

Evaluating the Therapeutic Potential of Idecabtagene Vicleucel in the Treatment of Multiple Myeloma: Evidence to Date

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Abstract: Over the past two decades, significant progress has been made in the diagnosis, risk assessment and treatment of patients with multiple myeloma, translating into remarkable improvements in survival outcomes. Yet, cure remains elusive, and almost all patients eventually experience relapse, particularly those with high-risk and refractory disease. Immune-based approaches have emerged as highly effective therapeutic options that have heralded a new era in the treatment of multiple myeloma. Idecabtagene vicleucel (ide-cel) is one such therapy that employs the use of genetically modified autologous T-cells to redirect immune activation in a tumor-directed fashion. It has yielded impressive responses even in patients with poor-risk disease and is the first chimeric antigen receptor (CAR) T-cell therapy to be approved for treatment in relapsed or refractory multiple myeloma. In this review, we examine the design and pharmacokinetics of ide-cel, audit evidence that led to its incorporation into the current treatment paradigm and provide insight into its clinical utilization with a focus on real-life intricacies.

Keywords: CAR-T, immunotherapy, multiple myeloma, cytokine release syndrome, neurotoxicity, resistance

Introduction

Multiple myeloma (MM) is a malignancy of terminally differentiated plasma cells (PCs) that is always preceded by asymptomatic phases of clonal plasma cell expansion, known as monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM).^{1–3} It is the second most common hematologic malignancy and is estimated to account for 34,920 new cases and 12,410 deaths in the US in 2021.⁴ The current treatment paradigm for newly diagnosed patients involves the use of novel drugs and combinations, including the proteasome inhibitors (PIs) bortezomib and carfilzomib, immunomodulatory agents (IMiDs) such as lenalidomide and pomalidomide, the anti-CD38 monoclonal antibody (mAb) daratumumab, and if eligible, an autologous stem cell transplant (ASCT). These strategies have resulted in dramatic improvements in the outcomes of patients with newly diagnosed MM (NDMM), with a median overall survival (OS) that extends beyond 8–10 years in recent clinical studies.^{5–8} However, outcomes remain dismal in patients with high-risk disease and in those refractory to multiple agents, with a median OS that is typically less than 1–2 years despite the use of novel agents.^{9–12} This represents a major unmet need in the field, and employing newer strategies to improve outcomes in these groups of patients has been a focus of robust clinical and research efforts.

One avenue that has captivated the interest of researchers in this regard is manipulation of the immune system by means of chimeric antigen receptor (CAR) T-cells. CARs are genetically engineered receptors that allow autologous effector T-cells to be redirected towards a specific target, enabling CAR-modified T cells to recognize specific tumor antigens in an HLA-independent fashion, and leading to the generation of an amplified antitumor response.¹³ Although exploration of CAR-T cells for treatment of various oncologic disorders has been under investigation for several decades,^{14,15} the promise of this approach was exemplified by its success in the management of various B-cell

malignancies, which led to approvals by the Food and Drug Administration (FDA) for four CD19-directed CAR-T cell therapies, including axicabtagene ciloleucel (axi-cel),^{16,17} tisagenlecleucel (tisa-cel),^{18,19} brexucabtagene autoleucel (brex-cel),^{20,21} and lisocabtagene maraleucel (liso-cel).²² In contrast, the only FDA-approved CAR-T cell treatments in MM are idecabtagene vicleucel (ide-cel), and more recently ciltacabtagene autoleucel (cilta-cel), both of which target B-cell maturation antigen (BCMA). In the ensuing discussion, we present a comprehensive overview of the rationale behind ide-cel use, examine relevant toxicities and mitigation strategies, discuss practical considerations, and provide a look into the future as it pertains to the clinical utilization of ide-cel in patients with MM.

BCMA as the Target

Since BCMA is the target of ide-cel, it is important to understand its relevance in MM and the reason behind its selection as a therapeutic target. Also referred to as tumor necrosis factor receptor superfamily member 17 (TNFRSF17) or CD269, BCMA is a type III transmembrane protein that is induced in late memory B cells destined for plasmacytic differentiation.^{23–25} It is uniformly expressed on PCs but is virtually absent on naïve B-cells, hematopoietic stem cells and nonhematopoietic tissue, making it an attractive target for therapeutic intervention in MM while minimizing off-target effects.

Overactivation of BCMA by ligands of the tumor necrosis factor (TNF) family, a proliferation-inducing ligand (APRIL) and B cell-activating factor of the TNF family (BAFF), leads to downstream signaling that converges on activation of various intracellular pathways, including nuclear factor-kappa B (NF- κ B), phosphatidylinositol 3-kinase (PI3K)/AKT, and mitogen-activated protein kinase (MAPK) pathways;^{26,27} upregulation of the antiapoptotic Bcl-2 family member proteins, Mcl-1 and Bcl-2;^{26,27} osteoclast activation;²⁸ and in some instances, dysregulation of the immune microenvironment.^{29,30} This confers a survival advantage upon malignant PCs, leading to further proliferation of the abnormal clone(s). In MM, BCMA overexpression and activation is associated with progressive disease, large tumor burden, and worse survival.^{31,32} Moreover, membrane-bound BCMA can undergo γ -secretase-mediated cleavage, leading to shedding of soluble BCMA (sBCMA) into the circulation,³³ which can then be detected in peripheral blood and allows for a rapid and more convenient diagnostic and prognostic assessment.^{34,35}

Understanding of these principles enabled exploration of BCMA as a target for various anti-multiple myeloma therapies. Anti-BCMA CAR-T cells showed encouraging preclinical efficacy,^{36,37} which was later confirmed in early clinical studies.^{38,39} However, support for targeting BCMA to clinical effect in MM was provided by the successful use of belantamab mafodotin (BLM) in treatment of patients with relapsed/refractory disease. BLM is a first-in-class, antibody–drug conjugate (ADC) that employs a humanized IgG1 anti-BCMA mAb, covalently linked to a microtubule-disrupting agent, monomethyl auristatin F (MMAF), via a noncleavable linker.⁴⁰ In preclinical studies, it exhibited several tumoricidal mechanisms, including caspase 3-dependent cellular apoptosis, antibody-dependent cellular cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP).⁴⁰ In clinical practice, this translated into impressive single-agent activity with overall response rates (ORR) ranging from 30% to 60% in heavily pretreated patients,^{41,42} resulting in FDA approval for its use in the fifth line of therapy.

CAR Design and Overview of Therapy

Deconstructing the Ide-Cel Construct

T-cell activation by T-cell receptors (TCRs) is a multistep process that is crucially dependent upon antigen presentation by major histocompatibility complex (MHC) proteins as well as subsequent signaling through costimulatory molecules.^{43–45} However, several factors limit the ability of naturally activated T-cells in mounting an enduring antitumor response, such as the need for repeated antigenic stimulation, immune exhaustion and antigen escape.^{46–48} CARs were designed to overcome some of these limitations while enhancing T-cell activation in a tumor-specific manner. First-generation CARs were composed of an extracellular antigen-recognition domain linked to an intracellular signaling domain via a transmembrane anchor. These molecules were able to activate T-cells independently of MHC proteins, but the lack of costimulatory domains resulted in limited *in vivo* efficacy.^{13,49} Second-generation CARs were then designed by addition a CD28 or 4-1BB costimulatory domain to the construct and showed more robust T-cell activation due to inflated cytokine production, modified intracellular signaling, enhanced T-cell proliferation, and delayed apoptosis.^{13,50}

Ide-cel (also known BB2121) bears a second-generation CAR that was originally crafted by bluebird bio (Cambridge, MA) and is now co-developed and co-promoted by Bristol Myers Squibb. It consists of an extracellular BCMA-detecting murine single chain variable fragment (scFv) that is attached to transmembrane and intracellular domains via a human CD8 alpha hinge (Figure 1, insert).⁵¹ The intracellular domain comprises a costimulatory 4-1BB (CD137) molecule linked to a CD3 zeta (CD3ζ) T-cell activation domain.⁵¹ While the scFv imparts antigen-specificity, the hinge domain improves CAR–antigen interactions by conveying flexibility in epitope detection, enhancing cytokine production, and promoting CAR-T persistence, resulting in an amplified antitumor effect.^{52–54} Furthermore, compared to CD28, 4-1BB costimulation appears to be associated with enhanced antitumor activity, persistence of CAR-T cells and a favorable toxicity profile.^{55,56}

Overview of Therapy

The treatment scheme begins with leukapheresis for collection of peripheral blood mononuclear cells (PBMCs) (Figure 1). The collected cells are then transported to a central facility where T-cells are enriched, activated, and subjected to transduction by a lentiviral vector (LVV) that encodes the CAR protein.^{51,57} Quality of CAR expression in transduced cells (bb2121) is confirmed using immunophenotyping, and the cells of interest then undergo ex vivo expansion until optimal cell count is reached. The CAR-modified T-cells are then washed, concentrated, and cryopreserved prior to being shipped back to the treatment site for infusion. The ratio of CD4+ to CD8+ cells in the final product is variable, with a median of 85% (range, 42–98) CD4+, and 13% (2–47) CD8+ bb2121 cells in the Phase 1 experience.⁵⁷

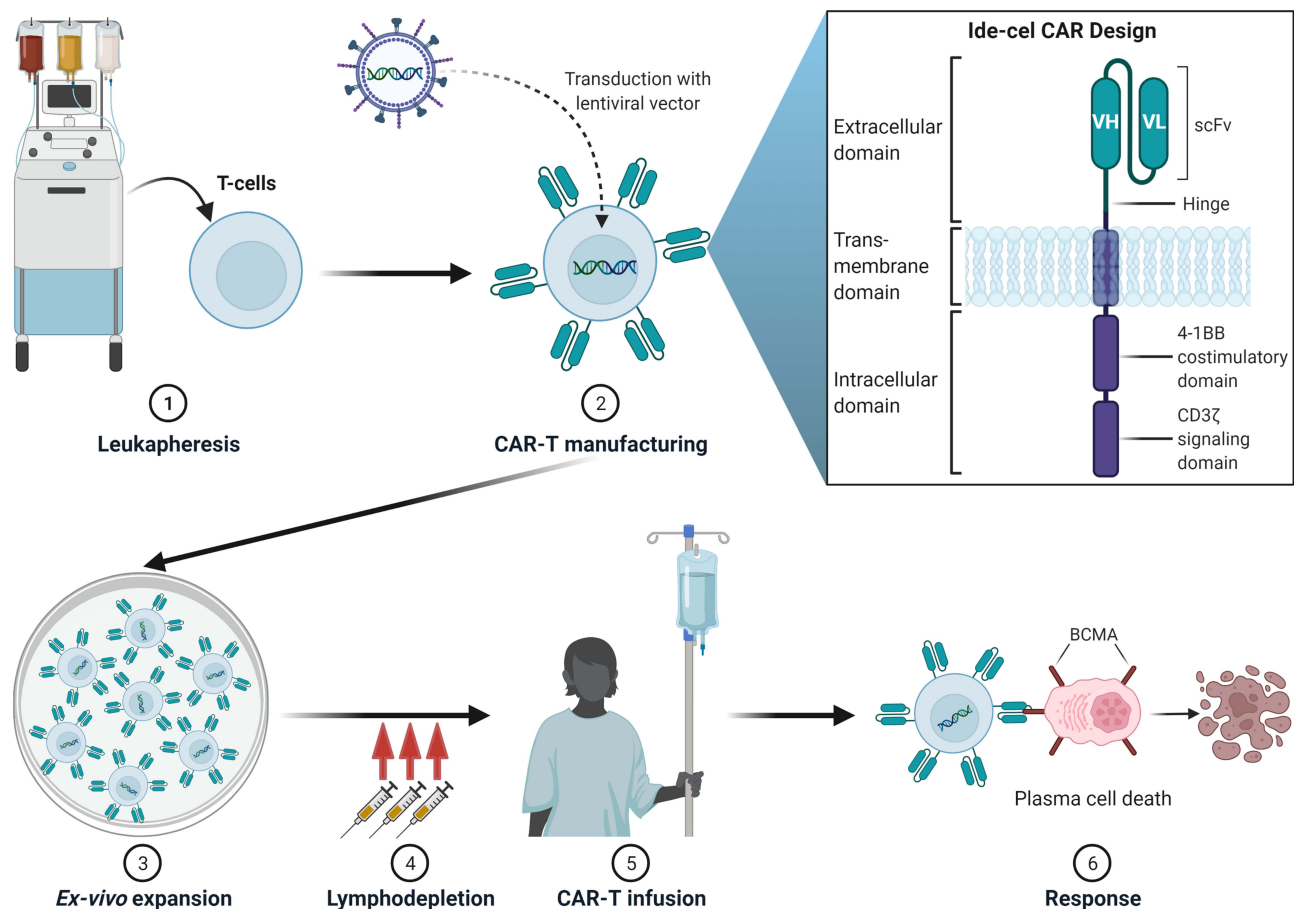


Figure 1 Overview of idecabtagene vicleucel therapy. Insert, ide-cel CAR design.

Note: Created with BioRender.com.

Abbreviation: scFv, single chain variable fragment.

Overall, the manufacturing process can take up to 6 weeks to complete, and production failures are rare at less than 0.1%.^{57,58}

Prior to CAR-T cell infusion, patients undergo lymphodepleting chemotherapy. With ide-cel, this was accomplished using a combination of fludarabine (Flu) 30 mg/m² and cyclophosphamide (Cy) 300 mg/m², administered on days -5, -4, and -3, followed by 2 days of rest, and CAR-T cell infusion on day 0.^{57,58} While lymphodepletion is not mandatory for *in vivo* CAR-T cell activity,⁵⁹ its use has long been known to heighten the efficacy of adoptive T-cell therapy by supporting T-cell persistence.^{60,61} Since then, numerous additional mechanisms have also been elicited that may explain the therapeutic benefits of lymphodepleting chemotherapy prior to CAR-T cell therapy. These include depletion of immunosuppressive regulatory T-cells to allow for enhanced tumor antigen detection, increased CAR-T cell recruitment to tumor sites, accentuated CAR-T expansion, modulation of the immune microenvironment, and immune stimulation by the gut microbiome.^{62–66} Lymphodepletion also augments CAR T-cell activity by increasing the availability of cytokines such as IL-2, IL-7 and IL-15 that would otherwise be unavailable when sequestered by homeostatic “sinks” established by naturally-occurring lymphocytes.^{67,68} Development of such a conducive cytokine milieu following Flu/Cy conditioning has been shown to correlate with favorable clinical outcomes,^{69,70} while subpar exposure to lymphodepleting therapy is associated with a higher risk of relapse.⁷¹ It is also worth noting that the optimal lymphodepleting regimen is not well-defined due to a lack of high-quality, randomized evidence. Instead, the selection of drugs for lymphodepletion in clinical use is primarily guided by expert consensus based on limited preclinical and clinical data. Therefore, standardizing the approach to pre-treatment conditioning remains a work in progress.

Another important consideration is that of the use of bridging therapy, which is often required to stabilize or debulk disease during the CAR-T manufacturing process, particularly in patients with aggressive disease. It is discussed at length in the subsequent text.

Preclinical Experience

The initial preclinical experience with ide-cel was reported by investigators from bluebird bio. In a study by Friedman et al,⁵¹ four different CARs – each with a unique anti-BCMA scFv – were evaluated in different MM and lymphoma models. Each scFv was sequentially linked to hinge, transmembrane, co-stimulatory, and T-cell signaling domains (Figure 1, *insert*). PBMCs obtained from healthy donors were transduced with LVVs encoding various CAR constructs, namely BB2120, BB2121, BB2122, and BB2123. An anti-CD19 CAR and a signaling-deficient anti-CD19Δ CAR (negative control) were also used for comparison. BCMA expression on different human myeloma cell lines (HMCLs) was analyzed using immunohistochemistry (IHC), while BCMA receptor density was assessed using flow cytometry and was noted to be high in all three HMCLs – NCI-H929, U266-B1, and RPMI-8226. Of the CAR-T cells of interest, bb2121 showed a high degree of transduction success, vector integration and cytokine production, leading to its selection for further evaluation. Cytotoxicity assessment demonstrated robust *in vitro* activity across all evaluated HMCLs when compared with anti-CD19 or negative control CAR-T cells.

In an NSG mouse model of human MM, a single bb2121 dose of 5×10⁶ CAR-T cells resulted in complete tumor eradication by day 15, whereas merely tumor shrinkage was observed in mice treated with twice weekly bortezomib, and progressive disease noted in those treated with controls. Moreover, only the mice treated with bb2121 survived to the end of the 85-day study period. In terms of pharmacokinetics, bb2121 concentration in the peripheral blood peaked at day 11, while sBCMA declined sharply with a return to near-normal levels by day 8. Histological assessment of tumor tissue showed intense CAR-T cell infiltration by day 12 in parallel with a loss of BCMA expression by IHC. Interestingly, bb2121 also induced incomplete responses in NSG mouse models of human lymphoma. These observations paved way for additional studies to investigate the clinical efficacy of bb2121, as detailed below.

Clinical Experience

Phase I Study – CRB-401

CRB-401 was an open label, phase 1, dose-escalation and dose-expansion study that evaluated the use of bb2121 in patients with RRMM who had progressed after at least three lines of therapy.⁵⁷ Different doses of the product were used, ranging from 50×10⁶ to 800×10⁶ CAR-T cells. The primary end point was safety, while secondary endpoints included

response rates and duration. Adverse event (AE) grading was done using the 2010 National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03. Exploratory endpoints included minimal residual disease (MRD) evaluation by next-generation sequencing (NGS) to a sensitivity of 10^{-4} , survival outcomes, cytokine profiling, and pharmacokinetic assessment.

At data cut-off in April 2018, 36 patients were enrolled in the study, of which 3 were unable to receive bb2121 due to progressive disease during the manufacturing period. The median age was 60 years (37–75), and most patients had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. Stage II or III disease was present in 67% of the patients, 45% had high-risk cytogenetics (defined by the presence of t(4;14), t(4;16) or del 17p), and about a quarter had extramedullary disease. Seven (3–23) median prior lines of therapy were used; and while all patients were exposed to PIs and IMiDs, 61% were refractory to bortezomib, 58% to carfilzomib, 73% to lenalidomide, and 79% to pomalidomide. Daratumumab had been previously used in 82% but only 55% were refractory, and almost all patients (97%) had received a prior ASCT. Bridging therapy was used in 42% during the manufacturing phase.

Safety

All patients experienced side effects, and 97% endured grade 3 or higher AEs. Hematologic toxicity was most common, and rates of grade ≥ 3 neutropenia were 85%, leukopenia 58%, anemia 45%, and thrombocytopenia 45%. The median time to absolute neutrophil count (ANC) improvement to more than 1000 cells/ μ L was 1.3 weeks, while that to platelet count of $>50,000$ cells/ μ L was 2 weeks, although delayed count recovery beyond 12 weeks was observed in some patients.

Cytokine release syndrome (CRS), graded according to the 2014 criteria proposed by Lee et al,⁷² was seen in 76% of the patients, and was predominantly grade 1 or 2 (70%). Grade 3 CRS was seen in 6% without any grade 4 events. Median time to CRS onset was 2 days (1–25), with a median duration of 5 days (1–32). Tocilizumab was used in seven patients and glucocorticoids in four. The incidence of CRS appeared to be higher with the use of CAR-T doses $>150 \times 10^6$ cells, baseline ferritin elevation, as well as elevated peak levels of C-reactive protein (CRP), TNF- α , and IL-10. Peak CAR-T expansion was also higher in patients with CRS and did not appear to be dampened by tocilizumab or steroid use. Neurotoxicity was seen in 42% of the patients, with no grade 3 events, and 3% grade 4 toxicity. Other non-hematologic AEs were predominantly grade 1 or 2, with the most common being fatigue (42%), infections (42%), headache (30%), hypocalcemia (27%), constipation (27%), fever (24%), and hypokalemia (24%). One patient with a grade 3 AE later died of a cardiorespiratory event.

Efficacy

The overall response rate (ORR) was 85%, with stringent complete response (sCR) observed in 36%, and complete response (CR) in 9% of the patients. No very good partial responses or better (\geq VGPR) were seen with the 50×10^6 CAR-T cell dose. Median time to first partial response or better (\geq PR) was 1 month (0.5–3). Parallel reductions in serum free light chains (FLCs) and sBCMA were observed, albeit with a lag in the decrease in serum monoclonal protein (M-protein). Early improvements in bone marrow and extramedullary disease were also seen in some patients. The median duration of response (DoR) was 10.9 months. In the 18 patients evaluable for MRD status, 16 were MRD-negative at a threshold of 10^{-4} , 15 were MRD-negative at 10^{-5} , and 3 were MRD-negative at 10^{-6} . In addition, 12 patients were MRD-negative at multiple time points, while 3 lost their MRD-negative status over time. With a median follow-up of 11.3 months (6.2–22.8), 52% experienced progressive disease, including six patients with a prior CR and six with prior MRD-negative disease. Median progression-free survival (PFS) was 12 months.

Pharmacokinetics

In vivo expansion of both CD4+ and CD8+ CAR-T cells was noted at doses greater than 150×10^6 cells, with significantly higher CAR+ T-cell numbers observed in responders as compared to non-responders. Persistent CAR-T cells were detected from the peripheral blood at 1, 3, 6, and 12 months in 96%, 86%, 57%, and 20% of the patients, respectively.

Phase II Study – KarMMa

The KarMMa study was conducted in follow-up to CRB-401.⁵⁸ It was a Phase 2 trial that enrolled 140 patients with RRMM who had progressed after three prior lines of therapy, including a PI, an IMiD, and an anti-CD38 mAb. After receiving Flu/Cy lymphodepletion as described above, patients were treated with one of three target doses of ide-cel – 150×10^6 , 300×10^6 , and 450×10^6 CAR-T cells. The primary endpoint was ORR, while key secondary endpoints included rates of CR or better (\geq CR), DoR, PFS, OS, MRD, and safety. Similar to CRB-401, AEs were assessed using NCI CTCAE, version 4.03 (2010), and CRS using the 2014 criteria proposed by Lee et al.⁷² MRD assessment was done using NGS to a sensitivity threshold of 10^{-5} .

At data cut-off in November 2018, 128 of the 140 enrolled patients had received ide-cel. Twelve patients were unable to proceed with CAR-T treatment, primarily due to physician decision to discontinue enrollment ($n=3$), withdrawal of patient consent ($n=3$), death ($n=2$), progressive disease ($n=1$), and manufacturing failure ($n=1$). Of the patients who received study treatment, the 150×10^6 dose was administered in 4 (3%), 300×10^6 in 70 (55%), and 450×10^6 in 54 (42%) patients. Median age in the overall cohort was 61 (33–78), 59% were male, and the median time from initial diagnosis was 6 years (1–18). Most patients (98%) had an ECOG PS of 0 or 1. Revised International Staging System (R-ISS) stage II disease was seen in 70%, while stage III disease was observed in 16% of the patients (Table 1). High-risk cytogenetics by R-ISS criteria ($t(4;14)$, $t(14;16)$ or $del 17p$) were encountered in 35% of the patients, whereas patients with other high-risk aberrations were also included, such as amplification of 1q (35%) and deletion of 1p (6%). Extramedullary disease was present in 39% of the patients. Median number of prior therapies was 6 (3–16), and 94% of the patients had received a prior ASCT with 34% having undergone more than one transplant. Triple-refractory disease (refractory to a PI, an IMiD and an anti-CD38 mAb) was seen in 84%, while penta-refractory disease was encountered in 26% of the patients (Table 1). Bridging therapy was employed in 88%, with a median treatment duration of 15 days (1–33). Most common agents used for bridging were dexamethasone (70%), cyclophosphamide (37%), daratumumab (28%), carfilzomib (23%), bortezomib (20%), and pomalidomide (19%).

Efficacy

At a median of 13.3 months (0.2–21.2) of follow-up, the cumulative ORR was 73% in the study population, with \geq CR rate of 33% and \geq VGPR rate of 52%. At target doses of 150×10^6 , 300×10^6 , and 450×10^6 , the respective ORRs were 50%, 69% and 81%; respective \geq CR rates were 25%, 29% and 39%; and respective \geq VGPR rates were 50%, 42% and 65% (Table 1). Of the patients who achieved \geq CR as response, 79% were MRD-negative to a threshold of 10^{-5} while MRD could not be evaluated in the remaining patients. In a subgroup analysis, higher ORRs were observed across most subgroups, including patients aged ≥ 65 years and those with extramedullary disease. The median time to first response was 1 month (0.5–8.8), and the median time to \geq CR was 2.8 months (1–11.8). The median DoR was 10.7 months (9–11.3), with longest responses seen in patients who had achieved \geq CR at 19 months. Median PFS for the overall cohort was 8.8 months, with 12.1 months (95% CI, 8.8–12.3) at the 450×10^6 , 5.8 months (95% CI, 4.2–8.9) at the 300×10^6 , and 2.8 months (95% CI, 1–not evaluable) at the 150×10^6 dose. The longest PFS of 20.2 months (95% CI, 12.3–not evaluable) was observed in patients who achieved \geq CR as a response. Median OS was 19.4 months (95% CI, 18.2–not evaluable), with 1-year survival of 78%. It is also important to note that of the patients who progressed after CAR-T, 28 underwent re-treatment with ide-cel; however, the best response in this group was VGPR (4%), while most patients continued to have disease progression (54%).

Safety

All patients experienced AEs, with 99% rate of grade 3 or higher toxicity. Hematologic AEs were most common, with grade ≥ 3 neutropenia observed in 89%, anemia in 60%, thrombocytopenia in 39%, and febrile neutropenia in 16%. Non-hematologic AEs were predominantly grade 1 or 2, most commonly being fatigue, GI toxicity, electrolyte imbalance, transaminitis, fever and hypogammaglobulinemia, although some grade 3 or 4 toxicity was also observed. Three hemorrhagic events were encountered involving the CNS, GI tract, and conjunctiva, while one was in the post-procedural setting. Infections occurred in 69% of the patients, with grade 3 or 4 in 22%, despite antibiotic and growth factor support in up to 95% of the patients. Most AEs were observed within the first 8 weeks following therapy with the notable exceptions of infections and hypogammaglobulinemia, which were frequently observed up to 6 months. In

Table I Reported Outcomes in Different Trials Employing CAR-T Cell and BiTE Therapies in RRMM

	Ide-Cel ⁵⁸	Cilta-Cel ^{102,109}	bb21217 ^{110,111}	Teclistamab ¹¹²	Cevostamab ¹¹³	Talquetamab ^{114†}
Drug class	CAR-T	CAR-T	CAR-T	BiTE	BiTE	BiTE
Target	BCMA	BCMA	BCMA	BCMA×CD3	FcRH5×CD3	GPRC5D×CD3
Phase	II	Ib/II	I	I/II	I	I
n	128	97	72	165	160	95
Dose	150–450 ×10 ⁶ cells	0.75 ×10 ⁶ /kg cells	150–450 ×10 ⁶ cells	0.06–1.5 mg/kg	0.05–198 mg	5–800 µg/kg
Median age (range)	61 (33–78)	61 (56–68)	62 (33–74)	64 (33–84)	64 (33–82)	61.5 (46–80)
Median prior therapies	6 (3–16)	6 (4–8)	6 (3–17)	5 (2–14)	6 (2–18)	6 (2–14)
R-ISS stage III (%)	16	14	NR	12	NR	11
Triple-class refractory (%)	84	88	68	78	85	77
Penta-drug refractory (%)	26	42	NR	30	NR	20
EMD (%)	39	13	NR	17	21	NR
Efficacy Outcomes						
ORR	73	98	69	63	55	70
≥CR	33	83	28	39	NR	13
≥VGPR	52	95	58	59	NR	57
Median PFS (months)	8.8	Not reached	NR	11.3	NR	NR
Median OS	19.4	Not reached	NR	18.3	NR	NR
Safety Outcomes						
CRS						
Any grade/grade ≥3 (%)	84/5	95/5	75/4	72/1	80/1.3	77/1
Median time to onset (days)	1 (1–12)	7 (5–8)*	2 (1–20)	2 (1–6)	NR	2 (1–22)
Median duration (days)	5 (1–63)	4 (3–6)*	NR	2 (1–9)	NR	2 (1–3)
Neurotoxicity/ICANS						
Any grade/grade ≥3 (%)	18/3	22/12	15/NR	15/1	May be up to 41/4	NR
Median time to onset (days)	2 (1–10)	7 (5–8)*	7 (2–24)	3 (1–13)	NR	NR
Median duration (days)	3 (1–26)	4 (3–6)*	NR	7 (1–291)	NR	NR

Notes: *Represents interquartile range (IQR). †Includes efficacy and safety data for the 405 µg/kg SQ weekly dose.

Abbreviations: BiTE, bispecific T-cell engager; CAR-T, chimeric antigen receptor T-cell; Dara, daratumumab; CRS, cytokine release syndrome; EMD, extramedullary disease; FcRH5, Fc receptor-homolog 5; GPRC5D, G protein-coupled receptor family C group 5 member D; ICANS, immune effector cell-associated neurotoxicity syndrome; NR, not reported.

patients with grade ≥3 cytopenias, median time to ANC recovery was 1.9 months (1.2–5.6), while that for platelet recovery was 2.1 months (1.2–13.8), without significant impact from the CAR-T cell dose employed.

CRS occurred in 84% of the patients with a median time to onset of 1 day (1–12) and median duration of 5 days (1–63) (Table 1). Grade 3 or higher CRS was seen in only 5%, including one death. Rates of CRS correlated with the CAR-T cell dose used, although grade 3 or 4 CRS rates were similar at 6% between the 300×10⁶ and 450×10⁶ doses. Tocilizumab was used in 52% and glucocorticoids in 15% of the patients for management of CRS. All grade neurotoxicity was observed in 18% of the patients with a median time to onset of 2 days (1–10), and a median duration of 3 days (1–26). Grade 3 neurotoxic AEs were

seen in 3%, with no grade 4 or 5 events, although rates of neurotoxicity were higher with increasing CAR-T cell doses. A total of 50 patients died on study, most commonly due to disease progression (42%) and treatment-emergent AEs (14%).

Pharmacokinetics

In the 127 patients in whom pharmacokinetics were evaluable, maximum CAR-T cell expansion was observed at a median of 11 days (7–30). Ide-cel peak exposure was higher in responders, and positively correlated with the depth of response and PFS. Patients who exhibited a response also demonstrated sharply declining sBCMA levels throughout the first 2 months following treatment, whereas no substantial change in sBCMA was appreciated in non-responders. Higher CAR-T cell expansion also inversely correlated with sBCMA levels. CAR-T cells were detectable in 59% of the patients at 6 months and in 36% at 12 months. While the risk of CRS or neurotoxicity did not correlate with baseline cytokine levels, patients who experienced CRS had higher levels of IL-6 and INF- γ compared to those who did not.

Health-Related Quality of Life

In data presented at the annual American Society of Hematology (ASH) meeting in 2021, assessment of health-related quality of life (HR-QoL) demonstrated clinically meaningful improvements in fatigue and pain in 40–70% of the patients at 24 months post-treatment. Physical and cognitive decline that occurred in many patients also seemed to improve at later timepoints. Furthermore, clinically meaningful improvements in symptoms and side effects were reported in 30–40% of the patients.⁷³

Select Adverse Effects and Mitigation Strategies

With the increased utilization of CAR-T cell therapy across multiple oncologic disorders, the associated toxicity profile has also become indisputable. While a comprehensive analysis of these AEs is beyond the scope of this review, it is worth briefly reviewing some of the representative toxicities in order to better understand the issues surrounding ide-cel use in clinical practice.

Cytokine Release Syndrome

CRS is the most common acute toxicity related to the use of CAR-T cell therapies. It was seen in 76–84% of the patients treated with ide-cel.^{57,58} While the relatively low rates of grade ≥ 3 CRS observed may be partly attributed to the grading criteria used in these studies, CRS carries the risk to evolve into fulminant hemophagocytic lymphohistiocytosis (HLH) and even death. It occurs due to an overproduction of cytokines, typically as a result of CAR-T cell expansion *in vivo* but also from T-cell mediated activation of bystander immune reactive cells, such as monocytes and macrophages.^{74,75} Various cytokines have been implicated, including INF- γ , IL-2, IL-2-receptor- α (IL2R α), IL-6, IL6-receptor (IL6R), IL-8, IL-10, TNF- α , granulocyte-macrophage colony-stimulating factor (GM-CSF), CXCL9 (MIG), CXCL10 (IP-10), macrophage inflammatory protein (MIP)-1 α , MIP-1 β , and monocyte chemoattractant protein (MCP)-1,^{72,74–78} which give rise to a “cytokine storm” as is often seen with other infectious and inflammatory syndromes.^{79–81} Clinical manifestations are variable and can range from constitutional symptoms at milder end of the spectrum to multiorgan failure and death in extreme cases. Numerous tools have been used over time to assess the severity of CRS,^{72,77,82} but recent consensus guidelines recommend the use of 2019 criteria proposed by the American Society for Transplantation and Cellular Therapy (ASTCT) in order to standardize measurement and management across different clinical settings (Table 2).^{83–86} Prompt detection and timely administration of the IL6R antagonist, tocilizumab, as well as corticosteroids remain the cornerstone of management along with aggressive supportive care.^{83–85} The use of third-line agents such as anakinra and siltuximab may be considered if CRS persists despite two doses of tocilizumab.⁸³

Neurotoxicity

Neurotoxicity is frequently associated with CAR-T cell therapy and includes the syndrome of immune effector cell-associated neurotoxicity syndrome (ICANS) (Table 2). Neurotoxic symptoms can be as subtle as headache, lethargy, agitation, difficulty concentrating and tremors, or may be more dramatic, presenting with delirium, aphasia,

Table 2 ASTCT Criteria for Grading CRS and ICANS. Adapted from Lee et al.⁸⁶

Toxicity	Parameter	Grade 1	Grade 2	Grade 3	Grade 4
CRS	Fever	Temp $\geq 38^{\circ}\text{C}$	Temp $\geq 38^{\circ}\text{C}$	Temp $\geq 38^{\circ}\text{C}$	Temp $\geq 38^{\circ}\text{C}$
			And		
	Hypotension	None	No pressor requirement	Pressor requirement with or without vasopressin	Multiple pressors excluding vasopressin
			And/or		
	Hypoxia	None	Requiring O ₂ by low-flow NC (≤ 6 L/min) or blow-by	Requiring O ₂ by HFNC, facemask, nonrebreather mask or Venturi mask	Requiring positive pressure ventilatory support*
ICANS	ICE score [†]	7–9	3–6	0–2	0
	Depressed consciousness not attributable to other cause	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Arousable with vigorous tactile stimuli, unarousable, stupor, or coma
	Seizures	NA	NA	Any seizure with rapid clinical resolution or with intervention on EEG tracings	Prolonged (>5 min), non-resolving or life-threatening seizures
	Motor findings	NA	NA	NA	Significant focal motor weakness (eg, hemiparesis or paraparesis)
	Elevated ICP/ cerebral edema [‡]	NA	NA	Focal edema on brain imaging	Diffuse edema on imaging, or decerebrate/decoricate posturing, CN VI palsy, or Cushing's triad

Notes: *Positive pressure ventilation includes continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP) or mechanical ventilation. [†]Immune Effector Cell-Associated Encephalopathy (ICE) score includes points for orientation (year, month, city, hospital; 4 points), naming (three objects; 3 points); following simple commands (1 point), writing a simple sentence (1 point), and attention (eg, counting backwards from 100 by 10; 1 point). [‡]Excludes intracranial hemorrhage or associated edema.

Abbreviations: Temp, temperature; NC, nasal cannula; O₂, supplemental oxygen; HFNC, high-flow nasal cannula (>6 L/min); NA, not applicable; EEG, electroencephalogram; CN, cranial nerve; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.

encephalopathy, seizures, and posterior reversible encephalopathy syndrome (PRES).^{77,87,88} Late-onset movement disorders, cognitive impairment and personality changes have also been described, particularly in patients with high tumor burden, coexisting CRS (grade ≥ 2) or ICANS (any grade), and high CAR-T expansion.⁸⁹ Rare instances of fatal cerebral edema have also been described.^{90,91} It is thought to result from an overproduction of various cytokines, including IL-2, IL-6, IL-10, IL-15, IFN- γ , TNF- α , GM-CSF, and MCP-1, as well as endothelial cell dysfunction and disruption of the blood–brain barrier (BBB).^{77,92,93} In severe cases, release of prothrombotic effectors such as von Willebrand factor (vWF) can ensue, leading to the development of a consumptive coagulopathy.^{77,92,93} More recently, BCMA expression on neurons and astrocytes in the basal ganglia has also been proposed as a potential mechanism for neurotoxicity⁹⁴; however, current data are limited and further studies are required for validation.

We use the Immune Effector Cell-Associated Encephalopathy (ICE) score proposed by the ASTCT for early detection and grading of ICANS (Table 2),⁸⁶ and perform the 10-point neurologic assessment at the bedside twice a day, in accordance with current guidelines.^{83,85,95} Management relies upon aggressive supportive care, including antiepileptic prophylaxis in patients at high risk for seizures, and the use of corticosteroids in patients with grade ≥ 2 ICANS. Tocilizumab has limited role in the treatment of isolated ICANS due to poor BBB penetration, but it should be administered in all patients who exhibit evidence of concurrent CRS.^{83–85}

Cytopenias and Infectious Prophylaxis

Prolonged cytopenias and hypogammaglobulinemia are also common with ide-cel use and may be consequent to the underlying disease, prior anti-MM treatment, bridging therapy and/or lymphodepleting conditioning. While the severity and duration vary, most patients remain at an increased risk for infectious complications following CAR-T cell therapy, particularly in context of immune dysfunction and reconstitution. This necessitates adoption of a proactive approach to the use of appropriate supportive and prophylactic measures. In our practice, we routinely prescribe acyclovir or valacyclovir to prevent against varicella zoster virus (VZV) reactivation, and trimethoprim-sulfamethoxazole (TMP-SMX) for prophylaxis against *Pneumocystis jirovecii* pneumonia (PJP) for up to 1 year. In the immediate post-treatment phase; however, we prefer inhaled pentamidine over TMP-SMX for PJP prophylaxis in patients with significant coexisting cytopenias. Additionally, we employ fluoroquinolones for antibacterial, and fluconazole for antifungal prophylaxis, at least until the resolution of neutropenia, in accordance with the National Comprehensive Cancer Network (NCCN) guidelines. We also consider recombinant human granulocyte colony-stimulating factor (G-CSF) support in patients with profound neutropenia, although we prefer to delay administration for at least 14 days after CAR-T cell infusion in order to avoid potential interactions with CAR-T expansion and peak CRS risk.⁸³

Practical Considerations

The use of ide-cel in clinical practice merits consideration of several additional factors. Patient selection is important, and outside of a clinical trial, ide-cel use should be reserved for those able to tolerate more intensive forms of therapy, at least until further data can establish its safety in the relatively “unfit” population. Ide-cel, like other CAR-T cell therapies, also has the benefit of being a one-time treatment; however, most patients are unlikely to enjoy enduring treatment-free intervals due to the substantial risk of relapse. Moreover, some patients with clinically aggressive disease are not able to wait for up to 6 weeks that can be required for manufacturing the CAR-T product. Others may require bridging therapy during this time for adequate disease control, which can also be challenging due to the theoretical risk of inducing ide-cel resistance, particularly if other BCMA-targeting agents are used.

Another important issue is that of cost. Ide-cel carries a price tag of \$419,500 for a single CAR-T cell infusion, discounting the ancillary expenditures for lymphodepleting conditioning, supportive medications and hospital accommodation.^{96–100} Furthermore, the cost of managing associated toxicities can range anywhere from \$18,497 to \$121,535, depending on the severity and duration of AEs, which can significantly increase the price point.¹⁰¹ Therefore, it is important to take the financial burden into account when considering ide-cel use, particularly if alternate treatment options are available.

The use of ide-cel is currently also restricted by availability due to limited manufacturing capacity and factors pertaining to supply-chain management. Some of these impediments are expected to improve with time but will continue to present a challenge at least in the immediate short-term. And while rare, manufacturing failures can happen, rendering it imperative for treating physicians to have an alternate management strategy when planning ide-cel use in their patients.

And finally, ciltacabtagene autoleucel (cilta-cel) gained FDA approval on February 28, 2022, for treatment of RRMM. It carries the same indication as ide-cel and is approved for patients in the fifth line of therapy following progression on a PI, an IMiD, and an anti-CD38 mAb. Design of the cilta-cel CAR is unique as it contains a camelid-derived nanobody comprising two heavy chain variable regions that target two distinct BCMA epitopes. Presence of the dual epitope-binding anti-BCMA single-domain antibodies in the extracellular domain imparts antigen specificity and avidity. Like ide-cel, however, cilta-cel also contains 4-1BB costimulatory and CD3 ζ T-cell signaling domains. Its efficacy was demonstrated in the open-label phase 1b/2 CARTITUDE-1 study,¹⁰² in which 97 patients with RRMM received cilta-cel infusion at a dose of 0.75×10^6 (range, $0.5\text{--}1.0 \times 10^6$) CAR-T cells per kg after a median of 6 (4–8) prior therapies. High-risk cytogenetic abnormalities (t(4;14), t(14;16) or del 17p) were observed in 24% of the patients, while 88% were triple-class and 42% were penta-drug refractory (Table 1). At a median follow-up of 12.4 months (10.6–15.2), ORR was 97% (95% CI, 91.2–99.4), with \geq VGPR rate of 93%, and a sCR rate of 67%. Median PFS was not reached, whereas PFS and OS rates at 12 months were 77% and 89%, respectively. Median time to first response was 1 month (0.9–1) while that to best response was 2.6 months (1–6.1). Of the 57 evaluable patients, 93% were able to achieve MRD-negativity at

a threshold of 10^{-5} by NGS. Evaluation of safety demonstrated AEs in all patients, as assessed by the NCI CTCAE, version 5.0 (2017). All grade CRS occurred in 95% of the patients, although only 5% developed grade ≥ 3 CRS, including one death in a patient with prolonged CRS and concurrent HLH. Median time to CRS onset was 7 days (5–8) and median CRS duration was 4 days (3–6). Neurotoxicity was observed in 21% of the patients overall, ICANS in 17%, and both in 8%. While most cases were grade 1–2, the rate of grade ≥ 3 neurotoxic AEs was 10%, including one death. Median time to ICANS onset was 8 days (6–8), and the median ICANS duration was 4 days (3–6.5). All patients additionally experienced hematologic AEs, with high rates of grade 3–4 neutropenia (95%), anemia (68%), and thrombocytopenia (60%). Grade 3–4 non-hematologic toxicities were relatively infrequent.

It is noteworthy that direct comparisons between ide-cel and cilta-cel have not yet been performed. Therefore, any apparent incongruences in efficacy and safety measures of the two therapies may be purely coincidental or a product of numerous involved variables, such as differences in trial design or the study populations. As such, the choice of therapy in practice should be guided by availability and other practical considerations, at least until further data can guide clinical decision-making.

Future Directions

Incorporation of ide-cel as a therapeutic option in the treatment landscape of MM represents a major scientific and clinical advancement. Ide-cel has the potential to induce responses in patients with heavily pretreated and high-risk disease; however, it is also worth emphasizing that the rates of functional “cure” remain modest at best with current treatment strategies, as evidenced by almost half of the patients on the KarMMA study who progressed within the first year of treatment even at the target dose of 450×10^6 CAR-T cells.⁵⁸ While efforts are ongoing, various resistance mechanisms have been identified. These include impaired CAR-T cell expansion and persistence, development of anti-CAR-T cell antibodies, dysregulation of the bone marrow microenvironment, and upregulation of pro-inflammatory chemokines, anti-apoptotic genes (MCL-1) and NF- κ B signaling.^{58,59,95,103} Another important resistance mechanism is a deletion in chromosome 16p that leads to a loss of the BCMA-encoding gene, *TNFRSF17*.^{104,105} In clinical practice, a complete absence of PC membrane BCMA expression at disease progression following CAR-T treatment appreciated by flow cytometry would indicate the presence of a likely del 16p, and could be potentially utilized to predict response to subsequent therapies.

In order to overcome resistance and alleviate toxicity, numerous approaches are also currently under investigation. These include exploration of CAR-T cells directed against non-BCMA targets, such as G protein-coupled receptor, class C group 5 member D (GPRC5D),¹⁰⁶ CD19, CD38, CD138 (SYND1), SLAMF7 (CS1), and NKG2D; development of dual-antigen targeting CARs, and concurrent use of drugs such as IMiDs for synergistic effect.^{95,107,108} Together with optimization of lymphodepleting regimens and streamlining production issues, these strategies will likely help enhance the efficacy and utilization of ide-cel in the near future. And lastly, with the emergence of newer therapies, such as bispecific T-cell engagers (BiTEs) and allogeneic CAR-T cell therapies, the optimal place for ide-cel in the treatment paradigm for MM will also become more discernable in the future. A summary of outcomes reported in different trials employing some of these novel therapeutic strategies is provided in Table 1.

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The authors report no conflicts of interest in this work.

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