of those with MRD-negative CR	7/7 (100%) of patients with MRD-negative CR relapsed
Laetsch et al. (2023)[51]	Mouse scFv, CD8α H/T, 4-1BB co-stimulatory domains; tisagenlecleucel; multicentre phase II	Children and young adults aged 3–24 years (79)	39 months	65/79 (82%)	Median EFS: 24 months	11/66 (17%)	NR
Jacoby et al. (2022)[50]	Mouse scFv, CD28 H/T, CD28 co-stimulatory domains; CD19 CAR T cells; single-centre phase II	Children and adults aged 1–36 years (37)	3 years	30/35 (86%)	Median EFS: 17 months (not censored for consolidative alloHSCT)	25/30 (83%)	4/5 (80%) of patients with CR relapsed; the remaining patient was on maintenance treatment
Wayne et al. (2022)[52]	Mouse scFv, CD28 H/T, CD28 co-stimulatory domains; KTE-X19; multicentre phase I/II	Children and young adults aged 3–20 years (24)	36 months (24–54 months)	16/24 (67%)	Median RFS: 5.2 months	14/16 (88%)	One patient died of progressive disease and the other was lost to follow-up
Hay et al. (2019)[43]	Mouse scFv, IgG4 hinge, CD28 transmembrane, 4-1BB co-stimulatory domains, delivered in a defined $CD4^+$-to-$CD8^+$ cell ratio[c,79]; CD19 CAR T cells; single-centre phase I/II	Adults aged 20–76 years (53)	31 months	45/53 (85%)	Median EFS: 7.6 months (in those achieving MRD-negative CR)	18/45 (40%) of those with MRD-negative CR	NR
Park et al. (2018)[44]	Mouse scFv, CD28 H/T, CD28 co-stimulatory domains[b,154]; 19-28z; single-centre phase I	Adults aged 23–74 years (53)	29 months (1–65 months)	44/53 (83%)	Median EFS: 6.1 months	17/44 (39%)	17/26 (65%) relapsed or died
Shah et al. (2021)[45]	Mouse scFv, CD28 H/T, CD28 co-stimulatory domains[b,25]; brexucabtagene autoleucel; multicentre phase I	Adults aged 18–77 years (45)	22 months (7–36 months)	31/45 (69%)	Median RFS: 7 months	6/45 (13%) of all patients received alloHSCT	8/31 (26%) of CRs were ongoing at data cut-off, with 5/8 (63%) not having received alloHSCT
Roddie et al. (2021)[46]	Mouse scFv from the CAT131E10 hybridoma, CD8α H/T domain, with a 4-1BB co-stimulatory domains[c,46]; AUTO1; multicentre phase I	Adults aged 18–62 years (20)	22 months (1–34 months)	17/20 (85%), MRD-negative CR	24-month EFS 44% by MRD relapse criteria	3/17 (18%)	NR
Shah et al. (2021)[18]	Mouse scFv, CD28 H/T, CD28 co-stimulatory domains[b,25]; brexucabtagene autoleucel; multicentre phase II	Adults aged 28–52 years (55)	16 months (IQR 14–20 months)	39/55 (71%)	Median RFS: 11.6 months	9/39 (23%)	18/30 (60%) relapsed, died or proceeded to other therapies
Wang et al. (2021)[47]	Humanized scFv, CD8α H/T, 4-1BB co-stimulatory domains[c,47]; hCART19s; single-centre phase I	Children aged 3–17 years (24)	16 months (3–45 months)	20/24 (83%)	EFS: 37% at 3 years	8/20 (40%)	9/12 (75%) relapsed
Frey et al. (2020)[48]	Mouse scFv, CD8α H/T, 4-1BB co-stimulatory domains[c,25]; tisagenlecleucel; single-centre phase I/II	Adults aged 20–70 years (35)	13 months (0.2–53 months)	24/35 (69%)	Median EFS: 5.6 months	9/24 (38%)	NR
An et al. (2020)[49]	Mouse scFv, IgG4 hinge, CD28 TM, 4-1BB co-stimulatory domains[b,49]; Sino19; multicentre phase II	Children and adults aged 3–72 years (47)	NR (survival data are from 1 year)	38/47 (81%)	Median RFS: 10.5 months	10/38 (26%)	19/28 (68%) relapsed

Studies meeting the following criteria were included in this table: median follow-up duration ≥1 year and had ≥20 patients on study in addition to including most of the above data in the manuscript. Studies are listed in order of longest duration of follow-up. Studies testing CARs targeting CD19 in addition to other antigens and retrospective or real-world studies were not included. alloHSCT, allogeneic haematopoietic stem cell transplantation; B-ALL, B cell acute lymphoblastic leukaemia; CAR, chimeric antigen receptor; CR, complete response; CRi, CR with incomplete blood count recovery; EFS, event-free survival; H/T, hinge and transmembrane; IQR, interquartile range; MRD, minimal residual disease; NR, not reported; RFS, relapse-free survival; scFv, single-chain variable fragment; TM, transmembrane. [a]CAR name is included if the CAR construct was developed into a commercial product. [b]These studies used a gammaretroviral vector for construct delivery. [c]These studies used a lentiviral vector for construct delivery. If a commercial product is not yet approved by the FDA, the construct name is listed.

T cell products, achieved a CR and did not proceed to consolidative allogeneic HSCT[42,47,49,50]. These studies showed a rate of relapse from CR in non-consolidated patients of 68–100%[42,47,49,50]. Therefore, a higher percentage of paediatric patients might have long-term remissions without consolidative allogeneic HSCT after treatment with tisagenlecleucel as compared with other CD19-targeted CAR T cell products. In contrast to data from the paediatric population, consolidative allogeneic HSCT is routinely recommended for adults with B-ALL with a CR after CD19-targeted CAR T cell therapy[56]. This recommendation reflects a markedly lower median EFS duration, regardless of the CAR construct used, in this population[18,43–46,48]. The importance of consolidative allogeneic HSCT is highlighted by data from a long-term follow-up study involving adult patients who received tisagenlecleucel, which showed markedly improved EFS in those who received consolidative allogeneic HSCT[48]. Factors that might have an important role in determining which patients require consolidative allogeneic HSCT are discussed in detail in an excellent recent review and include receipt of previous HSCT, loss of B cell aplasia, previous treatments received, cytogenetics, detection of MRD and disease burden prior to CAR T cell infusion[19].

Overall, data from patients with B-ALL indicate a very high CR rate with CD19-targeted CAR T cells, exceeding 80% in many studies[18,43,44,46,47,49–51]. However, even in paediatric patients who received tisagenlecleucel, ≤50% had long-term EFS[51]. Thus, in comparison to those with B cell lymphoma, patients with B-ALL are more likely to have a CR, although a lower proportion of patients with a CR are likely to be cured without subsequent therapy.

BCMA-targeted CAR T cell therapy for RRMM

In comparison with CD19-targeted CAR T cells, fewer data on the long-term outcomes of patients with RRMM who received BCMA-targeted CAR T cells are available owing to the later development of these constructs[57,58]. Outcomes are currently available from a total of six studies with a median follow-up duration of ≥1 year (range 13–48 months)[21,22,59–62] (Table 3). These studies involved patients with RRMM and reported ORRs of 73–100% and CR or stringent CR rates ranging from 33% to 83%[21,22,59–62]. MRD-negative remissions were frequently observed in many of these studies[21,22,59–61]. Furthermore, a subset of patients with prolonged remissions lasting several years was observed in all studies without the need for consolidative or maintenance therapies[21,22,59–62]. The frequency of prolonged remissions, defined as those with progression-free survival (PFS) of >1 year, varied markedly between studies with median PFS durations ranging from 5.2 to 27 months[21,22,59–62]. In our trial of a fully human BCMA-targeted CAR with a heavy-chain-only antigen-recognition domain, patients had a median PFS duration of 18 months without any maintenance therapy at the time of a report presented in November 2021 (ref. 62). This single treatment contrasts with monoclonal antibody-based approaches targeting BCMA in patients with RRMM, which require ongoing treatment[63,64].

Long-term follow-up data are available for both commercially available BCMA-targeted CAR T cell products, idecabtagene vicleucel[22] and ciltacabtagene autoleucel[21,59]. The longest reported follow-up data for idecabtagene vicleucel (median 13 months) demonstrate a median PFS duration of 8.8 months for all patients, increasing to 12.1 months for patients who received the highest dose level[22]. A CR or better was achieved in 33% of patients, and patients obtaining a CR had a median duration of response of 19 months[22]. Data are available from two important long-term follow-up studies testing the CAR construct used in ciltacabtagene autoleucel[21,59]. The first study was a multicentre trial conducted in the USA and Japan with a median follow-up duration of 28 months[21]. This study demonstrated a CR or

Table 3 | Long-term outcomes of patients with relapsed and/or refractory multiple myeloma receiving BCMA-targeted CAR T cells

Study and year of publication (*n*)	CAR design, name and trial phase	Median follow-up (range)	ORR and ≥CRR	PFS	DOR
Zhao et al. 2022 (74)[59]	Two BCMA-binding domains, CD8α H/T domain, 4-1BB co-stimulatory domain; LCAR-B38M[a,b]; multicentre phase I	48 months	ORR: 65/74 (88%); ≥CRR: 54/74 (73%)	Median PFS: 18 months	Median DOR: 23 months
Martin et al. 2023 (97)[21]	Two BCMA-binding domains, a CD8α H/T domain, 4-1BB co-stimulatory domain[b,117]; ciltacabtagene autoleucel; multicentre phase Ib/II	28 months	ORR: 95/97 (98%); ≥CRR: 80/97 (83%)	PFS: 55% at 27 months	Median DOR: NE (range 23 months to NE)
Mikkilineni et al. 2021 (25)[62]	Fully human scFv, CD8α H/T domain, 4-1BB co-stimulatory domain[c]; FHVH33-CD8BBZ	NR (median PFS of 78 weeks)	ORR: 23/25 (92%); ≥CRR: 12/25 (48%)	Median PFS: 18 months	Median DOR: NR
Munshi et al. 2021 (128)[22]	Mouse scFv, CD8α H/T domain, 4-1BB co-stimulatory domain[b,20,116]; idecabtagene vicleucel; multicentre phase II	13 months (0.2–21 months)	ORR: 94/128 (73%); ≥CRR: 42/128 (33%)	Median PFS: 8.8 months	Median DOR: 11 months in all patients and 19 months in those with CR or better
Wang et al. 2021 (18)[60]	Fully human scFv, CD8α H/T domain, 4-1BB co-stimulatory domain[b,60]; CT103A; single-centre phase I	13 months	ORR: 18/18 (100%); ≥CRR: 13/18 (72%)	1-year PFS: 58%	Median DOR: 325 days for all patients and 412 days for patients with CR or better
Li et al. 2021 (30)[61]	Mouse scFv, CD8α hinge, CD28 co-stimulatory domain[b,61]; anti-BCMA CAR T cells; phase I	13 months	ORR: 27/30 (90%); ≥CRR: 13/30 (43%)	Median PFS: 5.2 months	Median DOR: 148 days for responding patients (range 16–625 days)

Studies meeting the following criteria were included in this table: median follow-up duration ≥1 year and >15 patients on study in addition to including most of the above data in the manuscript. Studies are listed in order of longest duration of follow-up. Studies targeting B cell maturation antigen (BCMA) in addition to other antigens and retrospective or real-world studies were not included. Chimeric antigen receptor (CAR) name is included if the CAR construct was developed into a commercial product; otherwise, the construct name is listed. ≥CRR, complete response rate or better; CR, complete response; DOR, duration of response; H/T, hinge and transmembrane; NE, not estimable; NR, not reported; ORR, overall response rate; PFS, progression-free survival; scFv, single-chain variable fragment. [a]LCAR-B38M is the same CAR as used in ciltacabtagene autoleucel. [b]These studies used a lentiviral vector for construct delivery. [c]This study used a gammaretroviral vector for construct delivery.

better in 83% of patients, a PFS of 55% at 27 months of follow-up, and a median duration of response that was not estimable at the reported data analysis cut-off[21]. The PFS curve trended downwards over time, although the median PFS duration was still not reached at the time of the report. The second important long-term study of the CAR used in ciltacabtagene autoleucel was conducted in China, where this construct was originally developed[59]. This long-term follow-up study of 74 patients with RRMM had a median follow-up duration of 48 months[59]. The data indicate a median PFS duration of 18 months, and the PFS curves demonstrated that increasing numbers of patients develop disease progression with longer follow-up monitoring[59]. These data suggest that patients with RRMM can have prolonged maintenance-free remissions after BCMA-target CAR T cell therapy, albeit with a continued risk of disease progression over time.

Factors associated with long-term remissions

The factor most consistently associated with durable long-term remissions following CAR T cell therapy is the depth of initial response to treatment, which is usually quantifiable within the first few months after cell infusion and often in the first month[10,12,21,22,33,65,66] (Box 1). The importance of the depth of initial response in predicting duration of remission has been demonstrated in studies involving patients with various haematological malignancies, including B cell lymphomas[9,16,34,35,67], CLL[36,38], B-ALL[18,43,44,47] and MM[21,22,59]; in each of these malignancies, patients obtaining a deeper response remained in remission for longer than those who did not. The depth of response can be assessed by determining MRD negativity or by measuring circulating-tumour DNA: both approaches can predict the durability of remission[68,69]. Patients with B cell lymphoma, with a best response constituting a partial response, are unlikely to have subsequent long-term curative remissions[16]. By contrast, those with a CR can have curative remissions[16]. Importantly, patients with MM and those with B-ALL often have very deep MRD-negative CRs yet later have disease relapse[18,42,44,47,49]. Therefore, a deep initial response seems to be necessary, yet not sufficient, for long-term remissions after CAR T cell therapy.

Both the type and characteristics of the malignancy are also clearly predictive of response durability. Patients with B cell lymphomas are less likely to have a CR compared to those with B-ALL or MM; however, CRs of patients with B cell lymphoma are more likely to be durable once they are achieved. Baseline tumour burden is another factor that predicts response to CAR T cell therapy across malignancies. Patients with higher tumour burdens at the start of treatment are less likely to both attain and maintain a deep response compared to those with a lower tumour burden in all malignancies, including B cell lymphomas[70,71], B-ALL[42,44,47,50,54] and MM[21]. Another shared factor across malignancies is that the presence of extra-nodal B cell lymphoma[70,72] is predictive of inferior outcomes, as is the presence of extramedullary B-ALL[43,49] or extramedullary MM[21,59,60,73].

Receipt of lymphocyte-depleting chemotherapy is another factor consistently associated with response. Lymphocyte-depleting chemotherapy is given in the week prior to CAR T cell infusion and is usually a combination of fludarabine and cyclophosphamide, although other regimens can be used[28]. Studies involving patients with B cell lymphomas[74–77] and B-ALL[42,76,78,79] have shown improved responses when lymphocyte-depleting chemotherapy is given before CAR T cell infusion. Therefore, CAR T cell studies involving patients with MM included lymphocyte-depleting chemotherapy[27]. Lymphocyte depletion creates a favourable immune environment that enables optimal CAR T cell proliferation and function; the underlying mechanism of this effect that is currently best supported by human and mouse data involves enhancement of T cell proliferation and function owing to induction of an increase in certain serum cytokines such as IL-7 and IL-15 (refs. 74,80,81). The ideal lymphocyte-depleting regimen remains an active area of investigation[28].

CAR T cell levels following infusion are a final and very important factor in predicting response durability. CAR T cells expand rapidly after cell infusion, reach a peak level and can then persist at a much lower level for years after treatment. Higher peak CAR-expressing cell levels and higher levels of CAR-expressing cells during the first month of infusion, quantified by area under the curve, are consistently associated with improved responses in the majority of[9,10,16,23,35,74,82] but not in all[11,83] studies involving patients with B cell lymphoma. Higher peak CAR-expressing cell levels and CAR-expressing cell area under the curve within the first month of treatment have also been associated with response in patients with CLL[36,84], B-ALL[18,42–44,66,82,85] and RRMM[22,57,58,61]. The available data therefore clearly support the importance of robust early in vivo CAR T cell levels for durable responses. Long-term low-level persistence lasting many months to years after infusion has been

Box 1

Factors associated with durable remissions after CAR T cell therapy

- Depth of response
  - Patients with deeper initial remissions are more likely to have long-term responses[9,16,18,21,22,34–36,38,43,44,47,59,67]; however, disease relapse can occur even after deep minimal residual disease-negative remissions[18,42,44,47,49].
- Malignancy type
  - Patients with B cell lymphomas are less likely to have a complete response (CR) but are more likely to have sustained remission once a CR has been reached[16,23,31–38].
  - Patients with B cell acute lymphoblastic leukaemia[18,42–52] or multiple myeloma[21,22,59–62] are more likely to have a CR although less likely to have sustained remission.
- Tumour burden and location
  - Patients with a lower pre-infusion tumour volume are more likely to attain a deep response[21,42,44,47,50,54,70,71].
  - Extramedullary disease is associated with a reduced response rate[21,43,49,59,60,70,72,73].
- Lymphodepleting chemotherapy
  - Patients who receive lymphodepleting chemotherapy have better responses[42,74–79].
  - The most-effective lymphodepleting chemotherapy regimen and dosing strategy remain unknown, but fludarabine plus cyclophosphamide is the most commonly used regimen.
- Chimeric antigen receptor (CAR) T cell levels
  - Higher peak blood CAR T cell levels are often associated with an initial response and durable remissions[9,10,16,18,22,23,35,36,42–44,57,58,61,66,74,82,84,85].

documented in multiple studies with a range of different CAR construct designs[25,35,83,84,86]. Data from several studies indicate durable responses without a need for long-term persistence of CAR T cells in patients with B cell lymphomas, and evidence of durable responses without detectable persisting T cells also comes from patients with MM[12,16,21,35,67,87]. However, the evidence does indicate a role of long-term CAR T cell persistence for a durable response in patients with B-ALL[17,51]. Nonetheless, the length and degree of persistence necessary for a durable response are unclear from the available data and could conceivably vary with different CAR constructs and malignancies.

Long-term adverse effects

CAR T cells are associated with a substantial risk of acute adverse events, including, most notably, CRS and immune effector cell-associated neurotoxicity syndrome[29,88]. The majority of clinical studies have focused on these acute toxicities, which generally occur within the first month of treatment[29,88]. Data from studies designed to investigate longer-term adverse events, especially in patients who are in long-term remission after CAR T cell infusion, are much more limited. The most common long-term adverse effects observed thus far are B cell depletion (aplasia), hypogammaglobulinaemia, cytopenias and infections (Table 4).

CAR T cell therapy clearly has long-lasting effects on the immune system. In addition to being expressed on malignant cells, CD19 is expressed on non-malignant B cells and BCMA is expressed on non-malignant plasma cells[5,27]. Long-lasting B cell depletion following CD19-targeted CAR T cell therapy is a common occurrence, with data from long-term follow-up studies indicating persistent B cell depletion in 25–38% of patients even several years after CAR T cell infusion[16,23,31,67]. B cell depletion can persist for years in such patients, sometimes despite loss of detectable CAR-expressing T cells[16]. Immunoglobulin depletion is a consequence of both impaired B cell and plasma cell activity. Long-term follow-up data indicate IgG depletion persisting several years after cell infusion in 18–74% of patients who received CD19-targeted CAR T cells[16,31,89]. Prolonged immunoglobulin depletion has also been observed in patients who received BCMA-targeted CAR T cells[59]. Patients with persistent hypogammaglobulinaemia after CAR T cell therapy often receive immunoglobulin infusions, although data on whether this is necessary for all patients are unclear[90,91]. An impaired response to vaccines is an important effect of B cell depletion and hypogammaglobulinaemia in patients receiving CAR T cells[92,93].

Cytopenias, including anaemia, thrombocytopenia and neutropenia, are all common acute toxicities associated with CAR T cell therapy[29,88]. Data from several studies also indicate the occurrence of chronic cytopenias lasting ≥3 months after CAR T cell infusion. The incidence of grade 3–4 cytopenias at ≥3 months after CAR T cell infusion is approximately 15% in patients with B cell lymphoma[67,94]. In a long-term follow-up study, clinically significant cytopenias occurred in 3/19 (16%) of patients with B cell malignancies in CR following CD19-targeted CAR T cell therapy and lasted for 15–22 months after cell infusion[89]. Similarly, ongoing grade ≥3 neutropenia (in 20%) and thrombocytopenia (in 47%) can be observed in patients with MM at 100 days after infusion of idecabtagene vicleucel[22]. Chronic cytopenias are also common after ciltacabtagene autoleucel[21]. The mechanisms of prolonged

Table 4 | Long-term adverse effects of CAR T cells

Study (year of publication)	CAR name and patient population (*n*)	Median follow-up (range)	Prevalence of persistent B cell/IgG depletion in patients with a CR[a]	Prevalence of late severe cytopenias[b]	Incidence of late infections	Incidence of second malignancy
Chong et al. (2021)[31]	Tisagenlecleucel; adults with B cell lymphomas (38)	61 months	B cell: 4/12 (33%); IgG: 2/11 (18%)	1/38 (3%), ongoing at 57 months	NR	6/38 (16%)
Zhao et al. (2022)[59]	LCAR-B38M[c]; adults with multiple myeloma (74)	48 months (0.4–61 months)	NR	NR	NR	4/74 (5%)
Cappell et al. (2020)[16]	FMC63-28Z[d]; adults with B cell lymphoma or CLL (43)	42 months (1–123 months)	B cell: 9/24 (38%); IgG: 5/24 (21%)	NR	4/43 (9%) developed an infection requiring hospitalization ≥6 months after CAR T cell infusion	7/43 (16%)
Cordeiro et al. (2020)[89]	Lisocabtagene maraleucel; adults with ALL, NHL or CLL (86)	28 months (13–63 months)	B cell: NR; IgG: 14/19 (74%)	3/19 (16%) of patients in CR	33/54 (61%) developed an infection and 80% of these were non-severe infections (mostly URIs); 20% of infections required hospitalization at ≥3 months after infusion	13/86 (15%)
Locke et al. (2019)[67]	Axicabtagene ciloleucel; adults with B cell lymphomas (108)	27 months (IQR 26–29 months)	B cell: 8/32 (25%); IgG: NR	18/108 (17%) of all patients	2 grade 3 infections occurred ≥12 months in patients in ongoing remission	1 case of MDS
Locke et al. (2022)[23,e]	Axicabtagene ciloleucel; adults with B cell lymphomas (170)	25 months	B cell: 55/160 (34%) of all patients; IgG: NR	NR	NR	NR

Included studies must have documented long-term adverse events occurring at least 90 days after CAR T cell infusion and include data for most of the above categories. Studies are listed in order of longest duration of follow-up. Studies targeting multiple antigens or antigens other than CD19 and B cell maturation antigen are not listed. Chimeric antigen receptor (CAR) name is included if the CAR construct was developed into a commercial product; otherwise, the construct name is listed. ALL, acute lymphoblastic leukaemia; CLL, chronic lymphocytic leukaemia; CR, complete remission; IQR, interquartile range; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; NR, not reported; URI, upper respiratory tract infection. [a]Patients with persistent B cell/IgG depletion, defined as those with ongoing depletion at time of last follow-up. [b]Severe cytopenias were defined as cytopenias requiring either transfusion or growth factor support; grade ≥3 cytopenias were included in this category. All cytopenias must have occurred ≥3 months after CAR infusion. [c]The CAR used in this trial was later commercially developed into ciltacabtagene autoleucel. [d]The CAR used in this trial was later commercially developed into axicabtagene ciloleucel. [e]Trial included randomization of patients to axicabtagene ciloleucel versus standard of care. Data only from patients who received axicabtagene ciloleucel are presented here.

cytopenias after CAR infusion are poorly understood, although these events generally occur in patients who are in ongoing remission and with no evidence of myelodysplastic syndrome (MDS)[21,22,67,89,94,95]. The risk of cytopenias is associated with higher-grade CRS, multiple previous lines of therapy, receipt of allogeneic HSCT ≤1 year prior to CAR T cell infusion, baseline cytopenia and the presence of bone marrow malignancy[95,96].

Despite these widespread changes to the immune system, the incidence of severe infections >1 month after CAR T cell therapy is relatively low compared to the incidence of severe infections in the first month after CAR T cell infusion, and the incidence of such infections decreases with time after infusion[16,89,94,97]. However, data in this area are sparse because most studies have not focused on infections occurring many months after CAR T cell infusion[98]. Furthermore, survivors of lymphoma are already known to have increased long-term risks of infection, which makes interpretation of the effects of CAR T cell therapy difficult in this population[99]. In our long-term follow-up study involving 43 patients with B cell malignancies who received CD19-targeted CAR T cells at the National Cancer Institute, 4/43 (9%) required hospital admission for infections >6 months after CAR T cell therapy with a median follow-up duration of 42 months[16]. Similarly, data from a long-term follow-up study involving patients who received lisocabtagene maraleucel show that only 5% of patients had severe infections >91 days after infusion[37]. Patients who received CAR T cells seem to have an increased risk of mortality from COVID-19 (refs. 100–102) and also have impaired antibody production following COVID-19 vaccination[92]. However, studies in this area are limited in several respects, including being conducted early in the pandemic when fewer therapeutic options existed, having retrospective designs, including many patients who were not in remission after CAR T cell therapy and including many patients who were diagnosed with COVID-19 within a year of receiving CAR T cells, when immunosuppression is most prominent[100–102]. Whether patients in durable long-term remissions after CAR T cell therapy share these poor outcomes is currently unclear. Overall, the available data demonstrate an increased risk of infection following CAR T cell infusion, albeit less than would be expected in the context of substantial ongoing changes to the immune system in patients previously exposed to multiple lines of chemotherapy.

The possibility of malignant transformation of transduced cells was previously a concern surrounding the use of gene therapy approaches[103]. In the context of CAR T cell therapy, in which peripheral blood mononuclear cells undergo transduction for expression of the CAR, haematological malignancies, such as MDS, could theoretically emerge from adverse gene integration events. Data from large-cohort follow-up studies indicate an incidence of secondary malignancies after CAR infusion of 4–16%[16,31,59,89,104]. These incidences are not higher than expected given that all patients had a history of substantial chemotherapy exposure, which itself increases the risk of secondary malignancies[105,106]. The incidences of haematological malignancies, and particularly MDS, were also not higher than those expected in all trials using standard viral transduction approaches[16,23,31,59,67,89,104]. Overall, the available data provide no evidence of an increased risk of secondary malignancies with approved gammaretroviral or lentiviral CAR-delivery systems.

Ongoing research efforts

Investigational approaches designed to optimize nearly every part of the CAR T cell therapy process are currently being developed and/or tested (Fig. 2). A combination of changes at several different stages of this process will probably be needed to optimize the crucial parameters of CR rate and long-term PFS.

Antigen escape is a well-described mechanism of relapse after CAR T cell therapy, which occurs when malignant cells lose target antigen expression[107]. Antigen escape has been identified as the mechanism of disease relapse after CAR T cell therapy in 20–28% of patients with B cell lymphoma[9,83,108], in 16–68% with B-ALL[17,18] and at lower incidences in those with MM[22,58,109,110]. Antigen escape is therefore one of the most important factors affecting the durability of response to CAR T cell therapy. Dual antigen targeting is being actively investigated in several clinical trials in an attempt to overcome this problem. The most extensively studied additional antigens to target are CD20 and CD22, which are both expressed in malignant B cells. Thus far, long-term outcome data after CAR T cell therapy targeting both CD19 and CD20 are available from two studies involving patients with R/R B cell lymphoma[111,112]. One of these trials demonstrated no relapses owing to antigen loss[111] and, in the other trial, 1/12 (8%) of patients with a biopsy sample available on disease relapse had antigen loss[112]. Dual targeting of CD19 and CD22 has been reported in two trials involving patients with R/R B-ALL[113,114]. These trials included post-relapse biopsy sampling and reported loss of one or both antigens in 25–33% of patients with disease relapse[113,114]. Another trial in which patients with R/R B cell malignancies received CD19/CD22-targeted CAR T cells again identified CD19 loss in 5/10 (50%) patients with B-ALL and in 4/14 (29%) patients with B cell lymphomas[115]. These data suggest that targeting more than one antigen does not always circumvent the problem of antigen escape and this approach might need to be combined with other improvements in CAR therapies.

The antigen-binding domains of the CAR can also be optimized to improve CAR T cell function. The antigen-binding domains of all approved CAR T cell products, except ciltacabtagene autoleucel, are currently derived from mouse antibodies[20,25,116,117]. The inclusion of a mouse-derived component might promote anti-CAR immune responses and thus limit CAR T cell levels following infusion. Several groups have therefore developed fully human CAR T cell products that have been tested in clinical trials[27,60,118–120]. Some of these studies have shown improved persistence of the fully human CAR, although, thus far, this has not translated into an improvement in efficacy[58,60,120]. Another potential area of improvement in the antigen-binding domain is the substitution of single-chain variable fragments with a heavy-chain-only variable domain. Antigen-binding domains comprised of only heavy chains, without an associated light chain, were originally described in antibodies derived from camelids and cartilaginous fish[121,122]. These heavy-chain-only binding domains have the advantage of a smaller size, easier genetic manipulation and potentially reduced immunogenicity given the absence of a linker region[122,123]. An example of the success of heavy-chain-only binding domains is provided by ciltacabtagene autoleucel, which incorporates two linked camelid heavy-chain-only variable domains targeting BCMA[117]. Although not compared prospectively, patients receiving this product have been shown to have higher ORRs with longer response durations compared to those receiving the single-chain variable fragment-containing CAR idecabtagene vicleucel[21,22] (Table 3).

The trials leading to the approvals of all current CAR T cell therapies were conducted in patients with highly refractory malignancies who had previously received multiple lines of chemotherapy[9–11,21,22]. These patients often have baseline lymphopenia, and their previous treatments could impair T cell fitness[124]. Achieving a level of disease control that is sufficient to proceed to later-line CAR T cells might also

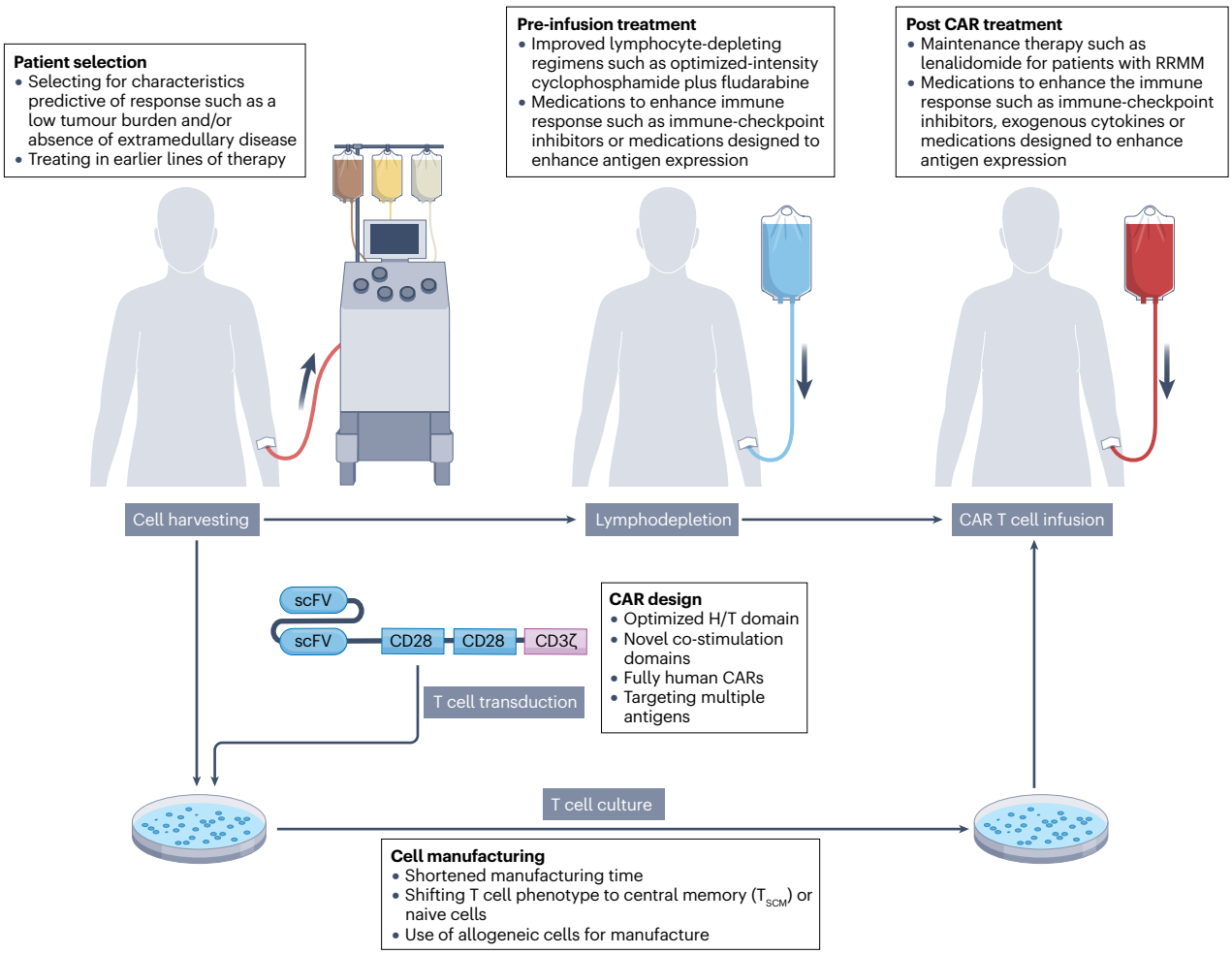

Fig. 2 | Investigational strategies designed to improve remission duration following CAR T cell therapy. The process of chimeric antigen receptor (CAR) T cell therapy involves harvesting peripheral blood mononuclear cells from a patient by apheresis, followed by transduction with viruses encoding the CAR, ex vivo T cell expansion, and re-infusion into the patient after completion of lymphocyte-depleting chemotherapy. Studies attempting to optimize each step of this process, and thus improve the durability of remissions following CAR T cell therapy, are currently ongoing. H/T, hinge and transmembrane; scFv, single-chain variable fragment; RRMM, relapsed and/or refractory multiple myeloma; T_{SCM}, stem central memory T.

not be feasible for patients with malignancies that are refractory to first-line chemoimmunotherapy given that the time from harvesting peripheral blood mononuclear cells to CAR T cell infusion can be as long as several weeks. Administering CAR T cells earlier in the course of malignancy might avoid these problems and improve response rates. Promising results with such an approach were described in a report from the ZUMA-12 trial. This trial involved patients with high-risk aggressive B cell lymphomas who had a positive interim PET scan after two cycles of first-line chemoimmunotherapy[65]. An impressive CR rate of 78% was observed, with 86% of these responses ongoing at a median follow-up duration of 16 months[65]. Circulating CAR T cell numbers were also higher in the ZUMA-12 study, in which CAR T cells were the second line of treatment, as compared to ZUMA-1, in which CAR T cells were the third line of treatment, despite the use of a similar methodology in both trials[125]. Multiple trials evaluating CAR T cell therapy in earlier lines of treatment are currently ongoing (such as NCT04923893 and NCT05605899).

The medications patients receive prior to apheresis, as bridging therapy between apheresis and CAR T cell infusion and as lymphocyte-depleting chemotherapy before infusion, is another area for optimization[28]. Limited data are available on how medications administered at any of these stages affect subsequent responses to CAR T cells[126–129] and most current practices are driven by a combination of the protocols used in previous trials and expert guidance[130]. Lymphocyte-depleting chemotherapy is an important area of investigation that clearly improves response rates, although more intensive lymphodepletion also leads to increased toxicities[28]. Agents aside from lymphocyte-depleting chemotherapy could be given before or after infusion either to alter antigen expression on malignant cells or to directly alter CAR T cell function. Examples of these approaches include γ-secretase inhibitors given prior to BCMA-targeted CAR T cells to increase BCMA expression[131], administration of ibrutinib concurrently with CD19-targeted CAR T cells in patients with CLL to alter the immune environment[132,133], delivery of IL-15 or other cytokines to enhance CAR T cell expansion,

and immune-checkpoint inhibitors given after CAR T cells to promote anticancer immunity[134]. Overall, we have much more to learn about the effects of specific medications at all steps of the CAR T cell process.

Cell manufacturing protocols are another area of potential improvement[135]. T cells can have a range of differentiation states with heterogenous functions[136,137]. Data from several studies suggest a link between the characteristics of T cells in the infusion product and subsequent CAR responses[120,138–140]. The ideal T cell composition is not yet known, although, in general, the presence of less-differentiated naive T cells or central memory T cells seems to be important for a response to adoptive cell therapies[141–143]. Shifting T cell phenotypes by growing the cells in the presence of specific cytokines[144–146] or inhibiting specific cell signalling pathways is another possibility[135,147,148]. Longer durations of ex vivo culture have also been associated with increased T cell exhaustion and less favourable T cell phenotypes[135,149]. Multiple efforts to shorten T cell manufacturing times are therefore currently ongoing[150,151]. The advent of new manufacturing methods might enable the generation of products both with improved phenotypes and with faster production times to ameliorate the problem of disease progression during cell manufacture. Similarly, efforts to use allogeneic cells might eventually improve efficacy because more robust T cells derived from donors without cancer could be used as the source material[152].

Conclusions

CAR T cells are a potent treatment option for patients with haematological malignancies, with long-term data demonstrating robust efficacy and overall low levels of toxicity. The highly durable remissions observed after CD19-targeted CAR T cell therapy in patients with B cell lymphoma demonstrate the potential of this therapeutic modality to induce curative remission in patients with chemotherapy-refractory malignancies. CAR T cells can also serve as an important bridge to allogeneic HSCT in patients with B-ALL and can provide prolonged treatment-free remission for patients with MM. Numerous promising areas of investigation have the potential to improve the durability of remission after this therapy. Overall, we are at an exciting time in the development of CAR T cells, with improving responses and additional treatment indications continuing to emerge.

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