

Review

Current Status of CAR-T Cell Therapy in Multiple Myeloma

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Abstract: Current data on CAR-T cell-based therapy is really promising in multiple myeloma, especially in terms of response. In heavily pretreated patients, who have already received proteasome inhibitors, immunomodulatory drugs and monoclonal antibodies, current trials report an overall response rate ranging from 81 to 97% and 45 to 67% of complete remission rates. Data are less encouraging in terms of duration of response, although most recent trials have shown significant improvements in terms of event-free survival, with medians ranging from 8 to 14 months and up to 77% progression-free survival at 12 months with an acceptable toxicity profile. These data will be consolidated in future years and will provide new evidence on the best timing for CAR-T cell therapy. Moreover, new CAR-T designs are underway and will challenge the current results.

Keywords: myeloma; CAR T-cells; target antigen



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1. Introduction

The introduction of proteasome inhibitors (PI) and immunomodulatory drugs (IMiDs) in the early 2000 has improved survival in patients with multiple myeloma (MM).

Currently, the standard treatment of MM is based on a combination of drugs with different mechanisms of action and synergistic effects, including proteasome inhibitors (bortezomib, carfilzomib, ixazomib), immunomodulatory drugs (thalidomide, lenalidomide, pomalidomide), alkylating agents (melphalan, cyclophosphamide, bendamustine), steroids and, recently, anti-CD38 monoclonal antibodies (daratumumab, isatuximab) and anti-SLAMF7 monoclonal antibody (elotuzumab). Furthermore, the addition of immunotherapy with conjugated antibodies (belantamab mafodotin) represents a therapeutic approach for refractory patients, improving survival expectations among this patient population.

Although all these drugs have improved the outcome of MM, most patients still die due to disease progression [1]. Patients who are refractory to PI, IMiDs and alkylating agents have a median overall survival of less than a year [2,3].

Therapy with genetically modified T-cells expressing a chimeric antigen receptor (CAR) represents a cutting-edge approach. Results reported in acute lymphoblastic leukaemia (ALL) [4] and non-Hodgkin lymphoma (NHL) [5–7] with CD19 CAR-T cells has led to the search for other targets and to expand this treatment to other diseases, such as MM. Therefore, the identification of new antigens in plasma cells which can be used as a potential target has become a priority in the development of new therapeutic approaches based on immunotherapy. Thus, extensive efforts are being put into the development of new CAR therapies to treat MM as well as novel bispecific T cell engagers/antibodies (teclistamab, talquetamab). Unlike CAR-T cell products, bispecific antibodies do not require long production times or adequate lymphocyte counts. By contrast, CAR-T cells require only one dose instead of continuous therapy with bispecific antibodies [8].

Selection of an adequate antigen is a key factor for the development of an optimal CAR-T cell product. As antigen recognition does not depend on the human leukocyte antigen (HLA) system, a tumour target should be present on the cellular surface.

One of these antigens is B-cell maturation antigen (BCMA), which is highly expressed on the surface of malignant plasma cells but not on normal tissues, except for a low expression on mature B-cells [9].

Different antigens are currently being evaluated as possible targets for CAR therapy, including CD138, CD19, kappa light chain and BCMA. Some trials using these antigens have shown promising results, mainly in terms of response rate. However, no plateau has been observed in overall survival and disease-free survival curves, which translates the lack of durable remissions. Therefore, it will be necessary to overcome potential limitations hindering the efficacy of CAR-T cells in MM, such as lack of effectiveness, off-tumour toxicities, loss of antigen or interference with soluble protein present in patients' plasma [10].

2. Results

Clinical trials of CAR-T cell therapy against MM have demonstrated promising clinical activity, providing unprecedented response rates in these heavily pretreated patients, the most commonly explored target being BCMA. There are more than 50 clinical trials ongoing using BCMA as a target. As mentioned previously, BCMA is a very specific antigen of plasma cells and mature B-cells, avoiding off-tumour toxicities following infusion [11,12].

The first clinical trial with BCMA-specific CAR was published in 2018 by Brudno et al. [13]. Sixteen patients received 9×10^6 CAR-BCMA T cells/kg. The patients had a median of 9.5 prior lines of therapy. The overall response rate was 81%, with 63% very good partial response or complete response. The median event-free survival was 31 weeks. Twelve patients (82%) developed CRS, including 6 (38%) with grade ≥ 3 CRS. Neurotoxicity was reported in 3 (19%) patients.

Idecabtagene vicleucel (ide-cel), initially known as bb2121, was developed by Bluebirdbio by transducing autologous T lymphocytes with a lentiviral vector to incorporate a second-generation CAR composed of an anti-BCMA single-variable chain domain, 41BB costimulatory domain and CD3-zeta as a signalling domain [14,15]. Lymphodepletion chemotherapy consisted of fludarabine and cyclophosphamide. In the dose escalating phase, the following doses were analysed: 50×10^6 , 150×10^6 , 450×10^6 and 800×10^6 CAR-positive (CAR+) T cells, with a 20% variation allowed. The expansion phase was achieved with 150×10^6 to 450×10^6 CAR+ T cells. A phase 1 trial using ide-cel included 33 patients who received multiple lines of treatment. The overall response rate was 85% with 45% of complete remission. Cytokine release syndrome (CRS) incidence was 76%, although only 2 patients developed CRS grade ≥ 3 . Results of the phase 2 trial (KarMMA) have been published by Munshi et al. [16,17]. Of 140 patients enrolled, 128 received ide-cel. Patients had a median of 6 prior lines of therapy, 84% were refractory to at least one PI, one IMiD and one anti-CD38. Eighty-eight percent received bridging therapy during the manufacturing process, but only 4% had some degree of response. With a median follow-up of 13.3 months, 94 of 128 (73%) patients had a response, and 42 of 128 (33%) achieved a complete remission (CR) or better. Thirty-three of 128 (26%) had CR with minimal residual disease (MRD)-negative status. Median progression-free survival (PFS) was 8.8 months and median overall survival was 19.4 months. The most common side effects among the 128 infused patients included neutropenia in 117 (91%) patients, anaemia in 89 (70%) and thrombocytopenia in 81 (63%). One hundred and seven (84%) developed CRS, including 7 (5%) with grade ≥ 3 CRS. Neurotoxicity was reported in 23 (18%) patients and were of grade 3 in 4 (3%) patients. Persistence of CAR+ T cells was documented in 59% of patients at 6 months and in 36% at 12 months following the infusion.

In addition to ide-cel, Wang B.-Y. et al. have developed a bispecific CAR with two BCMA binding sites (ciltacabtagene autoleucel or cilta-cel) [18,19]. A phase 1 study enrolled 57 patients, and lymphodepletion chemotherapy was based on single-agent cyclophosphamide. Fifty-one of 57 (90%) patients developed CRS, although only 7% had grade ≥ 3 CRS. Only one patient suffered from neurotoxicity. The overall response rate (ORR) was

88% with 47% of CR. Median PFS was 20 months. CAR+ T cells were not detectable in peripheral blood in 71% of patients at 4 months following infusion.

Similar results were reported in a phase 1b/2 study (CARTITUDE-1) performed in the United States [20]. Ninety-seven patients were enrolled; all of them had previously been exposed to PI, IMiDs and anti-CD38, and median lines of prior treatment was 6. Lymphodepletion included fludarabine and cyclophosphamide. The last update was presented at the European Hematology Association (EHA) congress in June 2021 [21]. The overall response rate was 97%, and 67% achieved CR. The median time to complete remission or better was 2 months (range, 1–15 months). Among 57 evaluable patients for MRD, 93% achieved MRD-negative status at 10^{-5} . At 12 months, PFS was 77%, and overall survival (OS) was 89%. Median PFS has not been reached yet. The most common grade 3/4 toxicities were neutropenia in 95% of patients, anaemia in 68% and thrombocytopenia in 60%. Cytokine release syndrome was reported in 95% of the patients, 4% were grade 3/4, median time to onset was 7 days and median duration was 4 days. One patient died due to grade 5 CRS and hemophagocytic lymphohistiocytosis (HLH). Neurotoxicity occurred in 21% of the patients, and 10% were grade 3/4.

Cohen et al. [22] conducted a phase I study (NCT02546167) to evaluate autologous T cells lentivirally-transduced with a fully-human, BCMA-specific CAR containing CD3 ζ and 4-1BB signalling domains (CART-BCMA). Twenty-five subjects were treated in 3 cohorts: (1) 1.5×10^8 CART-BCMA cells alone; (2) cyclophosphamide $1.5 \text{ g/m}^2 + 1.5 \times 10^7$ CART-BCMA cells; and (3) cyclophosphamide $1.5 \text{ g/m}^2 + 1.5 \times 10^8$ CART-BCMA cells. Toxicities included CRS 22/25 patients (88%) (32% g3-4) and neurotoxicity 8/25 patients (32%) (12% G3-4). The following responses were seen: 44% in cohort 1, 20% in cohort 2 and 64% in cohort 3 (including 5PR, 5 VGPR and 2CR)

Finally, the Memorial Sloan Kettering Cancer Centre group has developed a fully human anti-BCMA CAR-T cell (JCARH125, orvacabtagene-autoleucel, orva-cel) [23]. Infusion ratio CD4:CD8 is 1:1 to enhance memory T cell expansion [24]. Phase 1/2 trial (EVOLVE study) [25] still has a follow-up of only 6 months, but ORR of patients who received doses between 300 and 600×10^6 CAR+ T cells was 92% and 35% were CR. Ninety-four percent of patients were refractory to one PI, one IMiD and one anti-CD38, and median number of prior regimens was 6. Incidence of CRS was 89%, only 3% developed grade ≥ 3 . Neurotoxicity occurred in 13%, 3% were grade ≥ 3 . There were no data on PFS in this study at the time of writing this manuscript.

These encouraging results need to be confirmed in phase 3 studies. There are two ongoing phase 3 trials (KarMMa-3 and CARTITUDE-4) comparing the efficacy and safety of BCMA CAR-T cell versus other anti-MM therapies treatments, both given in early stages of the disease.

All these studies are summarized in Table 1.

Table 1. Summary of clinical trials on MM using CAR-T.

Study	n	Phase	Vector	Product	Costimulatory Domain	LD Chemo Therapy	CAR_T Cell Dose	Previous Lines Median	CRS \geq Grade 3	ICANS \geq Grade 3	ORR %	CR %	MDR neg %	Median PFS (Months)	Median OS (Months)
CRB-401 ¹	33	1	Lenti	Ide-Cel (bb2121)	4-1BB	FluCy	50/150/450/800 $\times 10^6$ cells	7	6	3	85	45	94	11.8	NA
KArMMA _{2,3}	128	2	Lenti	Ide-Cel (bb2121)	4-1BB	FluCy	150/300/450 $\times 10^6$ cells	6	6	3	73	53	33	8.8	19.4
LEGEND-2 ³	57/74	1	Lenti	Ciltacabtagene Autoleucel LCAR-B38M (JNJ68284528)	4-1BB	Cy	0.5 $\times 10^6$ cells / kg	3	7	0	89	74	68	19.9	36.1
CARTITUDE-1 _{4,5}	97	1b/2	Lenti	Ciltacabtagene Autoleucel LCAR-B38M (JNJ68284528)	4-1BB	Flu/Cy	0.75 $\times 10^6$ cells / kg	6	4	10	97	67	93	Not reached	NA
EVOLVE ⁶	44	1	Lenti	Orvacabtagene autocel (JCARH125)	4-1BB	Flu/Cy	50/150/450 $\times 10^6$ cells	7	9	7	82	27	67	NA	NA
EVOLVE ⁷	62	1	Lenti	Orvacabtagene autocel (JCARH125)	4-1BB	Flu/Cy	300/450/600 $\times 10^6$ cells	6	3	3	92	35	96	NA	NA
NCI ⁸	16	1	Retro	NA	CD28	Flu/Cy	9 $\times 10^6$ cells/kg	9	38	19	81	63	100	31 wks	NA
UPENN ⁹	25	1	Lenti	NA	4-1BB	None or Cy	10/50/100/500 $\times 10^6$ cells	7	32	12	63	28	33	65-125 d	502 d
CT053 ¹⁰	24	1	Retro	CT053	4-1BB	Flu/Cy	150 $\times 10^6$ cells	4.5	0	4	88	83	85	NA	NA
Dual CD19-BCMA ₁₁	10	1	Lenti	Sequential CART-CD19/CART-BCMA	CD28	Flu/Cy	CD19: 1 $\times 10^7$ cells BCMA: 3/5/6.5 $\times 10^7$ cells	4	10	0	90	40	30	5	NA

Table 1. Cont.

Study	n	Phase	Vector	Product	Costimulatory Domain	LD Chemo Therapy	CAR_T Cell Dose	Previous Lines Median	CRS \geq Grade 3	ICANS \geq Grade 3	ORR %	CR %	MDR neg %	Median PFS (Months)	Median OS (Months)
FHVH-BCMA-T ₁₂	21	1	Retro	FHVH-BCMA-T	4-1BB	Flu/Cy	0.75/1.5/3/6/12 $\times 10^6$ cells	6	19	10	90	NA	NA	NA	NA

Adapted from Wudhikarn ASH 2020; ¹. Raje NEJM 2019; ². Munshi 2020; ³ Berdeja Blood 2019; ³⁴ Wang Blood 2019, 134 (supl 1): 579; ⁴. Maduri Blood 2019, 134 (supl 1): 577; ⁵ Berdeja JCO 2020, 38 (supl 15): 8505; ⁶. Stadtmauer Science 2020; ⁷. Mailankody JCO 2020, 38 (supl 15): 8504; ⁸. Brudno JCO 2018; ⁹. Cohen JCO 2019; ¹⁰. Jie Blood 2019, 134 (supl 1): 4435; ¹¹. Yan Cancer Medicine 2021. ¹². Mikkilineni Blood 2020, 136 (supl 1): 50–51.

An important issue which will lead to discussion will be to define the place of new alternative approaches, such as conjugated antibodies or bispecific antibodies in the MM treatment algorithm, and whether, due to their safety profile, there will be a patient profile who will benefit more from these approaches than from CAR-T cell treatment.

Unfortunately, although most anti-BCMA CAR-T cell studies have described remarkable efficacy in terms of responses, event-free survival curves did not show a plateau, and most patients eventually relapse. Mechanisms related to CAR-T cell failure or resistance are multifactorial, including patient's characteristics and disease biological features [26]. Loss of antigen at the time of relapse is one of the main mechanisms of resistance. In this regard, a selection of a clone with homozygous deletion of BCMA has been recently reported as the underlying mechanism of immune escape after anti-BCMA CAR-T cell therapy [27].

There are three ways to overcome this obstacle, namely CAR-T cells directed towards other antigens, dual CAR-T cells and antigen overexpression strategies [28,29].

Regarding the development of dual CAR-T cells, one potential approach is the elaboration through a bicistronic vector of two different CARs on the same T cell [30,31], another approach is the administration of two CAR-T cells produced independently and infused together or sequentially. Fernandez de Larrea et al. [30] demonstrated that expressing two CARs on a single cell enhanced the strength of CAR-T cell/target cell interactions. Also, developing a single product significantly reduces cost resources and time.

There are different ongoing clinical trials evaluating the efficacy and safety of anti-CD38 CAR-T cells alone or in combination with other CARs. The phase 1 study NCT03464916 evaluates an anti-CD38 CAR-T cell in relapse/refractory (R/R) MM patients. No results have been published yet. A phase 1/2 study, NCT03767751, is testing a dual anti-CD38 and BCMA CAR-T cells [32], and the phase 1/2 study NCT03125577 is assessing the combination of an anti-CD19 CAR-T cell plus an anti-CD38 CAR-T cell.

Regarding antigen overexpression strategies, the administration of an oral gamma secretase inhibitor to increase BCMA expression on the plasma cell surface has been assessed in a clinical trial (NCT03502577), and preliminary results in 6 patients showed an ORR of 100% [33–35]. In this sense, various approaches are being evaluated at the pre-clinical level, such as the case of trans retinoic acid (ATRA) (García-Guerrero et al.) [36]. It has recently been reported that BCMA expression in myeloma cells can be increased by epigenetic modulation with ATRA. After ATRA treatment, MM cells have an increased susceptibility to anti-BCMA CAR-T cell treatment in vitro and in vivo preclinical models, which can be further increased by combined treatment of ATRA and g-secretase inhibitors. Some other relevant pre-clinical data has been recently published. In this sense, GPRC5D has been reported as a novel target antigen for the immunotherapy of MM. GPRC5D is a human orphan family C G protein-coupled receptor recently described to be expressed on 98% of CD138-positive cells [37,38]. The restricted expression pattern of GPRC5D makes it an ideal target for immunotherapy. Consequently, GPRC5D CAR-T cells were generated by Smith et al. [38], showing anti-tumour efficacy against myeloma cells both in vitro and in vivo. Of note, GPRC5D CAR-T cells were also effective in eradication of myeloma cells after BCMA CAR-T cell treatment in a mouse model, which might be an option to overcome BCMA antigen escape.

Preclinical studies have also shown that CD138 is an effective target for the treatment of MM [39]. There is only one published study with an anti-CD138 CAR-T cells for R/R MM patients treated with chemotherapy and autologous stem cell transplant (ASCT). The CAR gene was detectable in peripheral blood of all patients and persisted for at least 4 weeks after the infusion. Four patients responded, but none of them achieved a CR; response lasted from 3 to 7 months. The remaining patients progressed despite having detectable CAR in marrow samples until day +90.

Although CD19 expression is uncommon on plasma cells, there is a small population of CD19+ myeloma cells which could constitute a reservoir of myeloma-initiating stem cells. The presence of CD19+ myeloma cells has been associated with a higher relapse rate and poor overall survival [40]. Therefore, targeting CD19 represents an interesting

strategy to eliminate this subset of CD19+ cells. In the NCT02135406 study, ten patients with refractory MM received anti-CD19 CAR-T cells following an ASCT [41]. All patients received a previous ASCT, which resulted in a poor response with a PFS of less than one year. CD19 expression on myeloma cells was assessed by flow cytometry. As expected, the predominant myeloma population was CD19- in all patients. However, 7 out of 9 evaluable patients had subpopulations of CD19+ cells, ranging from 0.04% to 1.6%. In 10 of 11 subjects, the maximum planned dose of CTL019, 5×10^7 cells, was manufactured. In one subject, manufacturing was unsuccessful due to failure of autologous T cells to proliferate in culture. The median transduction efficiency was 10.1% (range 1.2–23.2), and the median total T cell dose was 4.4×10^8 (range 1.1×10^8 to 6.0×10^8). An ORR was achieved in 8 patients at 100 days after ASCT (including 1sCR, 4 VGPR, and 2 PR). This might be due to the fact that a significant fraction of myeloma cells expresses CD19 at molecular density, which is detectable by direct stochastic optical reconstruction microscopy (dSTORM) but not by flow cytometry [42]. Interestingly, less than 100 CD19 molecules are required for myeloma cell detection by CD19 CAR-T cells. In addition, evidence of a less differentiated MM subclone (CD19+ CD138-) with drug-resistance and disease propagating properties has emerged [40]. These results highlight antigen recognition by CAR even when it is present in very low density or not detectable by flow cytometry. Despite these encouraging findings, the use of CD19 CAR-T cells as a potential treatment for MM needs to be further explored. To determine whether CTL019 infusion improved PFS after ASCT, the authors compared each subject's PFS after ASCT versus ASCT followed by CTL019. Two patients had significantly increased PFS after CTL019 (479 versus 181 days, 249 versus 127 days).

Yan L et al., a cooperative group from China, have published a phase 1 trial with 10 patients treated with sequential infusions of an anti-CD19 CAR-T cell followed by an anti-BCMA CAR-T cell [43,44]. Patients received lymphodepletion chemotherapy with fludarabine and cyclophosphamide on days -5, -4 and -3. Patients were infused on day 0 with a fixed dose of 1×10^7 /kg antiCD19 CAR-T, on day 1 with 40% of anti-BCMA-CART and on day 2 with the remaining dose. Three dose levels were assessed for anti-BCMA CAR-T (3×10^7 /kg, 5×10^7 /kg and 6.5×10^7 /kg). Median follow-up was 20 months. Ninety percent of patients developed CRS grade 1-2. Overall response rate was 90% with 40% of strict CR. Three out of 4 patients in strict RC maintained PFS at 2 years of follow-up.

A host immune response against a murine CAR is another potential limitation to CAR T cell persistence. Thus, developing a fully human CAR construct is an area of active research for several groups.

Jie J et al. developed the first fully human anti-BCMA CAR-T cell called CT053 [45]. Twenty-four patients with a median age of 60.1 years were included in the phase 1 trial. The subjects had a median of 4.5 prior regimens of therapy. They enrolled a high-risk population with extramedullary involvement (45.8%), ECOG score 2–3 (33.3%) and ISS grade 3 (37.5%). Overall response rate was 87.5% with 79.2% of CR. Among 20 subjects who underwent the evaluation of minimal residual disease (MRD) status, 17 achieved MRD-negative status. Median duration of response was 21.8 months. They demonstrated a good safety profile. The most common grade 3 or higher toxicities were neutropenia (66.7%), decreased lymphocyte count (79.2%) and thrombocytopenia (25%). In view of these results, a phase 1b/2 study (LUMMICAR-2) with CT053 is ongoing [46]. Patients received fludarabine and cyclophosphamide on days -5, -4 and -3. CT053 dose was 1.5 – 3.0×10^8 , and it was administered in a single infusion. Median age was 59 years, and median number of prior lines of treatment was 6. Sixty-four percent of patients were refractory to 5 lines of treatment, and all received bridging therapy. Results published so far included 10 evaluable patients with a median follow-up of 4.5 months. Overall response rate was 100%, and 40% achieved at least a CR. Responses have been independent of BCMA expression in bone marrow. Peak CAR-T cell expansion was observed between 7 and 14 days after infusion. No grade 3 or higher CRS or neurotoxicity was observed.

Also, at the American Society of Hematology (ASH) meeting in 2020, the Kochenderfer group reported the results of a phase 1 trial with a fully human CAR-T cell which has a

BCMA heavy chain single binding domain (FHVH-CD8BBZ) [47]. The FHVH33 binding domain lacks the light chain, artificial linker sequence and 2 associated junctions of a scFv, which can be immunogenic leading to CAR rejection. FHVH33-CD8BBZ was encoded by a γ -retroviral vector and incorporated FHVH33, CD8 α hinge and transmembrane domains, a 4-1BB costimulatory domain and a CD3 ζ domain. Twenty-one patients were enrolled, median number of prior lines of treatment was 6 and median age was 64 years. Lymphodepletion consisted of fludarabine and cyclophosphamide on days -5, -4 and -3. The maximum tolerated dose was 6×10^6 CAR+ T cells /kg. The overall response rate was 90%. At the last cut-off, 10 patients maintained the response with a range of 0–80 weeks of follow-up. Ten patients discontinued the study, 9 due to disease progression and 1 due to death because of virus influenzae infection. Cytokine release syndrome occurred in 95% of patients, 20% were grade 3 and there were no grade 4 CRS. Thirty-eight percent developed neurotoxicity, but only 9% were grade 3.

Tumour microenvironment plays a crucial role in CAR-T cell resistance through immunological escape [48–51]. Some studies have shown that a high number of immunosuppressant cells, regulatory T cells, helper-2 T cells, cancer associated fibroblasts or osteoclasts contribute to decrease effector T cell activation and impair their function [51]. So, developing CAR-T cells against programmed death 1 and programmed death-ligand 1 (PD1/PDL1) might decrease the relapse risk related to the effect of microenvironment [52,53], but off-target toxicities might also increase.

Finally, and probably the most promising long-term strategy to overcome current limitations is the development of allogeneic CAR-T cells. There are already several phase 1 clinical trials assessing allogeneic CAR-T cells in R/R MM patients (UNIVERSAL trial, NCT04093596; MELANI-01 trial, NCT04142619; ALLO-605-201, NCT05000450; BCMA-UCART, NCT03752541; CTX120, NCT04244656; CYAD-211, NCT04613557). The reduction in time to infusion may be critical for life expectancy in a MM patient with refractory disease. Products from patients with fewer prior lines of treatment have a higher proportion of memory T cells and better ratio of CD4 T cell/CD8 T cells, which might improve the duration and depth of response [53]. This statement must be confirmed in further studies since Yan et al. [44] describe 3 patients infused with alloCAR products who had early relapses. In this sense, Shah et al. designed a clinical trial with a next-generation CAR-T cell (bb21217) [54]. bb21217 is an anti-BCMA CAR-T cell therapy that uses the same CAR molecule as idecabtagene vicleucel (bb2121) but adds the PI3K inhibitor bb007 during ex vivo culture to enrich the cell product for memory-like T cells, thereby reducing the proportion of highly differentiated or senescent T cells. In the update presented at the American Society of Hematology Annual Meeting 2020, response was assessed per investigator for 44 patients with ≥ 2 months of follow up or PD/death within 2 months. Twenty-four (55%) patients had confirmed response per IMWG criteria, including 8 (18%) with \geq CR and 13 (30%) with VGPR. CRS occurred in 67% of patients and neurotoxicity in 22% [55]. In the context of allogeneic CAR-T cells, to decrease the risk of graft-versus-host disease (GvHD) several bioengineering methods have been planned to regulate the expression of T cell receptor (TCR) and major histocompatibility complex (MHC) [56,57].

Another field under development is the use of CARs in natural killer cells (NK) as NK cells reduce the risk of GvHD and CRS [58,59]. There is an ongoing phase 1/2 study with anti-BCMA CAR NK cells (NCT03940833).

3. Conclusions

Exciting times are ahead of us, with this wide variety of options for improvement. Soon, the CARs we will be administering will differ greatly from the ones we have available now, including those not approved yet in Europe for commercial use. Furthermore, defining the profile of patients who will benefit from these treatments in an early stage of the disease remains an unsolved challenge.

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J.A.P.-S. supervised the manuscript, figures and references. All authors have read and agreed to the published version of the manuscript.

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