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Review

CAR-T Therapy in Multiple Myeloma: Looking Beyond

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Abstract: Multiple Myeloma is a hematological neoplasm that, over the recent few years, has benefited from numerous therapeutic options. Among the latter, CAR-T stands out as the most recent and one of the most promising treatments currently available. Despite its recent introduction, multiple CAR-T products have already been approved, and research regarding cellular therapy is rapidly increasing. We conducted a comprehensive search and review of the available literature, including published studies and abstracts from recent meetings (ASH, ASCO, ASTCT, IMS), regarding Multiple Myeloma and CAR-T therapy. We describe the discovery and research regarding promising targets like the B-Cell Maturation Antigen (BCMA) and others, the origin and nature of CAR-T cells, and the recent introduction of anti-BCMA CAR-Ts Idecabtagene-vicleucel and Ciltacabtagene-autoleucel, which are currently the only approved CAR-T products for MM. Additionally, we discuss non-BCMA-targeting CAR-Ts and their clinical implications. Given the significant impact of cellular therapy, we provide an overview of its limitations and possible adverse implications, as well as related resistance mechanisms. Finally, we describe the current research aimed at improving CAR-T therapy in MM, including structural innovations and new therapeutic approaches, such as in the earlier lines of treatment and maintenance therapy.

Keywords: Multiple Myeloma; CAR-T; BCMA; GPRC5D; CAR-NK; Ide-cel; Cilta-cel; universal CAR-T; NDMM; RRMM

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1. Introduction

Multiple Myeloma (MM) is a plasma cell neoplasm, accounting for nearly 1% of all cancers, with an estimated incidence of 3.5 per 100,000 [1]. Over the recent 20 years, the treatment of MM has undergone dramatic changes with the introduction of numerous drugs. Treatment regimens, including proteasome inhibitors (PIs), IMiDs, and monoclonal antibodies (mAbs), have led to improved survival and enhanced quality of life in newly diagnosed (NDMM) and relapsed/refractory MM (RRMM) patients [2].

Despite these advancements, relapse remains inevitable, and subsequent lines of therapy do not achieve the same levels of progression-free survival (PFS) and overall survival (OS), with increased toxicities due to comorbidities and disease burden. The discovery of new targets has fueled the development of therapies addressing the treatment of this increasingly growing unmet medical need in MM patients, while, at the same time, more limited hopes are placed in allogeneic transplant procedures [3,4].

Antibody conjugates, bispecific antibodies, and Chimeric Antigen Receptor-engineered T cells (CAR-T) are already part of the present treatment landscape for RRMM but are expected to play a more significant role in the immediate future [5].

This review will focus on CAR-T therapy in Multiple Myeloma, highlighting its current use and future directions.

2. CAR-T

2.1. Structure and Mechanism of Action

Chimeric Antigen Receptor-engineered T-cells (CAR-T) are autologous or heterologous T-cells engineered with a chimeric receptor. The structure of this receptor follows a basic scheme: The extracellular portion is made of a single-chain fragment (scFv) capable of binding tumor-specific antigens. This extracellular portion is linked to the T-cell through a transmembrane binding domain, usually derived from CD3, CD4, or CD8 molecules. The intracellular portion of the CAR is made of costimulatory domains and an effector signaling domain, mainly derived from CD3, responsible for signal transduction and cell activation. The activation of CAR through tumor-specific antigens leads to the secretion of granzymes, perforin, pro-inflammatory cytokines; the activation of Fas/FasL pathway targeting; and ultimately results in the killing of antigen-presenting cells [6].

The concept of CAR-T therapy was first introduced in the late 1980s in a landmark study by Dr. Kurosawa and colleagues, showing that T-cell activation was induced by a chimeric receptor in murine T-cell lymphoma [7]. A few years later, Dr. Eshhar et al. designed a single-chain variable fragment (scFv) linked to an intracellular signaling domain, thus developing what we now know as the first-generation CAR. Preclinical models showed anti-cancer activity, and two clinical trials were subsequently developed. However, this prototype of CAR-T therapy lacked efficacy due to suboptimal T-cell activation. Advancements in cellular therapy were made in the early 2000s by incorporating a costimulatory domain (CD28 or CD137) in the CAR, thus enhancing T-cell activation, antigen-dependent proliferation, and increased antitumor activity. This kind of CAR-T is known as the second-generation CAR-T, and currently available products are structured following this scheme [8]. Different CAR structures are depicted in Figure 1.

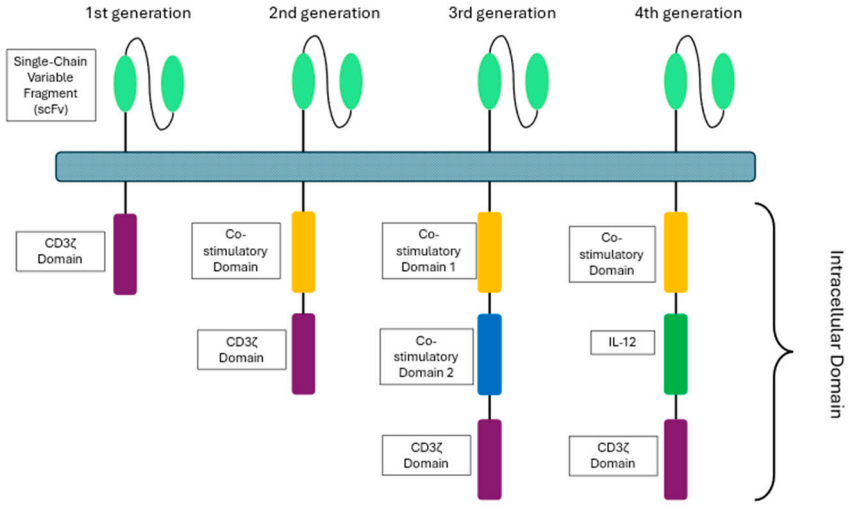

Figure 1. CAR-T structures. The basic scheme (1st generation) has been surpassed by the commonly used one, which consists of the 2nd generation of CAR with a co-stimulatory domain. The 3rd generation includes two co-stimulatory domains. An example of the immediate future of CAR-T therapy is the 4th generation, which includes an IL-12 secreting domain as well as activating and enhancing cytotoxic activity.

2.2. CAR-T Manufacturing

The manufacture of commercially available CAR-T products begins with leukapheresis, followed by the isolation and activation of T-cells [9,10]. The isolated and activated T cells are now ready to receive the CAR, generally via viral transduction, with the most common vector being lentiviral agents (>50% of all CAR-T products) [6]. Although mostly safe and effective, transduction by lentiviral agents has a few pitfalls, mainly represented by the high costs to develop and maintain cultures and the limited space to insert genomic material. More importantly, recent evidence has shown a potential risk of lentiviral agents

randomly integrating into the cellular genome, potentially enhancing oncogenes or silencing tumor suppressors [11–13]. To overcome these issues, non-viral transduction methods are currently under investigation. The more common techniques include transposon-based methods, such as Sleeping Beauty [14] and piggyBac [15], and gene editing through CRISPR-Cas9 [16]. CAR-T production, from leukapheresis to infusion, generally takes 4–6 weeks. Novel manufacturing platforms like T-CHARGE^{TM} [17] and non-autologous CAR-T products [18] are currently being studied to reduce the manufacturing time and therefore the potential risk of relapse in patients waiting with active hematological diseases, including MM.

3. BCMA-Targeting CAR-T

3.1. BCMA

B-cell maturation antigen (BCMA), also known as CD269 or TNFRSF17, is a member of the superfamily of Tumor Necrosis Factor Receptors (TNFRs). The gene encoding BCMA is located on the short arm of chromosome 16 (16p13.1), and the functional protein consists of an extracellular domain, a transmembrane domain, and an intracellular domain (107 amino acids) [19,20]. BCMA is mainly expressed in normal plasma cells (PCs) and plasmablasts during B cell development and is undetectable on other normal tissues, except for plasmacytoid dendritic cells. Its main ligands are the B-cell activating factor (BAFF) and the proliferation-inducing ligand (APRIL), with the latter having a stronger binding affinity to BCMA. Once bound to APRIL and/or BAFF, BCMA activation leads to multiple downstream responses, mainly activating the signaling cascades MEK/ERK, PI3K/AKT, and NF-κB [21]. BCMA is almost universally expressed in malignant PCs, and its activation through APRIL/BAFF in Multiple Myeloma (MM) has been shown to induce the overexpression of several molecules responsible for cell survival (Mcl1, Bcl2, Bcl-xL, and VEGF) and immune inhibition (PD-L1, TGFβ, IL-10), contributing critically to MM cell survival and its immunosuppressive microenvironment [22,23]. Numerous studies have shown that the extracellular domain of BCMA can be released from the cell surface due to its interaction with a membrane enzyme called γ-secretase, a protease that is continuously expressed and, in physiological conditions, aids in regulating B-cell maturation. The truncated domain, called soluble BCMA (sBCMA), is subsequently released into the bloodstream. In MM, sBCMA could potentially function as a composite biomarker in virtually all types of MM, including non-secretory MM, due to its direct correlation to disease burden [24]. Several studies evaluating BCMA-directed molecules use sBCMA as a surrogate biomarker to evaluate responses to treatment and the duration of these responses [25]. Unfortunately, the increased expression of sBCMA can potentially reduce BCMA-directed therapy due to the binding of the molecules to sBCMA instead of the membrane-bound domain [26]. In vitro models showed that sBCMA reduces the cytotoxic effects of BCMA-directed CARs in a dose-dependent manner; notably, no cell lysis occurred at sBCMA levels of 2343 ng/mL [27]. Given the importance of BCMA in MM physiology and its almost unique expression on malignant PCs, numerous therapies have been introduced targeting this specific molecule, including conjugate antibodies (Belantamab mafodotin) and bispecific antibodies (Teclistamab and Elranatamab) [28].

CAR-T agents have emerged more recently, with the two most studied products, Idecabtagene vicleucel (Ide-cel) and Ciltacabtagene autoleucel (Cilta-cel), described in more detail in the next sections. For other anti-BCMA CAR-T products, refer to Table 1.

Table 1. Ongoing trials involving CAR-cells in Multiple Myeloma.

ClinicalTrials.gov Identifier	Phase	Title	Target	Sponsor
NCT03601078	II	An Efficacy and Safety Study of bb2121 in Subjects With Relapsed and Refractory Multiple Myeloma and in Subjects With High-Risk Multiple Myeloma (KARMMA-2)	BCMA	Celgene/BMS, Lawrence, NJ, USA
NCT03710421	I	CS1-CAR T Therapy Following Chemotherapy in Treating Patients With Relapsed or Refractory CS1 Positive Multiple Myeloma	CS1	City of Hope Medical Center, Duarte, CA, USA
NCT03758417	II	A Study of LCAR-B38M CAR-T Cells, a Chimeric Antigen Receptor T-cell (CAR-T) Therapy Directed Against B-cell Maturation Antigen (BCMA) in Chinese Participants With Relapsed or Refractory Multiple Myeloma	BCMA	Nanjing Legend Biotech Co., Nanjing, China
NCT04727008	I	CXCR4 Modified Anti-BCMA CAR T Cells for Multiple Myeloma	BCMA	Sichuan University, Chengdu, China
NCT04816526	II	Descartes-08 Consolidation Treatment in Patients With High-Risk Multiple Myeloma Who Have Residual Disease After Induction Therapy	BCMA	Cartesian Therapeutics, Gaithersburg, MD, USA
NCT04923893	III	A Study of Bortezomib, Lenalidomide and Dexamethasone (VRd) Followed by Cilta-cel, a CAR-T Therapy Directed Against BCMA Versus VRd Followed by Lenalidomide and Dexamethasone (Rd) Therapy in Participants With Newly Diagnosed Multiple Myeloma for Whom ASCT is Not Planned as Initial Therapy (CARTITUDE-5)	BCMA	Janssen Research and Development, LLC, Beerse, Belgium
NCT04935580	I/II	Study of FasT CAR-T GC012F Injection in High Risk TE NDMM Patients	BCMA/CD19	Shanghai Changzheng Hospital, Shanghai, China
NCT04960579	I	P-BCMA-ALLO1 Allogeneic CAR-T Cells in the Treatment of Subjects With Multiple Myeloma	BCMA	Poseida Therapeutics, Inc., San Diego, CA, USA
NCT05020444	I	TriPRIL CAR T Cells in Multiple Myeloma	APRIL	Marcela V. Maus, M.D., Ph.D., Boston, MA, USA
NCT05113342	I/II	Descartes-25 in Relapsed/Refractory Multiple Myeloma	BCMA	Cartesian Therapeutics, Gaithersburg, MD, USA
NCT05117008	II	Maintenance Belantamab Mafodotin (Blenrep®) After B-cell Maturation Antigen-Directed Chimeric Antigen Receptor T-cell Therapy in Patients With Relapsed and/or Refractory Multiple Myeloma (EMBRACE)	BCMA	Medical College of Wisconsin, Milwaukee, WI, USA
NCT05181501	I	A Study of Fully Human BCMA CAR-T (CT103A) in Patients With Newly Diagnosed High-risk Multiple Myeloma (FUMANBA-2)	BCMA	Nanjing IASO Biotechnology Co., Ltd., Nanjing, China

Table 1. *Cont.*

ClinicalTrials.gov Identifier	Phase	Title	Target	Sponsor
NCT05257083	III	A Study of Daratumumab, Bortezomib, Lenalidomide and Dexamethasone (DVRd) Followed by Ciltacabtagene Autoleucel Versus Daratumumab, Bortezomib, Lenalidomide and Dexamethasone (DVRd) Followed by Autologous Stem Cell Transplant (ASCT) in Participants With Newly Diagnosed Multiple Myeloma (CARTITUDE-6)	BCMA	Stichting European Myeloma Network, Amsterdam, Netherlands
NCT05325801	I	A Study of CAR-T Cells Targeting Both BCMA and GPRC5D in Treatment of Relapsed or Refractory Multiple Myeloma	BCMA/ GPRC5D	Zhejiang University, Hangzhou, China
NCT05411497	I	Genetically Engineered Cells (MUC1-Activated T-Cells) for the Treatment of MUC1 Positive Recurrent or Refractory Multiple Myeloma	MUC1	Mayo Clinic, Scottsdale, AZ, USA
NCT05412329	I	Study of Dual Targeted CD19/BCMA FASTCART GC012F in Relapsed/Refractory Multiple Myeloma	CD19/ BCMA	Shanghai Changzheng Hospital, Shanghai, China
NCT05431608	I	A Study of MCARH109 and MCARH125 in People With Multiple Myeloma	BCMA/ GPRC5D	Memorial Sloan Kettering Cancer Center, New York, NY, USA
NCT05498545	I	Universal BCMA-targeted LUCAR-B68 Cells in Patients With Relapsed/Refractory Multiple Myeloma	BCMA	Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China
NCT05509530	II	Safety and Efficacy of Anti-BCMA/GPRC5D CAR-T Cell Therapy in Treating Relapsed and Refractory Multiple Myeloma(rr/MM)	BCMA/ GPRC5D	Xuzhou Medical University, Xuzhou, China
NCT05632380	I/II	ASCT in Combination With C-CAR088 for Treating Patients With Ultra High-risk Multiple Myeloma (MM)	BCMA	Institute of Hematology and Blood Diseases Hospital, China, Tianjin, China
NCT05698303	I	A Study of Fully Human BCMA Chimeric Antigen Receptor Autologous T Cell Injection (CT103A) in the Treatment of Patients With Relapsed/Refractory Multiple Myeloma	BCMA	Nanjing IASO Biotechnology Co., Ltd., Nanjing, China
NCT05722418	I	CRISPR-Edited Allogeneic Anti-BCMA CAR-T Cell Therapy in Patients With Relapsed/Refractory Multiple Myeloma (CaMMouflage)	BCMA	Caribou Biosciences, Inc., Berkeley, CA, USAs
NCT05739188	I/II	Safety and Efficacy of Anti-GPRC5D CAR-T Cells Therapy in the Treatment of r/r MM	GPRC5D	920th Hospital of Joint Logistics Support Force of People's Liberation Army of China, Kunming, China
NCT05767359	II	CAR-PRISM (Precision Intervention Smoldering Myeloma)	BCMA	Dana-Farber Cancer Institute, Boston, MA, USA

Table 1. *Cont.*

ClinicalTrials.gov Identifier	Phase	Title	Target	Sponsor
NCT05801939	II	Cevostamab Following CAR T Cell Therapy for RRMM	FcRH5	University of Pennsylvania, Philadelphia, PA, USA
NCT05846737	II	BCMA CAR-T Cell Therapy in High-risk NDMM Patients With Positive MRD After First-line ASCT	BCMA	Institute of Hematology and Blood Diseases Hospital, Tianjin, China
NCT05850286	II	A Study of X-VRD Combined With CART-ASCT-CART2 Treatment in NDMM Patients With P53 Abnormalities	XPO-1/ BCMA	Institute of Hematology and Blood Diseases Hospital, Tianjin, China
NCT05950113	I	CART-BCMA/CS1 in Treating Patients With Relapsed or Refractory Multiple Myeloma	BCMA/ CS1	Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA
NCT05976555	I	Phase I Trial of BCMA-TGF-BETA CAR-T Cells in Relapsed, Refractory Myeloma	BCMA	Medical College of Wisconsin, Milwaukee, WI, USA
NCT05998928	II	A Clinical Study to Evaluate the Safety and Efficacy of BCMA-GPRC5D CAR-T in Patients With Relapsed/Refractory Multiple Myeloma Who Received Three or More Lines of Therapy	BCMA/ GPRC5D	Wuhan Union Hospital, Wuhan, China
NCT06045806	III	A Study to Compare the Efficacy and Safety of Idecabtagene Vicleucel With Lenalidomide Maintenance Therapy Versus Lenalidomide Maintenance Therapy Alone in Adult Participants With Newly Diagnosed Multiple Myeloma Who Have Suboptimal Response After Autologous Stem Cell Transplantation (KarMMa-9)	BCMA	Bristol-Myers Squibb, Lawrence, NJ, USA
NCT06048250	I	Mezigdomide (CC-92480) Post Idecabtagene Vicleucel in Treating Patients With Relapsed Multiple Myeloma	BCMA	City of Hope Medical Center, Duarte, CA, USA
NCT06066346	II	A Study of Talquetamab for People With Multiple Myeloma Who Have Received BCMA CAR T-Cell Therapy	BCMA	Memorial Sloan Kettering Cancer Center, New York, NY, USA
NCT06066359	I/II	Phase I/II Randomized Trial of Cord Blood-derived NK Cells Genetically Engineered With NY-ESO-1 TCR/IL-15 Cell Receptor for Relapsed/Refractory Multiple Myeloma	NY-ESO-1	M.D. Anderson Cancer Center, Houston, TX, USA
NCT06132711	I/II	Safety and Efficacy of APRIL-BAFF-Bicephali CAR-T in Relapsed, Refractory Multiple Myeloma	APRIL/ BAFF	Xuzhou Medical University, Xuzhou, China
NCT06179888	II	Iberdomide versus Observation Off Therapy after Idecabtagene Vicleucel CAR-T for Multiple Myeloma	BCMA	National Cancer Institute (NCI), Bethesda, MD, USA
NCT06182696	I/II	OriCAR-017 Chimeric Antigen Receptor (CAR) Modified T Cells for the Treatment of R/RMM	GPRC5D	OriCell Therapeutics Co., Ltd., Shanghai, China

Table 1. *Cont.*

ClinicalTrials.gov Identifier	Phase	Title	Target	Sponsor
NCT06185751	I	Safety and Efficacy of CS1 CAR-T (WS-CART-CS1) in Subjects With Multiple Myeloma	CS1	Washington University School of Medicine, Saint Louis, MO, USA
NCT06196255	I/II	Safety and Efficacy of Anti-FcRL5 CAR-T Cell Therapy in Treating Relapsed and Refractory Multiple Myeloma (R/R MM)	FcRL5	Xuzhou Medical University, Xuzhou, China
NCT06223646	I/II	A Study of KQ-2003 CAR-T Cell Therapy for Patients With Relapsed or Refractory Multiple Myeloma	BCMA/CD19	Novatim Immune Therapeutics (Zhejiang) Co., Ltd., Beijing, China
NCT06242249	I/II	Anti-BCMA CAR-NK Therapy in Relapsed or Refractory Multiple Myeloma	BCMA	Shahid Beheshti University of Medical Sciences, Tehran, Iran

3.2. Idecabtagene Vicleucel

Ide-cel, also known as bb2121, is a second-generation CAR-T product structured with a murine-derived anti-BCMA single-chain variable fragment (scFv) bound to a 4-1BB costimulatory motif and a CD3-zeta signaling domain. Its preclinical efficacy, published in 2018 by Friedman et al., showed anti-MM activity in 100% of cases, regardless of sBCMA levels [29]. Based on these results, Ide-cel was studied in a cohort of patients with relapsed/refractory Multiple Myeloma (RRMM) who were exposed to at least three previous lines of therapy in a phase 1 trial (NCT0265929). Results from 33 patients were published in 2019. Patients received Ide-cel at doses ranging from 50×10^6 to 800×10^6 in the dose-escalation phase and 150×10^6 to 450×10^6 in the dose-expansion phase. The overall response rate (ORR) was 85%, with a complete response (CR) or better observed in 45% of patients, according to IMWG response criteria. Adverse events (AEs) were primarily hematological (97% Grade 3 or higher), with cytokine release syndrome (CRS) reported in 76% of patients, mostly of grade 1 or 2, and immune effector cell-associated neurotoxicity syndrome (ICANS) was reported in 42% of patients, with one grade 4 event [30]. A post hoc analysis of this study, which included 29 additional patients enrolled after publication, with a median follow-up of 18.1 months, showed a median duration of response (DOR) of 10.3 months and a median progression-free survival (PFS) of 8.9 months in patients receiving doses > 150×10^6, highlighting a dose-dependent response to Ide-cel [31].

Based on these data and the results from the pivotal KarMMa trial (128 patients treated with Ide-cel at doses of 150–450 $\times 10^6$) [32], the first phase 3 trial, named KarMMa-3, was designed to compare CAR-T therapy to the standard of care (SOC) in patients with MM. KarMMa-3 compared Ide-cel with five standard regimens in patients with RRMM who had received 2–4 lines of therapy, including immunomodulatory drugs (ImiDs), proteasome inhibitors, and anti-CD38 agents. In the Ide-cel group, 225 patients successfully underwent leukapheresis and CAR-T infusion, with a median dose of 445×10^6. In the control group, 126 patients were assigned and received SOC treatment. Patients' characteristics were similar in both groups, with high-risk cytogenetics observed in 46% and 42% of patients, respectively. Notably, 65% of patients in the Ide-cel group and 67% of patients in the SOC group were triple-class refractory (TCR). The median follow-up was 18.6 months, with PFS and DOR of 13.3 and 14.8 months, respectively, in the Ide-cel group. AEs reported for Ide-cel were consistent with previous data: 87% were hematological events of grade 3 and 4, CRS was reported in 88% with one grade 5 event, and ICANS was reported in 15% of patients receiving Ide-cel. Notably, 28 patients experienced grade 3 or worse infections, with 11 patients dying due to complications in the Ide-cel group. sBCMA was detected in 82 out of 84 patients who relapsed after an Ide-cel infusion [33].

3.3. Ciltacabtagene Autoleucel

Cilta-cel is a second-generation CAR-T product that differs from Ide-cel due to its epitope-binding motif. Its structure consists of a camelid-derived single-chain variable fragment (scFv) capable of recognizing two different epitopes of BCMA, resulting in high-avidity binding. The intra-cellular part of the construct includes 4-1BB and CD3-zeta. Cilta-cel was initially tested in a phase 1 trial named LEGEND-2, which was conducted at multiple sites in China [33]. The overall response rate (ORR) was 88%, with 42 out of 57 patients (74%) achieving a complete response, and a median duration of response of 22 months. These promising results led to the development of the pivotal phase 1b/2 study CARTITUDE-1 [34].

In CARTITUDE-1, 97 triple-class exposed patients with relapsed/refractory Multiple Myeloma (RRMM), treated with at least three lines of therapy, received Cilta-cel with a median dose of 0.75×10^6 per kg bodyweight (range $0.5–1.0 \times 10^6$). Of these patients, 88% were triple-class refractory and 24% had high-risk cytogenetics. The median follow-up was 12.4 months, with an ORR of 97% and 67% of patients achieving a stringent complete response. A subsequent final analysis of the study, published in 2023, showed a median progression-free survival (PFS) of 34.9 months with a duration of response (DOR) of 33 months [35]. Hematologic adverse events (AEs) of reversible grade 3–4 were reported in 99% of patients, while CRS was observed in 95% of patients, with grade 3 and 4 in 4%. Notably, neurotoxic events occurred in 21% of patients, with 7% being non-ICANS-related neurotoxicities, including parkinsonism-like symptoms, with one grade 5 event [36]. Based on these promising results, a phase 3 trial (CARTITUDE-4) was initiated, with its results being published in 2023.

CARTITUDE-4 compared Cilta-cel with standard-of-care (SOC) regimens in RRMM patients resistant to Lenalidomide and previously treated with 1–3 lines of therapy, including a proteasome inhibitor and an immunomodulatory drug (ImiD). The Cilta-cel group comprised 176 patients, while 206 patients were assigned to the control arm. In the Cilta-cel group, 59.4% of patients had high-risk cytogenetics, and 14.4% were triple-class refractory. The ORR was 84.6%, with a complete response or better in 73% of patients. At data cutoff, the PFS was not reached with a median follow-up of 15.9 months. Hematologic AEs were the most common, with 94.2% being grade 3 and 4. Infections occurred in 62% of patients, with 27% being grade 3 and 4. CRS and ICANS of all grades were reported in 76% and 4.5% of patients, respectively. Non-ICANS-related neurologic AEs were reported in 17% of patients, with five patients developing non-reversible neurotoxicity at data cutoff [37]. Despite CARTITUDE-4 suggesting a deeper and longer response compared to KarMMa-3, numerous discrepancies were noted between the two trials, such as differences in triple-class-refractory patients and varied inclusion criteria. A recent matching-adjusted indirect comparison (MAIC) analysis, grouping patients with triple-class refractory RRMM exposed to 2–4 lines of therapy from KarMMa-3, CARTITUDE-1, and CARTITUDE-4, showed that Cilta-cel maintains a deeper and longer response compared to Ide-cel, with an adjusted PFS of 24 and 12 months, respectively [38].

4. Non-BMCA CAR-T

As known, BCMA is not the sole target currently under investigation in MM therapy. The next section will provide a brief description of the main targets used as CAR-T antigens in ongoing trials.

4.1. GPRC5D

G protein–coupled receptor class C group 5-member D (GPRC5D), located on chromosome 12p13, is an orphan G-protein coupled receptor, mainly expressed by pathological MM cells and, with much lower intensity, by keratinized tissue [39]. Its mechanism of function is not fully understood, but the higher and, more importantly, specific expression has drawn attention to its potential in MM therapy [40].

MCARH109: In 2022, Maylankody and colleagues published the results of a second-generation CAR-T product (MCARH109) targeting GPRC5D in a phase 1 trial. A total of 17 patients with RRMM received therapy with a dosing range from 25×10^6 to 450×10^6 CAR-T cells. Ten patients were previously treated with anti-BCMA agents, including eight treated with CAR-T. Seventy-one percent of patients obtained a partial response or better, and the maximum tolerated dose was identified at 150×10^6. Adverse events were predominant in the 450×10^6 group, with three out of five patients developing at least grade 3 CRS or ICANS; two patients developed persistent cerebellar disorders. On-target off-tumor events were grade 2 or lower and regarded as skin and keratinized-tissue toxic effects throughout all groups, with 11 patients developing grade 1 nail loss [41].

BMS-986393: Also called CC-95266, it is a second-generation CAR-T, and a phase 1 dose-escalation study is in its final stages; the first results regarding Part A of the study (RRMM $\geq$ 3 LOT including anti-BCMA therapy) were presented at the last EHA congress. Thirty-three patients enrolled and received CC-95266 at a dose level ranging from 25 to 450×10^6 CAR-T cells, with an overall response rate of 87%, including seven out of nine patients previously treated with anti-BCMA agents. Dose escalation did not exceed the maximum tolerated dose (MTD), and CRS and ICANS were mostly grade 1 or 2. On-target off-tumor toxic effects were similar to MCARH109 and were time-limited, with nail loss being the most frequent AE [42].

OriCAR-017: This second-generation CAR-T product has a signal activation domain named Ori, which is hypothesized to improve CAR-T expansion and durability; therefore, its structure varies slightly relative to the other anti-GPRC5D products previously described. Preliminary data of the ongoing phase I/II POLARIS study were recently published. The results of ten patients with RRMM treated with Ori-CAR-017, nine in the dose-escalation phase ($1–6 \times 10^6$ CAR-T cells) and one in the dose expansion phase (3×10^6 CAR-T cells), were promising. Fifty percent of the patients had received prior anti-BCMA CAR-T therapy, and all patients obtained a response. CRS was described in all patients without grade 3 or higher, and ICAN or other neurological effects were not reported. GPRC5D-related off-tumor events were reversible and mostly grade 1 [43].

4.2. FcRL5

Fc receptor-like 5 (FcRL5), also known as FcRH5, IRTA2, or CD307, is a B cell lineage-specific surface marker specifically expressed on plasma cells and, in particular, on malignant PCs. Its biological significance is largely unknown, but its specific expression has led to the development of numerous agents. Cevostamab, a bispecific antibody, has recently shown significant activity in RRMM; therefore, FCRL5 has emerged as a promising target with a phase I/II trial currently ongoing [44,45]. Cellular therapy targeting FcRL5 is mostly in a preclinical phase, and numerous studies have shown significant cytotoxic activity. In a preclinical study, a second-generation CAR-T product targeting FcRL5 was used in a murine xenograft model, exhibiting potent anti-MM activity, even in a model not expressing BCMA. An important aspect was the evidence of the influence of soluble FcRL5. MM cells shed FcRL5, producing two forms, sIRTA2c, and more frequently, sIRTA2a. In this study, sIRTA2a did not impair CAR-T activity, but notably, sIRTA2c did. Therefore, to increase durability and effectiveness of the CAR-T, the product was engineered to include a motif that secreted IL-15. This modified product enhanced anti-MM activity due to its increased durability and provided the CAR-T with stemness-like characteristics [46]. Currently, a phase I/II trial is undergoing evaluation of the efficacy of anti-FcRL5 CAR-T [47].

4.3. CS1

CS1, also known as SLAMF7, is a transmembrane receptor expressed on immune cells but mostly on plasma cells, including MM cells. One important function of CS1 is NK cell activation and thus anti-MM activation. However, in T-cells, CS1 determines the activation of STAT1 and STAT3 and consequent T-cell exhaustion. Currently, there is an antibody available for the treatment of MM, Elotuzumab. Its activity is significant, but its efficacy

is reduced when it is administered in monotherapy [48]. Similarly, CAR-T products are under scrutiny in clinical trials to assess toxicity and efficacy. Notably, anti-CS1 CAR-T has been proven to undergo fratricide in CD8+ T-cells. Therefore, O'Neal and colleagues, in a study which showed important anti-MM activity but significant immunodeficiency in preclinical models, deleted the CS1 gene to verify if the absence of CS1 in non-CAR T cells would improve anti-MM activity, but the results showed no difference [49]. There are currently two phase I clinical trials ongoing (NCT06185751, NCT03710421) [50,51], and, notably, there is mounting curiosity for the results of CARAMBA, a first-in-human phase I/II trial assessing the efficacy of anti-SLAMF CAR-T transduced with virus-free transposon Sleeping Beauty [14]. Finally, two bispecific CAR-T products targeting BCMA and CS1 are currently under investigation. One study recently published its first results; in this phase I study, 16 RRMM with at least 2 previous lines of therapy (LOTs) were treated with CS1/BCMA CAR-T. The most frequent AEs were CRS and significantly high infection rates, with five patients experiencing grade 3 infections (31%). ORR was 81%, and the median PFS was 9 months. BCMA and CS1 expression at baseline did not influence treatment responses, and no major on-target off-tumor toxicity was reported [52,53].

5. Limitations of CAR-T Therapy in MM: Toxicities and Resistance Mechanisms

5.1. CAR-T Toxicities

Cellular therapy, particularly CAR-T therapy, has revealed the emergence of adverse events that have not been previously documented. The majority of these are related to the mechanism of action of CAR-Ts, while a few are antigen-related.

Cytokine release syndrome (CRS) is a frequent adverse event secondary to CAR-T cell activation, resulting in the release of various cytokines and chemokines, including IL-1, IL-6, and TNF-α. Its clinical manifestation usually includes fever, arthralgias, and myalgias, with onset occurring within 1–2 weeks following CAR-T infusion. International consensus groups have defined a grading score for CRS, evaluating fever, hypotension, and hypoxia [54]. The incidence of CRS in patients with MM treated with CAR-T therapy varies slightly; KarMMa-3 and CARTITUDE-4 reported CRS in 88% and 76% of patients, respectively, with nearly all being represented by grade 1 or 2 episodes and one grade 5 episode in KarMMA-3. Studies evaluating non-BCMA CAR-Ts had a comparable incidence [33,37,41]. A real-world study on patients treated with Ide-cel confirmed the incidence of CRS in patients with MM at a rate of 81%, with 7% experiencing grade 3 or higher [55]. The management of CRS starts with ruling out infections or non-CRS-related causes that might determine the onset of symptoms. Nonetheless, antipyretics are typically the first line of treatment for CRS. Other options for grade 1 and grade 2 events include intravenous fluids and supportive measures. If non-responsive, or in the presence of a grade 3–4 event, infusion of the anti-IL-6 antibody Tocilizumab is warranted. Corticosteroids are also an option, despite the potential risk of interfering with CAR-T expansion. If CRS persists despite the use of Tocilizumab, Anakinra, an anti-IL-1 antibody, has shown efficacy as a next-line treatment [56].

Neurotoxicity represents another common adverse event. The underlying mechanisms behind neurotoxicity are not fully understood. The onset of neurotoxicity secondary to CAR-T therapy in MM can be distinguished into two different manifestation. Events involving the central nervous system are grouped under the definition of Immune effector cell-associated neurotoxicity syndrome (ICANS). Other neurotoxicities, defined as non-ICANS events, include specific symptoms and have been primarily described in patients treated with BCMA-CAR and GPRC5D-CAR. ICANS is a clinical diagnosis, graded using the Immune Effector Cell-Associated Encephalopathy (ICE) score [54]. In patients with MM treated with CAR-T, ICANS is a rare occurrence mainly represented by grade 1 and grade 2 events. The onset of ICANS varies; usually, it arises a few days after a CRS event. Its clinical manifestation varies from the more frequent symptoms represented by headache to cerebral edema. Common symptoms at onset include dysgraphia, tremors, confusion, and agitation. The management of ICANS should always start with a neurological evaluation;

moreover, based on its severity, treatment measures include corticosteroids, Tocilizumab, and anakinra. Diagnostic measures such as lumbar punctures, imaging, and EEGs are recommended for monitoring symptoms until resolution [3].

Non-ICANS neurotoxicities have been documented in patients treated with BCMA-CAR-Ts, particularly Cilta-Cel. These events differ from ICANS due to their late onset and atypical symptoms, including Bell's palsy, Parkinsonism, and movement disorders, which can become chronic [56]. In the CARTITUDE-4 study, 36 patients reported neurotoxic events, with 4 of them being ICANS, while the remaining majority were classified as non-ICANS events, including Bell's palsy, parkinsonism, peripheral neuropathy, and ataxia, with 5 patients reporting persistent symptoms after data cutoff. In patients treated with GPRC5D-CAR, reports of cerebellar palsy were documented. These non-ICANS neurotoxicities are unusual and result from on-target off-tumor effects by CAR-T cells on CNS tissue expressing BCMA and GPRC5D [37,41].

Immune Cell-Associated Hematotoxicity (ICAHT) is the most frequent adverse event associated with CAR-T therapy. More than 80% of patients with MM treated with CAR-T products develop multilineage cytopenias, the majority of which are long-term. Risk factors include high tumor burden before infusion, high-grade CRS/ICANS, and the number of lines of therapy (LOTs) [57]. The risk associated with prolonged hematotoxicity (>90 days) is mainly represented by infections and increased bleeding. If persistent multilineage cytopenia is documented, a bone marrow evaluation is warranted to exclude secondary hematological malignancies, which are rare but significant events that prompted an investigation by the FDA to evaluate the potential risk of CAR-T products (FDA, [58]). The management of hematotoxicity mainly involves transfusion support and antimicrobial prophylaxis. The use of stimulating factors, such as granulocyte colony-stimulating factors or Thrombopoietin agonists, is generally not recommended due to insufficient data; however, recent studies are showing promising results [59,60]. Recently, a prognostic score called CAR-HEMATOTOX has been developed to identify patients at risk of developing hematotoxicity. The score measures levels of ferritin, hemoglobin, platelet count, absolute neutrophil count, and C-reactive protein [61].

Infections in patients with MM treated with CAR-T products are an important and potentially life-threatening adverse event that can occur even months after infusion. The main risk factors are prolonged hematotoxicity, previous infections, hypogammaglobulinemia, and the depletion of normal plasma cells. In BCMA-CAR-Ts, the depletion of its antigen significantly reduces immune cell activity; therefore, close monitoring and adequate preventive measures are needed to overcome these significant factors. Infections are distinguished based on their onset after the infusion of the CAR product. Early infections (<30 days) tend to be predominantly bacterial and severe. Studies have shown that frequent infections caused by C. difficile are mainly due to prolonged hospitalization and antimicrobial measures. Viral infections, such as HSV and influenza, are frequent early infections. Late infections (30–100 days post-infusion) are more frequent in patients treated with CAR-T and are usually less severe. Viral and bacterial agents are more frequent, but fungal agents tend to become more significant in this stage and are increasingly more frequent in infections developing after 100 days of infusion [62–64]. Reactivation of CMV and VZV has been documented months after infusion; therefore, antiviral prophylaxis is strongly recommended by several consensus statements. Severe cases of Pneumocystis jiroveci-related pneumonia have been documented in numerous studies months after infusion, following the cessation of prophylaxis. This has resulted in recommendations to administer Pneumocystis jiroveci prophylaxis for at least 6 months after infusion and until the normalization of CD4 count (>200/uL). Bacterial and fungal prophylaxis is recommended if patients have a history of previous or recurrent infections, hypogammaglobulinemia, prolonged neutropenia, and a high CAR-HEMATOTOX score [3,65].

5.2. Resistance Mechanisms

Multiple Myeloma, especially in heavily pretreated patients, is characterized by spatial and molecular heterogeneity, with subclones potentially harboring resistance mechanisms and mutations [66]. CAR-T has been used in patients with RRMM; nonetheless, it has been effective, with deep and durable response periods. Despite its incredible impact, patients relapsed. An important tumor-intrinsic mechanism of resistance has been described as antigen downregulation or loss. In an important study, Samur and colleagues performed a longitudinal single-cell analysis of a patient who relapsed after 8 months of infusion of anti-BCMA CAR-T and a lack of response after retreatment. The analysis showed the selection of a clone with a biallelic loss of BCMA, thus developing a lack of proliferation of CAR-T and, subsequently, progression [67]. Despite being rare, BCMA loss due to clone selection or downregulation has a significant impact on MM therapy and needs to be further researched, with an analysis using single-cell and whole-genome sequencing being necessary to determine the mutational landscape of patients with MM. Numerous studies are ongoing, and the first results have improved our understanding of the clonal heterogeneity of MM [68]. Other antigens are currently in the early stages of investigation; therefore, data regarding their mechanisms of resistance is scarce. Nonetheless, GPRC5D loss of expression was recently reported. Mi and colleagues obtained DNA from six patients treated with MCARH109 (phase I) and who relapsed after 3–9 months. Digital droplet PCR was performed and revealed a bi-allelic loss in one case. In the other five patients, transcriptional downregulation was the main mechanism of GPRC5D loss [69].

Anti-CAR immunity is another significant mechanism of escape. Currently, CAR-T products for MM use murine-derived epitopes to target antigens, and their non-human nature has been shown to elicit anti-CAR activity through the production of antibodies. In a trial using a bi-epitopic anti-BCMA CAR-T, patients who relapsed showed a development of antibodies targeting non-human fragments, thus impeding CAR activity [70]. Immunity against CAR-T is unfortunately not limited to the development of antibodies, but it is limited to T-cell redirection through non-human antigen presentation, with cell activation towards CAR-T already been documented [71].

An important aspect of CAR-T resistance is T-cell exhaustion. Autologous T-cells harvested from heavily treated patients with RRMM express senescent or exhausted phenotypes that reduce CAR-T activity, thus reducing the response duration [72]. Not only could anticipating CAR-T in earlier lines of treatment reduce T-cell senescence, but, as recently reported, sequencing lines of therapy are becoming increasingly more important. As Hashmi and colleagues reported, previous anti-BCMA therapy, especially with bispecific antibodies, increases the risk of relapse in patients treated with anti-BCMA CAR-T [73,74].

The tumor microenvironment (TME) has been shown to negatively influence CAR-T activity. In particular, it has been demonstrated that tumor-associated macrophages (TAMs) support PC proliferation and activate STAT3, thus reducing the antitumor response in MM [75]. An interesting study by Mishra and colleagues found a consistent expression of PD1, TIGIT among other co-inhibitory markers expressed in the TME of RRMM treated with CAR-T, confirming that the interaction between malignant PCs and the TME induces anti-apoptotic activity and immune escape [76].

Overall, mechanisms of resistance can be attributed to tumor and TME-related activity as well as CAR-T dysfunction due to senescence or inactivity. Studies that are currently undergoing are trying to better understand the mechanisms of resistance in MM and the methods to overcome these hurdles. The main mechanisms are depicted in Figure 2.

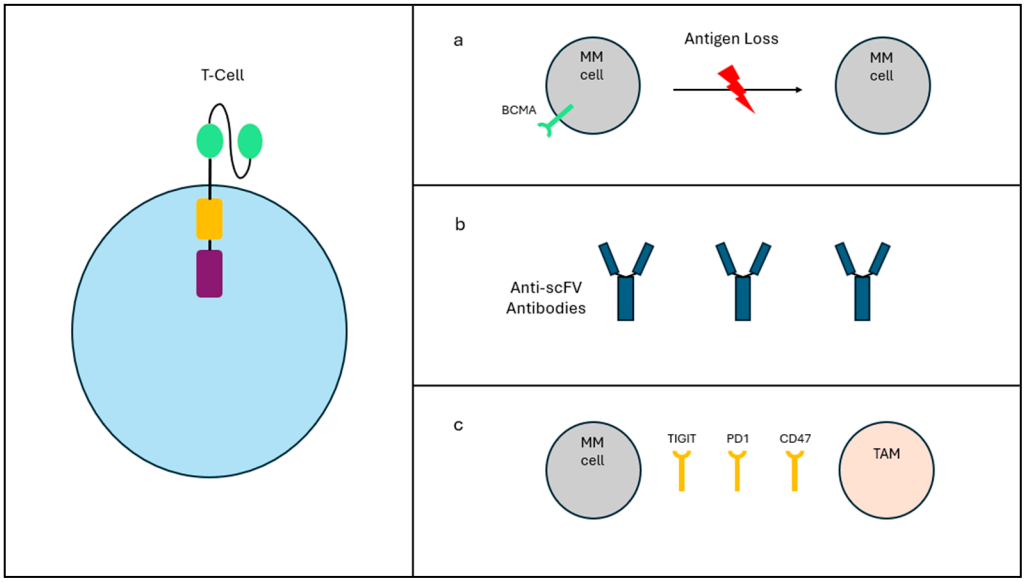

Figure 2. The main mechanisms of CAR-T resistance: (**a**) antigen loss due to downregulation or gene deletion; (**b**) development of anti-scFv antibodies due to the non-human nature of the CAR structure; (**c**) non-permissive tumor microenvironment with upregulation of anti-apoptotic pathways and expression of molecules enhancing tumor escape.

6. Overcoming Limitations and Future Directions

Numerous studies are currently investigating techniques and strategies to overcome the potential pitfalls in CAR-T therapy in MM. Nowadays, virtually all CAR products are engineered with a standardized method that, on average, requires 4–6 weeks from apheresis to infusion. This aspect brings potential pitfalls in terms of the risk of relapse during manufacturing time, as the need for bridging therapy potentially increases the toxicity in already-frail patients [77]. An innovative method to reduce the time from harvest to actual therapy has been presented recently: FasT CAR-T and T-ChargeTM are novel manufacturing platforms aspiring to reduce time-to-treatment and increase stemness-like characteristics in CAR-T products. FasT CAR-T was used in the development of a dual-targeting CD19 and BCMA CAR-T (GC012F) in patients with NDMM enrolled in a phase I trial; overall, 22 patients received GC012F, and the median time from diagnosis to infusion was 100 days, including two cycles of induction treatment. The median follow-up was 13 months, and 95% obtained an sCR [78]. T-ChargeTM, another novel manufacturing platform, was used in the development of a CAR-T product (PHE 885) as part of a phase I trial in patients with RRMM; data from 32 patients were presented, and, notably, manufacturing time was a maximum of 48 h. ORR was 98%, and, as hypothesized, stemness activity increased, enhancing durability and potential self-renewal [17].

Another main issue in CAR-T manufacturing is the absence of academic platforms. Recently, preliminary results of ARI0002h, an autologous academic point-of-care CAR-T product, were presented, and another academic CAR-T trial, Papilio-1, is currently being enrolled [79,80].

Antigen loss is a major factor of relapse after CAR-T therapy. Different ways to overcome this are under scrutiny. Numerous trials investigating dual-targeting CAR-T efficacy are currently enrolling patients. In an elegant preclinical study, Larson and colleagues constructed two CAR-Ts, one targeting TACI alone and one dual-targeting TACI and BCMA. The results showed responses in cell lines expressing BCMA, including those naive to anti-BCMA treatment, in both cases. Notably, in cell lines previously exposed to BCMA target therapies, the dual-targeting construct overcame antigen loss and retained cytotoxic activity; this was not the case with the mono-targeting construct, suggesting the potential of dual-targeting CAR-Ts in clinical settings [81].

The use of dual-targeting CAR-Ts is currently in the early clinical stages, but a few studies with preliminary data have been published. In a phase I trial, 16 patients with RRMM received tandem CS1/BCMA targeting CAR-T with an ORR of 81%; notably, one patient who relapsed after BCMA-CAR-T therapy has shown a durable response [52]. Finally, the preliminary results of an innovative tri-specific CAR-T targeting BCMA were published, with an ORR of 55%, two of which had received prior anti-BCMA treatment [82].

In addition to multiple targets, the new frontier in CAR-T therapy is represented by next-generation products. The 4th generation of CAR-Ts are constructs able to secrete transgenic cytokines, like IL-12 and IL-15, thus inducing more potent antitumor activity and mitigating potentially toxic effects by "guiding" the cytokines on target; these so-called "armored" CAR-Ts are in the early stages of research [83]. In a preclinical study, an anti-BCMA CAR was armored with a dominant negative TGF-β receptor II domain. This prevented the mitigating effects of TGF-β, which is known for its activity in tumor survival and immune silencing. The results showed a high cytotoxic activity, even in cell culture with high TGF-β expression [84]. In a more recent publication, a sophisticated CAR was constructed using the piggyBac transposon method with important antitumor activity.

The CAR construct consists of an anti-BCMA targeting the NK92 cell armored with a domain secreting the soluble tumor necrosis factor-related apoptosis-inducing ligand (sTRAIL) [15]. Another preclinical study analyzing, in this case, a dual-targeting BCMA/CD28, which is an IL-15 secreting armored CAR-NK, was recently published [85]. The use of cells other than T-cells is also an innovative approach. In particular, NK cells are safer and less immunogenic. Importantly, CAR-NK therapy can be manufactured through mass production and infused into patients at any time, potentially being accessible in a few days if needed [86].

The need for universally accessible CAR therapy is increasing. Other than CAR-NK therapy, universal, allogeneic CAR-T products can become a feasible option in the future. Early safety results of an allogeneic CAR product were recently published; P-BCMA-ALLO-1 is a phase 1 study investigating a fully allogeneic CAR-T targeting BCMA in RRMM. Manufacturing was based on T-cell harvest from healthy donors; through the piggyBac transposon system, a human anti-BCMA V H-based CAR and an iCas9 safety switch to inhibit graft-versus-host disease (GVHD) were created. The results showed tolerable safety, and the median manufacturing time from leukapheresis to infusion was 7 days [87]. Another recently published study reported the preclinical efficacy of a universal allogeneic CAR-T product, BC404-UCART. T-cells were obtained from healthy donors, and Crispr/Cas9 was used to inhibit GVHD through a knockout of T-cell receptor (TCR) and beta-2 microglobulin (B2M) genes. A peculiar aspect of this CAR-T product is the knockout of the CD47-SIRPα pathway. BC404-UCART blocks this immune checkpoint through the secretion of anti-CD47, possibly due to the encoding of anti-CD47 nanobodies in the CAR construct [88,89].

To limit T-cell exhaustion and improve its antitumor activity, using CAR-T in earlier lines of therapy or maintenance therapy with ImiDs or cereblon E3 ligase modulatory drugs (CELMoDs) is currently an approach under scrutiny. Recently, two major phase III studies evaluating the two most used CAR-T products, Ide-cel and Cilta-cel, have started enrolling patients with NDMM [90,91]. Other ongoing trials are currently evaluating maintenance with CELMoDs (Mezigdomide, Iberdomide) after CAR-T therapy [92,93].

Finally, to improve tumor specificity, a novel approach in CAR engineering is the use of "AND-gates", a multi-antigen recognition system in which a CAR T cell must recognize two different antigens for full activation and target cell elimination. Currently, there are studies being carried out researching feasible targets to produce "gated" CAR-Ts in MM [94].

7. Conclusions

CAR-T therapy has emerged as a cornerstone in the therapeutic approach to patients with MM. While two products have already received approval, many more are under investigation. Despite recent safety concerns and potential risks for secondary malignan-

cies [12,95], CAR therapy remains the most promising option due to its remarkable results in terms of response duration and depth. The scientific community has seldom encountered such a plethora of therapeutic options for a single disease. Nevertheless, a personalized approach and proper sequencing for each patient are imperative [96]. Despite its recent approval in RRMM from the second line of therapy onwards, ongoing trials are currently investigating the potential use of CAR-T in NDMM.

Considering the increase in approved bispecific antibodies in RRMM, CAR-T therapy in MM could be considered in the near future as a fundamental therapeutic tool in NDMM and earlier lines of therapy. This could be beneficial due to the increased fitness of patients exposed to fewer lines of therapies, and the reduced risk of T-cell exhaustion, potentially resulting in a deeper response. However, CAR-Ts in earlier lines of therapy may not be ideal. Currently, outside of clinical trials, manufacturing costs and the regulatory aspects of cellular therapy are hindering the global use of CAR-T therapy. In addition, the potential toxicities associated with cellular therapy are significant and potentially long-term. Currently, there are only a few prognostic tools capable of predicting the risk associated with CAR-T therapy. More data are needed to improve the efficacy and safety of CAR-T therapy in MM.

The journey towards a cure for Multiple Myeloma remains challenging, but the advent of CAR-T therapy represents a notable step forward.

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