Published in final edited form as:

Cancer J. 2014 ; 20(2): 112–118. doi:10.1097/PPO.0000000000000031.

CD19-CAR Trials

Carlos A. Ramos, MD^{1,2}, Barbara Savoldo, MD, PhD^{1,3}, and Gianpietro Dotti, MD^{1,2}

¹Center for Cell and Gene Therapy, Baylor College of Medicine, The Methodist Hospital and Texas Children's Hospital, Houston, TX, USA

²Department of Medicine, Baylor College of Medicine, Houston, TX, USA

³Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA

Abstract

CD19 is a B-lineage specific transmembrane glycoprotein, the expression of which is maintained on more than 95% B-cell malignancies. This strict lineage restriction makes CD19 an ideal target for immune therapies using chimeric antigen receptors (CARs). Here we review published phase I trials of T cells expressing CARs targeting CD19 and describe briefly the biological questions that they addressed. All patients treated in these trials had relapsed B-cell malignancies, which in many cases were chemorefractory. Nonetheless, major responses have been observed, especially in patients with CLL and ALL. Many of these responses were accompanied by a systemic inflammatory reaction syndrome that could be life-threatening but was almost always reversible with adequate medical management. Given their remarkable activity, CD19-CAR T cells are likely to be quickly incorporated into the management of B-cell neoplasms and have become the paradigm for similar strategies targeting other cancers.

Introduction

CD19 is a 95-kDa B-lineage specific transmembrane glycoprotein, which functions as a central response regulator in B lymphocytes by decreasing the threshold for antigen receptor-dependent stimulation, thereby enabling B cell activation when few receptors are engaged.¹ With the important exceptions of hematopoietic stem cells and plasma cells, CD19 is expressed during all stages of B-cell differentiation and is maintained on cells that have undergone neoplastic transformation,² being expressed on more than 95% of B-cell non-Hodgkin lymphoma and chronic lymphocytic leukemia. Recent studies have also shown that CD19 expression is maintained despite loss of CD20 expression following treatment with CD20 antibodies, which are frequent components of regimens currently used in the management of these disorders.³ This strict lineage restriction makes CD19 an attractive immunotherapeutic target and strategies directed at this antigen have become the paradigm for therapies employing chimeric antigen receptors (CARs). Here we will review in an approximate chronological fashion published phase I trials, summarized in table I, of T cells expressing CARs (CAR-T cells) that target CD19 (CD19-CAR) and briefly describe the biological questions that they have tried to address or allowed to answer. All CD19-CARs used in these trials contain a single-chain variable fragment (scFv) derived from one of two CD19 monoclonal antibodies, FMC63⁴ or SJ25C1,⁵ as noted in the table. For a detailed discussion of the history, design and T-cell transfer of CARs, we refer the reader to the other articles in this issue.

Corresponding author: Carlos A. Ramos, MD, Assistant Professor of Medicine, Center for Cell and Gene Therapy, Department of Medicine, Baylor College of Medicine, One Baylor Plaza BCM 505, Houston, TX 77030, caramos@bcm.edu, Phone: 832-824-4817, Fax: 832-825-4732.

ζ-chain signaling is insufficient for CAR-T cell persistence

Similar to initial phase I studies using CARs in cancer patients with renal cell carcinoma,⁶ neuroblastoma⁷ and ovarian cancer,⁸ early experience in treatment of B-cell malignancies with CD19-CAR T cells showed the feasibility of the approach, but also a lack of objective antitumor effects. All of these trials used so-called first-generation CARs, which contain a single signaling domain, most often the ζ chain of the CD3/TCR complex.

In one of these studies, 2 patients with refractory follicular lymphoma received T cells expressing a CD19-CAR after undergoing treatment with lymphodepleting doses of fludarabine. These T cells had undergone polyclonal activation with a CD3 antibody (OKT3), plasmid electroporation and hygromycin selection (for which the plasmid also encoded a resistance gene). After CAR-T cell infusion, patients received low-dose subcutaneous IL-2 injections. Detection of transferred T cells by PCR was shorter than 7 days. As expected from this limited persistence, neither clinical responses nor overt toxicities were observed. Of note, cellular antitransgene immune rejection responses were documented in both patients, although it is unknown whether this activity was directed at the CAR or the hygromycin resistance gene.⁹ Results from trials such as this using first generation CAR-T cells demonstrated that a single stimulatory domain was insufficient to fully activate the chimeric T cells. In addition, they raised the concern that immune anti-transgene product responses can occur, although this would not be a significant issue in later trials.

Costimulatory domains and host lymphopenia are important for CAR-T cell persistence and proliferation

Costimulatory signals are crucial for T cell function since αβ-TCR stimulation in absence of costimulation by other immune accessory receptors induces T cell anergy. Since CAR activation by its ζ-chain simulates only stimulation of the αβ-TCR, the absence of costimulatory signals is very likely implicated in the limited activity seen with first-generation CARs. Indeed, a pre-clinical study of CD19-CARs indicated that concomitant stimulation of CD28 by CD80 was required for optimal antitumor activity.⁵

To improve CAR-T cell function and persistence, so-called second-generation CARs incorporate costimulatory endodomains (such as CD28, OX40 or 4-1BB) to ensure the transgenic T cells are fully activated after their encounter with their specific target.^{10–14} In pre-clinical studies, T cells expressing CARs encoding co-stimulatory endodomains exhibit potent antitumor activity and secrete significant amounts of IL-2, enhancing their persistence in vivo.^{13, 15}

An early report of a trial using a second generation, CD28-containing CD19-CAR described one patient with advanced follicular lymphoma, who was treated with a preparative chemotherapy regimen followed by autologous T cells that were retrovirally modified to express the CAR. The patient's tumor underwent partial regression and B cells were absent from circulation for at least 39 weeks after T-cell infusion, despite recovery of other blood cells. The CD19-CAR transgene was detected in the peripheral blood up to 27 weeks after infusion.¹⁶

Although the use of chemotherapy precluded attribution of the full therapeutic effect to the activity of CAR-T cells, results of these and similar studies corroborated the notion that host lymphopenia facilitates expansion of adoptively transferred T cells. On one hand, lymphopenia creates space for the oncoming adoptively transferred cells and, on the other, induces their homeostatic expansion. The latter effect is likely mediated through

chemotherapeutic ablation of endogenous regulatory T cells, which normally secrete inhibitory cytokines (e.g. TGF- β and IL-10) that limit effector T cell expansion.¹⁷ Additionally, T-cell growth homeostatic cytokines, such as IL-7 and IL-15, which ordinarily exist in limiting amounts, may become readily available due to less competition and increased production by lymphopoietic stromal cells.¹⁸ Thus, induction of lymphodepletion prior to infusion of CAR-T cells continues to be often incorporated in trials using CAR-T cells.

The superiority of second- over first-generation CAR-transduced T cells was decisively demonstrated in study comparing two constructs head to head.¹⁹ This phase I trial treated subjects with refractory or relapsed B cell lymphomas, mostly diffuse large B-cell lymphomas, who were simultaneously infused with two autologous T cell products, both retrovirally transduced with a CD19-CAR but with one CAR encoding both CD28 and ζ endodomains while other including only the ζ endodomain. This strategy allowed direct measurement of the consequences of adding a CD28 costimulatory endodomain to CAR-redirected T cells in the same subject and established that T cells bearing a CAR that contains the CD28 endodomain (second generation) have enhanced in vivo proliferation and survival compared to T cells expressing a CAR lacking CD28 (first generation). As in most other CD19-CAR trials, CAR-T cells could be detected at sites of disease. Nonetheless, in vivo CAR-T cell expansion was still modest and clinical responses were limited, with only two patients having transient stable disease and four showing progression of disease. This inadequate activity suggested that alternative costimulatory domains (or a different CAR design) might be more potent activators of chimeric T cells. As in the trials reported until then, no significant side effects were seen.

Later acting costimulatory domains may be more efficacious than CD28

While costimulatory signals from CD28 seemed to improve expansion and persistence, the most dramatic results regarding expansion and clinical activity in indolent B-cell malignancies were reported in a trial using a second generation CAR incorporating 4-1BB (CD137) as a costimulatory domain.²⁰ CD28 costimulation is usually provided physiologically by professional APCs and represents an “early” costimulatory signal, but crucial roles are played by “late” costimulatory molecules, including members of the tumor necrosis factor receptor family (TNFR) such as OX40 (also known as CD134) and 4-1BB. After binding to their specific ligands, these molecules recruit TNFR-associated-factor (TRAF) adapter proteins, which represent an entirely distinct activation pathway from CD28 costimulation and may be associated with more potent activation of T cells,²¹ at least in particular disease settings.

The first 3 patients reported from this second-generation, 4-1BB-containing CD19-CAR trial had large burden, relapsed B-cell CLL and were infused with autologous CAR-T cells after receiving lymphodepleting chemotherapy.^{20, 22} In contrast to other trials, a lentivirus was used to transfect T cells. These CAR-T cells had a greater than 1,000-fold expansion, trafficked to bone marrow, and continued to express functional CARs at high levels for at least 6 months. Despite large tumor burdens, impressive results were obtained, with 2 long term complete remissions and 1 prolonged partial remission seen in the 3 CLL patients treated. Each infused CAR-bearing T cell was calculated to have eradicated at least 1,000 CLL cells on average. Significant adverse effects were noted, however, including an acute systemic inflammatory response syndrome (fever with hypotension, respiratory distress or tumor lysis syndrome) as well as late on-target, off-tumor toxicities, such as B-cell aplasia associated with decreased numbers of plasma cells and hypogammaglobulinemia (see section on toxicities).

Nonetheless, whether “late” costimulatory domains are always better than “early” ones is far from being settled. Other reports of CD28-containing CD19-CAR trials have continued to show encouraging activity, while reinforcing the need for lymphodepletion prior to CAR-T cell infusion, at least in the autologous setting. For example, the outcomes of 7 additional patients were described in an update to the single patient report mentioned in the previous section.²³ Five patients achieved partial remissions and one patient had a complete remission that lasted longer than 60 weeks. Four patients had long-term depletion of normal B cells and an equal number had prominent elevations in serum levels of the inflammatory cytokines IFN- γ and TNF- α , which appeared to correlate with the severity of acute toxicities (fever and hypotension).

A similar second-generation, CD28-containing CAR was used in another trial in which 8 CLL and 1 ALL patients were treated.²⁴ All patients tolerated the CAR-T cell infusions well, but one patient had rapid clinical deterioration and died less than 48 hours after CAR-T cell infusion (see section on toxicities). Some of the other patients developed fever with or without hypotension a few days after T-cell infusion. One of the patients with CLL had a partial response and none of them developed B-cell aplasia. In contrast, the ALL patient, who was treated in remission, developed B-cell aplasia despite recovery of other hematopoietic series, which lasted until he received an allogeneic transplant 8 weeks later. Persistence of infused CAR-T cells was inversely proportional to the tumor burden but enhanced by prior cyclophosphamide administration, further favoring the use of lymphodepleting chemotherapy before CAR-T cell infusion.

Highly aggressive hematopoietic malignancies are also susceptible to killing by CAR-T cells

Likely because the graft-versus-leukemia effect is known to be more marked against indolent NHL and CLL, and because the slower pace of these diseases is more forgiving regarding manufacture timing, most initial CD19-CAR T-cell protocols treated only patients with those conditions. Nonetheless, recently published results suggest that highly aggressive malignancies, such as B-cell acute lymphoblastic leukemia (ALL), even when chemorefractory, are also excellent targets for this technology.

In one trial using T cells transduced with a second-generation, CD28-containing CD19-CAR for the treatment of B-cell ALL, of the 5 patients treated, 2 had significant refractory disease (more than 60% blasts in the bone marrow) and 2 had minimal residual disease at the time of T-cell infusion.²⁵ All achieved complete remission (negative minimal residual disease) after lymphodepleting doses of cyclophosphamide and CAR-T cell infusion. The potential duration of these responses is unknown because all but one of the patients proceeded to allogeneic stem cell transplantation. The patient who was not eligible for allogeneic transplantation had evidence of relapse 90 days after T-cell infusion. Of note, in this study, the reappearing leukemic cells were still positive for CD19. A systemic inflammatory syndrome (fever and hypotension with elevation in circulating cytokine levels) was seen in the patients with the highest burden of disease at the time of treatment, starting 3 to 5 days after CAR-T cell infusion. Transient mental status changes were also observed in these patients. Symptoms abated rapidly and cytokine levels normalized quickly after high dose steroids were administered approximately 6 days after cell infusion.

Another report on the use of CAR-T cells for treatment of patients with B-cell ALL describes the outcomes of two patients.²⁶ Both had active disease, which had multiple relapses after chemotherapy. One patient had received an allogeneic unrelated cord blood transplant and at time of T cell collection, her PBMCs were 68% donor origin; the other received autologous cells. Both patients entered complete remission. The post-allogeneic

transplant patient experienced relapse 2 months after T cell infusion, with CD19-negative leukemic cells, suggesting emergence of a leukemic clone that escaped immune recognition by CAR-T cells. As in the other study treating patients with ALL, a systemic inflammatory reaction syndrome with fever and hypotension, leading to respiratory failure in one of the patients, was observed in both patients. One of the patients had also transient neurological abnormalities.

CAR-T cell approach can be extended to the allogeneic setting

Because of the theoretical risk of inducing graft-versus-host-disease (GVHD) when polyclonal activated T cells are used, most CD19-CAR T cell trials reported so far used autologous T cells. An alternative to using polyclonal, non-specifically activated transduced T cells is to transfer the CAR into T lymphocytes with well-defined specificity (such as viral specificity) through their native antigen receptor, so as to exclude alloreactive cells.²⁷⁻²⁹ Another potential advantage of these virus-specific T cells is that they should be repeatedly boosted and activated in vivo by the engagement of their native $\alpha\beta$ -TCR with viral epitopes on professional antigen presenting cells, provided their specificities are directed against latent or frequent infections. By providing all necessary costimulatory signals, this strategy should maintain a pool of transgenic virus-specific T cells, allowing the CAR to redirect the activated cells to tumor cells. This principle has been tested in pre-clinical studies²⁷⁻²⁹ and in a clinical trial of neuroblastoma, in which patients were treated with both polyclonal T cells and EBV-specific T cells that were genetically modified to express two distinguishable, but functionally identical, CARs that target GD2, a neuroblastoma antigen. This trial showed that costimulation of GD2/EBV-specific T cells by latently infected B lymphocytes in EBV-seropositive patients increases their persistence compared to polyclonal GD2-specific T cells.^{30, 31}

This rationale was used in a clinical trial of patients with B-cell malignancies (high risk CLL, transformed CLL and ALL) who had relapsed or were at high risk for relapse after allogeneic hematopoietic stem cell transplantation (allo-HSCT).³² CD19-CAR T cell products were generated from the hematopoietic stem cell transplant donor and were given without pre-infusion chemotherapy (initially, only patients with documented relapsed disease were allowed on study and thus the first 6 patients were treated months to years after their stem cell transplant). T cells were activated and expanded with EBV, CMV and adenoviral antigens before being transduced with the CD19-CAR, with resulting lines that were specific against these 3 viruses through their native TCRs. A total of 8 patients were treated. All infusions were well tolerated without any evidence of systemic inflammatory effects and, importantly, no GVHD was observed. These multivirus-specific CD19-CAR-expressing T cells were detectable in peripheral blood up to 12 weeks following infusion. Objective responses were observed in 2 of 8 patients, 1 complete remission and 1 partial remission, both transient. As in many of the autologous trials, there was no correlation between transgene levels in the peripheral blood and clinical response. Moreover, patients for which long term follow up is available did not develop B cell aplasia or agammaglobulinemia. These data suggest that allogeneic virus-specific T cells expressing CD19-CAR are well tolerated by patients with relapsed B-cell malignancies post allo-HSCT and that, at periods of CAR-T cell persistence, these cells demonstrate antitumor activity.

In any case, in spite of the theoretical concerns, a recent report suggests that (as hinted by some pre-clinical models) polyclonal CAR-modified allogeneic T cells may not be associated with significant GVHD.³³ The 10 patients treated in this trial had hematologic malignancies that persisted after allo-HSCT and conventional donor lymphocyte infusions (DLI). CAR-T cells were prepared in a similar fashion to other protocols by the same group but the PBMCs used to prepare the products were obtained from the allogeneic stem cell

donors. Patients received a single infusion of these allogeneic CAR-T cells and 3 patients had objective responses, including one complete remission in a CLL patient. Toxicities included transient hypotension, fever and tumor lysis syndrome, but none of the patients developed GVHD. Notably, CAR-T cells were able to expand and exert their activity without lymphodepleting chemotherapy given immediately preceding their infusion.

CAR-T cell activation can be associated with toxicity

In contrast to drug therapies, the toxicities of which tend to improve with their discontinuation, T- cell therapies may cause prolonged toxicities, especially when these cells persist long term. As already mentioned, several recent serious adverse events have been reported in subjects receiving CD19-CAR T cells. While some are acute and potentially reversible, some chronic effects related to long-term persistence of these cells have also been described.

The first significant adverse event reported in one of these trials involved a second-generation, CD28-containing CAR.^{24, 34} A patient with bulky CLL and extensive previous treatment, who received autologous CAR-T cells after lymphodepletion with cyclophosphamide, developed fever, hypotension and dyspnea 6 hours post infusion, which progressed rapidly, leading to his death. In this patient, elevated cytokine levels were seen and an autopsy failed to reveal an obvious cause of death. The investigators concluded that sepsis was the most likely cause in this heavily pre-treated, immunosuppressed patient but the possibility that a cyclophosphamide-induced “cytokine storm” might have enhanced the in vivo activation of the modified T cells could not be excluded.³⁴

Later, it was reported that the patients treated with T cells expressing a second-generation, 4-1BB-containing CD19-CAR had also clinical pictures consistent with a systemic inflammatory reaction syndrome or cytokine storm (fever, tachycardia, hypotension requiring pressors, capillary leak syndrome, respiratory distress) and required hospitalization, although in this case symptoms occurred 7 to 21 days after T-cell infusion. All recovered without sequelae, in some cases after receiving steroids. In addition, this is was the first report describing that patients with complete remission of their CLL also developed persistent B-cell aplasia due to elimination of non-neoplastic B cells by the CAR-transduced T cells, which persisted long-term.

Similar inflammatory syndromes have been described in other CD19-CAR trials reported by the same and other groups, as already noted.^{23, 25, 26, 33} Elevation of circulating cytokine levels, including IL-6, TNF- α and IFN- γ is observed in parallel with these syndromes. In some cases, a constellation of findings resembling macrophage activation syndrome or hemophagocytic lymphohistiocytosis (elevated ferritin levels, coagulopathy and hepatosplenomegaly) has also been described. As already noted, in ALL patients, central nervous system toxicity (including confusion) of unclear etiology has also been observed.²⁶

Overall, the data suggest that this cytokine release syndrome or systemic inflammatory reaction syndrome is commonly associated with anti-leukemic effects. These syndromes can occur up to 3 weeks after CAR-T cell infusion, although they seem to be more common within the first to second weeks, and their severity seems to be roughly proportional to the tumor burden. In most cases, these symptoms resolve quickly with steroids and neutralizing monoclonal antibodies targeting TNF- α and the IL-6 receptor.^{35–38}

Given reports of these toxicities, there is a renewed interest in developing means to control the activity of engineered T cells employing on-demand suicide systems.^{39, 40} In addition, targeting even more restricted B cell antigens, such as the kappa and the lambda light chain

common regions may be a way to prevent long term B-cell aplasia if CAR-T cells persist long term.⁴¹

Conclusions

CD19-CAR expressing T cells have evidenced remarkable activity against B-cell malignancies, especially CLL, indolent NHL and ALL, with significant responses seen even in chemorefractory disease, although follow-up is short and thus the duration of remissions is unknown. More modest activity has been seen to date in DLBCL. Although any conclusions are limited by the restricted number of patients treated so far, a few generalizations have emerged. To be effective, CARs need to contain an integrated costimulatory domain. Moreover, effective cell doses are 1 to 3 logs lower than those used in other T-cell therapies (DLI, tumor infiltrating lymphocytes, or transgenic $\alpha\beta$ -TCR T cells). Furthermore, there appears to be a threshold dose for antitumor effect to occur but it is unclear if there is a classic dose-response or dose-toxicity relationship. Finally, the most effective treatment protocols have employed pre-infusion chemotherapy and, despite some exceptions, lymphodepletion prior to CAR-T cell administration may be an important component of this treatment approach.

Despite their remarkable activity, many unanswered questions remain regarding CAR engineering and specific clinical applications. Thus far, it is unclear if there is an optimal method for CAR transfer into T cells (retroviral, lentiviral or other) and whether specific costimulatory domains are better than others. Also uncertain is whether the nature of other portions of the CAR (including the hinge and transmembrane regions) affect the activity of CAR-T cells, and whether there is an affinity range for the scFv that is optimal for CAR-T cell activation. Furthermore, we do not know if differential transduction of specific T-cell subpopulations (for example, memory versus effector cells) is crucial for the activity and persistence of these cells, as it has been proposed in primate models.⁴² In addition, although it is clear that severe side effects due to lysis of tumor cells and release of inflammatory cytokines can occur after administration of these cells, it is not established if the occurrence of this systemic syndrome is required for full antitumor response, or if and when this inflammatory cascade should be interrupted. Finally, it is unknown if CD19-CAR T cells will be effective enough so as to replace hematopoietic stem cell transplantation altogether or whether their major role will be as a consolidation strategy or a bridge to transplantation.

Nevertheless, the results seen with CD19-CAR T cells were unimaginable a decade ago. Numerous trials are currently expanding these findings and addressing many of these questions.^{35–38,43} Given the data so far, it is fair to expect that T cells carrying CARs directed at CD19 and other B-cell restricted targets will soon become part of our armamentarium against B-cell malignancies, and hopefully pave the way for similar therapies for other cancers.

Acknowledgments

Financial support: This work was supported in part by Leukemia and Lymphoma Society Specialized Center of Research (SCOR; grant number 7001-14) and by National Cancer Institute (grant 2P50CA126752).

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Clinical trials using CD19-targeted CAR-modified T cells with published results

Table 1

Reference	CD19-positive Targeted diseases	N	Construct	CAR gene transfer	T cell origin	T cell activation	Auxiliary therapy	Cell dose range (×10 ⁶)	Persistence	SAEs	Outcomes	Best response duration
Jensen (2010) ⁹	FL	2	FMC63 scFv + CH ₂ CH ₃ + CD4 _{TM} + CD3 ζ (1 st generation)	Electroporation (hygromycin selection)	Autologous	OKT3, feeders	FLU (post T-cell infusion) and IL-2	100–2,000/ m ²	< 1 wk	None	2 NR	N/A
Kochenderfer (2010) ¹⁶	FL	1	FMC63 scFv + CD28 + CD3 ζ (2 nd generation)	Retroviral	Autologous	OKT3	Lymphodepletion (CTX/ FLU) and IL-2	5/kg	Up to 27 wk	None	1 PR	PR × 39+ wk
Savoldo (2011) ¹⁹	DLBCL, transformed FL	6	FMC63 scFv + CH ₂ CH ₃ ± CD28 + CD3 ζ (1 st and 2 nd generation)	Retroviral	Autologous	OKT3	None	40–400/m ²	Up to 6 wk	None	2 SD, 4 NR	SD × 6 wk
Porter (2001) ²⁰ Kalos (2011) ²²	CLL	3	FMC63 scFv + CD8 _{TM} + 4-1BB + CD3 ζ (2 nd generation)	Lentiviral	Autologous	CD3/CD28 beads	Lymphodepletion (BEN or CTX/PTS)	0.15–16/kg	Up to 26 wk	TLS, SIRS, BC aplasia	2 CR, 1 PR	CR × 48+ wk
Brentjens (2011) ²⁴	CLL, ALL	9	SI25C1 scFv + CD28 + CD3 ζ (2 nd generation)	Retroviral	Autologous	CD3/CD28 beads	None or lymphodepletion (CTX)	2–30/kg	Up to 6 wk	Fever, death	1 PR, 2 SD, 1 cCR, 4 NR, 1 death	PR × 12 wk
Kochenderfer (2012) ²³	FL, CLL, SMZL	8	FMC63 scFv + CD28 + CD3 ζ (2 nd generation)	Retroviral	Autologous	OKT3	Lymphodepletion (CTX/ FLU) and IL-2	5–55/kg	Up to 26 wk	Mild SIRS, BC aplasia	1 CR, 5 PR, 1 SD, 1 NE	CR × 60+ wk
Brentjens (2013) ²⁵	ALL	5	SI25C1 scFv + CD28 + CD3 ζ (2 nd generation)	Retroviral	Autologous	CD3/CD28 beads	Lymphodepletion (CTX)	1.5–3/kg	Up to 8 wk	SIRS	4 CR, 1 cCR	CR × 13 wk
Grupp (2013) ²⁶	ALL	2	FMC63 scFv + CD8 _{TM} + 4-1BB + CD3 ζ (2 nd generation)	Lentiviral	Autologous (±allogeneic)	CD3/CD28 beads	None or etoposide/CTX	10–100/kg	Up to 26 wk	SIRS, CNS toxicity	2 CR	CR × 48+ wk
Cruz (2013) ³²	ALL, CLL, transformed CLL	8	FMC63 scFv + CH ₂ CH ₃ + CD28 + CD3 ζ (2 nd generation)	Retroviral	Allogeneic	EBV (LCL), CMV and Adv peptides (Mon)	Allo-HSC T preparative regimen; none immediately before T-cell infusion	19–110/ m ²	Up to 12 wk	None	1 CR, 1 PR, 1 SD, 2 cCR, 3 NR	CR × 12 wk
Kochenderfer (2013) ³³	CLL, DLBCL, MCL	10	FMC63 scFv + CD28 + CD3 ζ (2 nd generation)	Retroviral	Allogeneic	OKT3	Allo-HSC T preparative regimen, DLLi, none	1–10/kg	Up to 4 wk	TLS, SIRS, fever	1 CR, 1 PR, 6 SD, 2 NR	CR × 39+ wk

Reference	CD19-positive Targeted diseases	N	Construct	CAR gene transfer	T cell origin	T cell activation	Auxiliary therapy	Cell dose range (×10 ⁶)	Persistence	SAEs	Outcomes	Best response duration
immediately before T-cell infusion												

Abbreviations: FL: follicular lymphoma, DLBCL: diffuse large B-cell lymphoma, CLL: chronic lymphocytic leukemia; SMZL: splenic marginal zone lymphoma, ALL: acute lymphoblastic leukemia, scFv: single-chain variable fragment; patient, TM: transmembrane segment, –: none, EBV: Epstein-Barr virus, LCL: lymphoblastoid cell line, CMV: cytomegalovirus, AdV: adenovirus, Mon: monocytes, CTX: cyclophosphamide, FLU: fludarabine, BEN: bendamustine, PTS: pentostatin, Allo-HSCT: allogeneic hematopoietic stem cell transplantation, DL: donor lymphocyte infusion, TLS: tumor lysis syndrome, SIRS: systemic inflammatory syndrome, BC: B cell, CNS: central nervous system, NR: no response, SD: stable disease, PR: partial response, cCR: continued complete response (i.e. patient had no evidence of disease before and after infusion), CR: complete response; NE: not evaluable