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The role of idecabtagene vicleucel in patients with heavily pretreated refractory multiple myeloma

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***Abstract*:** The development of several treatment options over the last 2 decades has led to a notable improvement in the survival of patients with multiple myeloma. Despite these advances, the disease remains incurable for most patients. Moreover, standard combinations of alkylating agents, immunomodulatory drugs, proteasome inhibitors, and monoclonal antibodies targeting CD38 and corticoids are exhausted relatively fast in a proportion of high-risk patients. Such high-risk patients account for over 20% of cases and currently represent a major unmet medical need. The challenge of drug resistance requires the development of highly active new agents with a radically different mechanism of action. Several immunotherapeutic modalities, including antibody–drug conjugates and T-cell engagers, appear to be promising choices for patients who develop resistance to standard combinations. Chimeric antigen-receptor-modified T cells (CAR-Ts) targeting B-cell maturation antigen have demonstrated encouraging efficacy and an acceptable safety profile compared with alternative options. Multiple CAR-Ts are in early stages of clinical development, but the first phase III trials with CAR-Ts are ongoing for two of them. After the recent publication of the results of a phase II trial confirming a notable efficacy and acceptable safety profile, idecabtagene vicleucel is the first CAR-T to gain regulatory US Food and Drug Administration approval to treat refractory multiple myeloma patients who have already been exposed to antibodies against CD38, proteasome inhibitors, and immunomodulatory agents and who are refractory to the last therapy. Here, we will discuss the preclinical and clinical development of idecabtagene vicleucel and its future role in the changing treatment landscape of relapsed and refractory multiple myeloma.

Keywords: B-cell maturation antigen, chimeric antigen receptor modified T cells, idecabtagene vicleucel, relapsed and refractory multiple myeloma

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Introduction

The use of combinations of new drugs with different mechanisms of action for the treatment of multiple myeloma (MM) in the last decade has dramatically prolonged life expectancy of patients.[1] These combinations, triplet or even quadruplet regimens, of proteasome inhibitors (PIs), immunomodulatory agents (IMIDs) and monoclonal antibodies (MoAbs) have emerged as game-changer agents,[2,3] particularly when used in association with high-dose therapy and autologous stem-cell transplantation (ASCT).[4] As a consequence, combinations for MM patients at relapse have shifted accordingly from lenalidomide or bortezomib-based triplets to carfilzomib or pomalidomide-based alternatives.[5–10] Despite these advances, most patients are expected to relapse, and a proportion of them will develop resistance to several drugs relatively early in the course of disease. Patients who are refractory to PIs, IMIDs, and anti-CD38 MoAbs, also designated triple-class refractory MM, have poor prognosis with median overall survival (OS) of less than 1 year.[11] The benefit of triplet combinations in patients relapsing soon after contemporary frontline treatments is limited in time, even when

based on drugs to which the patient was not exposed in the previous line.[12] Therefore, efficacious and well-tolerated therapeutic options for the treatment of triple-class refractory MM remains an unmet need. Several novel immunotherapeutic approaches have been developed targeting these population. Bispecific antibody T-cell engagers (TCEs), antibody–drug conjugates (ADCs) and chimeric antigen receptor-modified T cells (CAR-Ts) have demonstrated encouraging early efficacy in clinical trials.[13–16] Most of these agents are targeting B-cell maturation antigen (BCMA). The present review will discuss preclinical and clinical data that led to the regulatory approval of idecabtagene vicleucel (ide-cel; bb2121), the first available CAR-T against BCMA for the treatment of relapsed and refractory MM patients who have received at least three prior therapies including an anti-CD38 MoAb, a PI, and an IMID.

Limits of standard treatment for multiple myeloma

The combination of IMIDs, PIs, antiCD38 MoAbs, and dexamethasone has become standard treatment of MM in the frontline and in the relapse setting. Bortezomib, thalidomide and dexamethasone (VTD) became standard frontline induction treatment after proving its superiority over bortezomib and dexamethasone[17] or thalidomide and dexamethasone.[18,19] Also, lenalidomide, bortezomib, and dexamethasone (VRD) is superior to lenalidomide and dexamethasone alone[20] and constitutes an adequate induction in the transplant setting.[4,21] The addition of MoAbs to both backbones also has a positive impact in depth of initial response and progression-free survival (PFS).[22,23] Similarly, the addition of daratumumab or isatuximab to VRD or carfilzomib, lenalidomide, and dexamethasone (KRD) backbones is being explored in several ongoing trials. High-dose melphalan and autologous stem-cell transplantation (ASCT) is a standard procedure for all patients who are fit enough,[4] and tandem ASCT may also benefit at least a subset of patients.[24] After ASCT, the current maintenance standard with lenalidomide[25] is already being challenged in ongoing trials with two drug maintenance combinations including PIs or MoAbs. In the non-transplant setting, the addition of continuous daratumumab up to progression to the prior standard melphalan, prednisone, and bortezomib,[26] or the addition of daratumumab to the prior standard lenalidomide and dexamethasone,[26] improved the complete remission (CR) rates to almost 50% and extended the PFS to 3 years or more.[26,27] This last trial included continuous treatment with both lenalidomide and daratumumab up to progression.[27] For patients intolerant to any of these continuous treatment alternatives, ixazomib, an oral PI, has also proved better than placebo as maintenance therapy.[28] Standard-risk patients and the patients achieving the deepest responses are those benefitting most from optimized frontline treatment strategies, and there is already evidence of a proportion of them being disease-free for more than 10 years following high-dose melphalan.[29] Still, the projected proportion of 'operationally cured' patients is under 20% and most of individuals are expected to relapse at some point. The patient profile at relapse is also changing as a consequence of upgrading frontline treatment strategies. In contrast with patients that relapsed a decade ago, relapse occurs after exposure to a combination of different drug classes. More importantly, patients relapse while still receiving one or more drugs as maintenance. Time to relapse after initial treatment is already defining subgroups of patients with a different prognosis and a dramatically different likelihood of response to salvage treatment. Primary refractory patients, and patients relapsing early (less than 1 year) after initial therapy, including ASCT, will be of an exceptionally high risk. A second group, including the largest proportion of standard-risk patients, will relapse after a relatively prolonged disease-free period while on treatment with lenalidomide. Despite the heterogeneity of situations at relapse, subsequent treatment is essentially based on prior bortezomib- or lenalidomide exposure and, more importantly, on bortezomib- or lenalidomide refractoriness. A growing proportion of patients exposed to both drugs and mostly refractory to lenalidomide is expected in following years. Refractoriness should be viewed more as a continuous variable than a category in any patient previously exposed to an agent in combination therapy. The safer choice at relapse is likely to be an alternative combination based in, at least one, but optimally two, drugs to which the patient is still naïve. The most promising combinations are likely to be anti-CD38 MoAbs with the next-generation PI carfilzomib[5,6] or immunomodulatory agent pomalidomide.[8,10] Also, the

combination of pomalidomide, carfilzomib and dexamethasone (KPD) has been explored[30,31] and may be the adequate option for patients refractory to a frontline combination including a MoAb until progression. Median PFS with anti-CD38 MoAbs in combination with carfilzomib and pomalidomide are in the 1–2 year range. It may be anticipated that patients who relapsed soon after a frontline triplet or quadruplet combination are those likely to benefit less from these alternative triplets in the second line.

Bortezomib and lenalidomide have become mainstay agents of initial MM treatment and consequently combinations of carfilzomib, pomalidomide and MoAbs provide the best chances of success in the salvage setting. However, the use of different triplet therapies up to progression both in first and second line implies that patients suffering a second relapse will have already exhausted most of the currently available therapeutic resources. New agents with different mechanisms of action such as venetoclax or selinexor[32,33] offer most benefit in combination with PIs or IMIDs; in consequence, their place in the salvage treatment remains to be determined. Until recently, available data for immunotherapeutic agents, including ADCs, TCEs, and CAR-Ts were derived from relatively small phase I trials, and had to be considered with extreme caution. Recent data provide solid evidence that immunotherapy is likely to offer much more benefit than other alternatives, at least in the triple-class refractory setting.

Current immunotherapeutic options

Immunotherapy is rapidly evolving in this scenario. Because of its alternative mechanisms of action, they probably are the optimal choice after failure of IMIDs, PIs, and naked MoAb combination therapies. BCMA, a protein belonging to the tumor necrosis factor receptor (TNFRS17) is a transmembrane protein that critically regulates B-cell proliferation and survival,[34] as well as maturation and differentiation into plasma cells.[35,36] Its limited distribution in normal tissue, almost exclusive presence in terminally mature plasma cells and its overexpression in myeloma plasma cells[37] have revealed BCMA as a most attractive target for immunotherapeutic approaches.[37,38] Furthermore, BCMA plays an important role in MM pathogenesis and pathophysiology by engaging the a proliferation-inducing ligand (APRIL) and/or the B-cell-activating factor of the tumor necrosis factor family (BAFF) to activate growth and survival signaling cascades.[39] BCMA expression is upregulated during MM pathogenesis and the evolution from monoclonal gammopathy of undeterminate significance to active MM.[40] Surface BCMA is modulated by γ-secretase (GS), a multi-subunit protease that mediates protein cleavage, resulting in release of a soluble BCMA (sBCMA) fragment composed of the extracellular domain and part of the transmembrane region.[41] Soluble BCMA is considered a marker of tumor burden and increased levels are associated with worse outcomes.[42] Relatively mature results with anti-BCMA ADCs[13] and TCEs[14] have been recently communicated.

Belantamab mafodotin is an anti-BCMA immunoconjugate using an antimitotic agent, monomethyl auristatin as a payload.[43] Results of the phase I trial in which patients, PI and IMID exposed and mostly refractory (97% to PIs and 94% to IMIDs),[43,44] showed a 60% overall response rate (ORR) and a median PFS of 12 months.[44] Results of the subsequent phase II trial included also anti-CD38 exposed, were less striking,[13] with a 31% ORR, a 7% CR rate and a median PFS of 3 months, highlighting the major prognostic relevance of prior exposure and resistance to prior drugs in RRMM. Belantamab mafodotin presented a characteristic corneal toxicity in up to 72% of patients.[45] Thrombocytopenia (35% grade 3) was the most common hematological toxicity. Several trials are exploring belantamab mafodotin in combination with PIs and IMIDs in a less refractory population.

AMG-420 was the first bispecific TCE targeting BCMA and CD3 that proved capable of inducing selective lysis of BCMA-positive MM cells, activation of T cells and release of cytokines and T-cell proliferation with negligible impact on BCMA-negative cells.[46] The drug will be no further developed because of the need to use a continuous infusion. However, a number of longer-life constructs are being explored that can be given on a weekly or bi-weekly basis. Results of the largest phase I dose-finding trial with an ongoing expansion cohort have been communicated recently.[14] Teclistamab was explored in 128 patients with heavily treated MM in increasing intravenous and subcutaneous doses. Most participants were triple-class exposed (95%) or refractory (79%), and

a relevant proportion of them were penta-drug exposed or refractory, 70% and 38%, respectively. At the most active dose levels the ORR was 65%, including a 20% CR rate with minimal residual disease (MRD) negativity at a 10^{-6} sensitivity level. Median time to first response was 1 month, and the median duration of response (DOR) had not been reached at the time of communication. Teclistamab had a favorable safety profile with mostly hematological toxicity. Cytokine-release syndrome (CRS) appeared in 53% of individuals; severity was up to grade 2, and generally with initial doses only. Frequency and severity of CRS was similar with subcutaneous and intravenous formulations. All patients received prophylactic medication, and several step-up doses were explored to minimize CRS. Neurotoxicity was infrequent (5% of patients), although 2% of patients had grade 3 or higher (all of them in the intravenous cohorts). Other constructs targeting BCMA[47–50] or other plasma cell-surface antigens, such as GPRC5D,[15] have shown similarly interesting results, although in smaller samples or with shorter follow up (Table 1). When analyzed as a whole, it is apparent that several anti-BCMA TCEs under clinical development will be likely to have a notable efficacy and maintain durable responses. They are also expected to have a manageable CRS and will be able to maintain adequate plasma levels with once-weekly infusions or less.

Finally, several genetically modified T cells to express a chimeric antigen have been developed against BCMA[51–53] and have shown impressive results. The first fully published phase II trial, including relatively mature data in a number of patients with sufficient follow up is the KARMMA trial with ide-cel.[16] Different immunotherapeutic approaches may be more adequate for different patient profiles. The main differences among immunotherapeutic approaches are summarized in Table 1.

Idecabtagene vicleucel development

Preclinical data

The National Cancer Institute (NCI) was the first to provide the proof of principle that CAR-T cells targeting BCMA were able to induce responses in patients with MM.[50] A phase I trial of their CAR-T-cell product in MM patients resistant to standard therapies was able to induce responses in 13 of the 16 patients treated with the highest dose level. CRS after CAR-T-cell infusions was a major disadvantage of the procedure; 6 out of 16 patients receiving the highest dose level required vasopressors, and grade 3 or higher CRS was associated with a high tumor burden. It was also noted that CAR-T persistence was of importance to prevent or delay relapse. The NCI CAR-T used a CD28 co-stimulatory domain.[54] Vector design elements appear to be important factors in the activity of CAR-Ts. Several studies suggested that 4-1BB co-stimulation may offer some advantages over CD28, more specifically a significant survival increase has been suggested.[55] CAR constructs using CD28 co-stimulatory domains are associated with a more rapid activation than 4-1BB containing CAR vectors due to a faster increase in levels of T-helper-cell-2-like cytokines.[56] Such rapid activation of CAR-T cells using the CD28 co-stimulation pathway may make these cells more prone to cause an early-onset CRS. When comparing CAR constructs with identical single-chain variable fragments (scFvs) in tumor treatment models, 4-1BB-containing vector-transduced T cells developed into more central memory-like T cells with enhanced respiratory capacity, increased fatty-acid oxidation, and enhanced mitochondrial activity than CD28 co-stimulatory-containing vectors.[57] However, such comparisons must be viewed with caution in the absence of direct comparisons in humans of identical CARs containing either CD28 or 4-1BB, as many other variables may contribute to the persistence or exhaustion of T cells. Moreover, the scenario may be dramatically modified with the availability of third-generation products incorporating more than one co-stimulatory domain. In any case, these observations clearly suggest the critical influence of T-cell metabolism on the function of T cells and, consequently, in CAR-T-cell clinical efficacy. Friedman *et al.* sought to produce a series of anti-BCMA CAR-encoding lentiviral vectors (LVVs) to generate anti-BCMA CAR-T cells.[58] Anti-BCMA CAR LVVs were replication defective, self-inactivating, third-generation human immunodeficiency virus type 1 (HIV-1) based, pseudotyped with the vesicular stomatitis virus–glycoprotein envelope protein. Four different anti-BCMA CARs were constructed using distinct anti-human BCMA MoAbs shown to have high specificity to human plasma cells. Sequences from the MoAbs were used to construct scFvs (in orientation V_L-linker-V_H), which were assembled into a CAR architecture using a CD8α extracellular hinge

Table 1. Advantages and disadvantages of different immunotherapeutic approaches in the treatment of relapsed and refractory multiple myeloma: comparison of characteristics and treatment requirement of different anti-BCMA modalities.

	Antibody-drug conjugate (ADC)	T-cell engager (TCE)	CAR-T cell
Efficacy			
For		Better response rates than ADCs	Higher response rates
Against	Lower response rate than TCEs or CAR-Ts		
Safety			
For	No CRS, no neurotoxicity	Limited CRS	
Against	Ocular toxicity	Uncertainties in long term use	Higher CRS and neurotoxicity Deeper thrombocytopenia rates than TCEs
			Prolonged cytopenias
Applicability			
For	Off the shelf	Off the shelf	One-time intervention
	Only one infusion every 3 weeks		
	No hospitalization required		
	Applicable in small centers		
	Data on combinations and earlier use in the course of disease		
Against	Ophthalmologist requirement	Weekly infusions	Not applicable in small centers
	Continuous treatment	Hospitalization required	Manufacturing delay, need for bridging therapy or use in stable disease
		Continuous treatment	Hospitalization required

BCMA, B-cell maturation antigen; CAR-T, chimeric antigen-receptor-modified T cells; CRS, cytokine-release syndrome.

and transmembrane domain followed by 4-1BB (CD137) co-stimulatory domain and CD3ζ T-cell signaling elements (Figure 1). The study proved that the specific scFv used to target the CAR-T cells also affects T-cell-effector function. Preclinical studies proved that the bb2121 vector presented more favorable expression than other constructs despite similar transduction efficiency;[58] additionally, given a similar CAR expression, T cells in which constructs differed only in their scFv domain displayed significantly different cytokine release in co-culture assays and different lytic activity.[58]

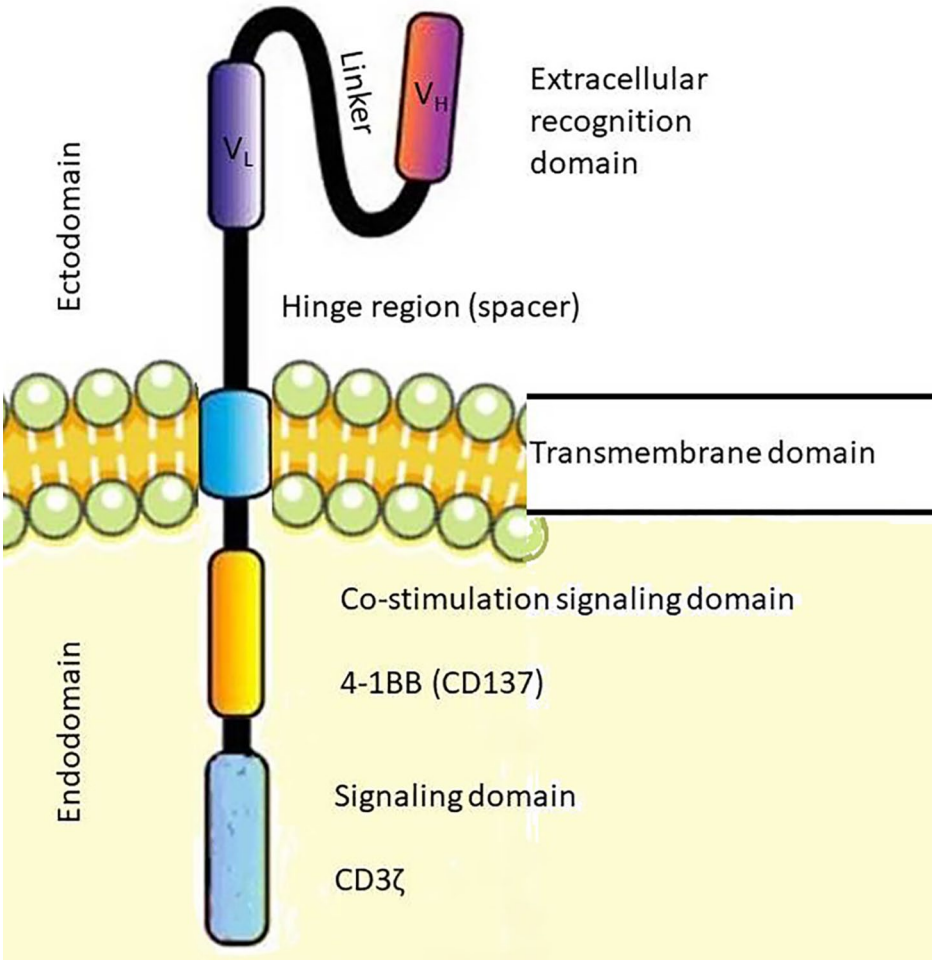

Figure 1. Chimeric antigen receptor structure of idecabtagene vicleucel.

Consequently, T-cell activity is also influenced by scFv affinity and a relationship between scFvs with lower binding constants and enhanced activity has been observed.[59] bb2121 was selected for additional studies due to its gene transfer efficiency, antigen-specific cytokine release, and cytolytic activity of anti-BCMA CAR-T cells, anti-tumor activity of bb2121 was confirmed in a wide panel of cell lines. Activity could be observed in cell lines with as few as 222 BCMA molecules/cell. Consistent with prior reports showing absence of BCMA expression in healthy precursor bone-marrow cells, no activity against normal donor bone-marrow cell lines was observed. *In vivo* activity of BB2121 also demonstrated proving rapid expansion and MM-cell clearance in mice xenografts, despite the presence of soluble BCMA protein. Mice received a single intravenous administration (5×10^6 CAR+ T cells/mouse). Mice treated with bb2121 had complete tumor elimination and long-term survival (up to day 85 post-CAR-T treatment), in contrast to mice treated with control CAR-T cells, vehicle treated or treated with bortezomib. CAR+ T cells were observed in peripheral blood starting at day 2 and markedly increased at 11 days after adoptive transfer, and then declining over the next 3 weeks. Post CAR-T cell infusion, sBCMA levels precipitously declined in parallel with tumor regression. The levels of sBCMA post day 8 were at or near the background detection level of this assay. There was no apparent inhibition of the product by soluble BCMA protein.

After these preclinical data, centralized manufacturing of bb2121 was developed to launch a phase I multicenter clinical trial to evaluate the safety and efficacy of bb2121 for relapsed refractory MM [ClinicalTrials.gov identifier: NCT02658929].

Phase I trial: CRB-401

The phase I open-label trial was conducted in the United States and consisted of a dose-escalation and a dose-expansion phase.[60] The primary endpoint was safety, and the main secondary endpoint was ORR. The trial included adult patients with a good performance status and adequate organ function, measurable disease, and at least three previous lines of therapy, including a PI and an IMID, or disease refractory to both drug classes. The dose-escalation phase also required 50% or more BCMA expression in marrow plasma cells. Levels of BCMA expression were not necessary in the dose-expansion phase but previous exposure to daratumumab and refractoriness to the most recent line of therapy were required. Thirty-six patients were enrolled and underwent leukapheresis. No minimum absolute lymphocyte count was required to proceed to apheresis. The manufacturing of bb2121 was successful for 100% of the patients but three of them progressed before bb2121 infusion. Bridging therapy during manufacturing was allowed but had to be stopped at least 14 days before the start of lymphodepletion. Bridging therapy was given to 14 patients (42%), mostly with dexamethasone, daratumumab, bortezomib or bendamustine and all treated patients still had measurable disease after the completion of bridging therapy and before the start of lymphodepletion. Lymphodepletion consisted of fludarabine 30 mg/m^2/day and cyclophosphamide 300 mg/m^2/day on days −5, −4, and −3, infusion of bb2121 on day 0 ranged from 50×10^6 to 800×10^6 total CAR-T cells in the dose-escalation phase, and then 150×10^6 to 450×10^6 cells in the expansion phase. Up to 20% deviation from assigned dose was allowed in the actual product to be infused. The final bb2121 CAR-T cell product had a highly variable proportion of CD4 and CD8 T cells, with a median of 85% (from 42 to 98) CAR-T CD4 and 13% CAR-T CD8+ cells. The characteristics of the 33 patients who finally received bb2121 were those expected in a relatively fit relapsing–remitting MM (RRMM) population. The median age was 60 years, 45% had a high-risk cytogenetic profile, and 27% had extramedullary disease. The median time since diagnosis was 5 years, and the median number of previous regimens was eight. Almost 80% of patients were exposed to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab, 79% were refractory to both a PI and an IMID, and 18% were penta-refractory.[60]

The most common toxicity was hematological; neutropenia grade 3 or higher was observed in 85% of the patients. Within a month, most patients recovered absolute neutrophil count and platelet count to grade 1 (97% and 65%, respectively); however, a proportion of patients presented delayed recovery from cytopenias. CRS was observed in 76% of individuals, 70% grade 1–2. No patient presented CRS higher than grade 3. CRS had a median time to onset of 2 days (range 1–25) and a median duration of 5 days (range 1–32). CRS correlated with the CAR-T-cell dose and a higher peak of CAR-T-cell expansion. In patients requiring treatment, the most common approach was tocilizumab; only four patients also received glucocorticoids. CAR-T expansion did not appear to be negatively affected by use of tocilizumab or glucocorticoids. Neurologic adverse events occurred in 42% of patients, mostly grade 1–2. One patient presented grade 4 neurologic toxicity starting 11 days after the infusion and requiring 1 month for resolution. Infections affected 42% of patients; none grade 4 or 5.[60]

The ORR was 85%, with 45% of the patients having a CR (9%) or stringent CR (36%). Both response rate and DOR appeared to be dose dependent; very good partial responses (PRs) or better were observed only with doses of at least 150×10^6 CAR-T cells. Response did not appear to be influenced by baseline sBCMA or BCMA expression in myeloma cells. Although the number of patients did not allow exploration of prognostic factors, the authors suggested that patients with a high-risk cytogenetic profile, who did not have CRS and who had received 150×10^6 or fewer CAR+ T cells presented less *in vivo* CAR-T-cell expansion and lower response rates. Median time to achieve a PR or better was 1 month. Tumor responses were also seen within the first month in most patients with extramedullary disease. Only 18 patients could be evaluated for MRD status; 16 who had a response and 2 who presented less than a PR; only 3 were MRD negative at the 10^{-6} level. Typically, full clearance of M protein to achieve a CR could be delayed in some patients despite rapid bone-marrow clearance of plasma cells. Moreover, early MRD negativity was observed in patients with detectable M component with later evolution to CR. At a median follow up of 11 months, 17 patients (52%) suffered disease progression, of whom 6 had achieved a CR. The median PFS was 11.8 months. Patients having detectable CAR-T cells were 96%, 86%, 57% and 20% at 1, 3, 6 and

12 months, respectively. Blood CAR-T-cell levels were higher in patients who responded than in those who did not have response. Overall, 85% of patients with heavily pretreated relapsed or refractory MM presented a response that lasted a median of 10.9 months, and 40% of the patients were free of progression at 12 months, without any subsequent therapy. Importantly, response appeared to be independent of tumor BCMA expression. Toxicity was manageable, and the use of tocilizumab or glucocorticoids to treat CRS did not appear to negatively affect CAR-T-cell expansion or treatment response. The high rate of deep responses did not translate into continuous remission for all patients warranting a deeper analysis of the relapse mechanisms, particularly in patients achieving an MRD-negativity status.[60]

Phase II trial: KARMMA trial

The phase I results prompted a pivotal phase II trial (KARMMA) [ClinicalTrials.gov identifier: NCT03361748] to confirm the observed efficacy and safety of ide-cel (bb2121) in triple-class-exposed RRMM.[16] The KARMMA trial was, again, a single-arm study for patients who had had at least three prior regimens, including an IMID agent, a PI, and an anti-CD38 antibody, and were refractory to their last treatment. Other inclusion criteria were similar to those of the expansion cohort of the prior phase I trial. The trial design also allowed bridging therapy, restricted to drug classes that patients had previously received, up to 14 days before lymphodepletion. Target doses of ide-cel were 150, 300 and 450×10^6 CAR+ T cells. The primary study endpoint was ORR and secondary endpoints included CR rate, MRD status, time to response, DOR, PFS and OS, along with safety, pharmacokinetics, and immunogenicity. The trial enrolled 140 patients, of whom 12 (9%) discontinued prior to ide-cel infusion, including 1 manufacturing failure. Most patients (88%) received bridging therapy during the manufacturing period, but only five (4%) presented a response. After completion of bridging therapy, all patients maintained measurable disease. Ide-cel infusion could be performed to 128 patients who had received a median of six prior antimyeloma regimens, 84% were triple-refractory, 60% were penta-exposed (bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab) and 26% penta-refractory. High-risk cytogenetics and extramedullary disease were present in 39% and 35% of individuals, respectively. Baseline expression of BCMA was evaluable in 110 tumor samples, and 97% of them had ⩾50% BCMA-positive plasma cells. All patients had detectable levels of sBCMA at baseline. CAR-T-cell doses were 150, 300, and 450×10^6 in 4, 70 and 54 patients, respectively. The ORR was 73% and the CR rate was 33%. The median time to response was 1 month, and the median time to CR, 2.8 months. MRD negativity was evaluated in bone marrow by next-generation sequencing with a cutoff of 10^{-5} nucleated cells. The 33 patients with a CR and evaluable MRD achieved an MRD-negative status at a sensitivity level 10^{-5}, representing 26% of the total treated population. Response rates were generally consistent in subgroups of patients, including those with high and low tumor BCMA expression, aggressive disease features, high tumor burden or triple- or penta-refractory disease. As observed in the prior study, responses were correlated with the doses of CAR-T cells; the ORR was 50%, 69%, and 82%, respectively, and the CR rate was 25%, 29%, and 39%, respectively, for 150, 300, and 450×10^6 cell doses. Maximum CAR-T-cell expansion occurred at a median of 11 days, and, again, higher expansion and exposure was associated with deeper response. Median DOR was 10.7 months for the full cohort, and 11.3 months at the 450×10^6 dose. Similarly, the median PFS was 8.8 months in the full cohort, and it increased to 12.1 months at the 450×10^6 dose. CAR+ T cells were detected in 29 of 49 (59%) and 4 of 11 (36%) patients at 6 and 12 months post-infusion, respectively.

Levels of sBCMA appeared to be an adequate surrogate of MM tumor mass. Baseline sBCMA levels were elevated in all patients at baseline, and decreased rapidly post-infusion, particularly in responders, with nadir values achieved within the first 3 months. Higher expansion was associated with deeper reductions of sBCMA. Undetectable sBCMA levels were associated with depth of response (63% of patients with PR, 95% with CR). Duration of undetectable sBCMA correlated also with durability of tumor response. The 450×10^6 dose was associated with longest time to rebound of sBCMA from undetectable levels. Rising sBCMA levels (>40 ng/ml) at the time of disease progression were observed in 69 of 71 (97%) patients. In 16 responders with evaluable bone-marrow biopsies at progression, 15 (94%) retained BCMA-expressing tumor cells. Loss of tumor BCMA expression was suspected in three patients and in one of them,

bi-allelic genomic loss of BCMA on chromosome 16p was subsequently confirmed.[61] A similar case of homozygous loss of BCMA expression has been reported in a patient in the phase I CRB-401 trial who was unsuccessfully treated at relapse, 9 months after the first infusion.[62] Although homozygous loss of BCMA genes is extremely rare, the 16p monosomy, leading to a heterozygous BCMA-deficient phenotype is relatively common and it has been suggested that it may be a mechanism leading to resistance to anti-BCMA therapies.[61] At the time of analysis, OS was immature, with 66% of patients still censored, 78% of patients were alive at 12 months, and the estimated median OS was 19.4 months [95% confidence interval (CI), 18.2–non-evaluable]. The protocol allowed ide-cel retreatment for patients meeting disease progression criteria, and 28 patients were retreated with ide-cel, of whom 6 (21%) achieved a second response ranging from 1.9 to 6.8 months' duration.

The safety profile observed in the phase I trial was also confirmed. With the exception of hypogammaglobulinemia and infections, most adverse events occurred within the first 2 months after infusion. As expected, grade 3 or 4 hematologic toxicity was common, neutropenia (89%), anemia (60%), and thrombocytopenia (52%), and usually short-lived, although in a proportion of patients, grade 3 or 4 neutropenia ($n=52$) or thrombocytopenia ($n=62$) persisted over 1 month after infusion. Serious bleeding events were observed in three patients, including cerebral hemorrhage (after myeloma progression), gastrointestinal, and conjunctival. Infections occurred in 88 individuals (69%), although grade 3 or 4 in only 28 (22%). CRS occurred in 107 patients (84%) and reached grade 3 in 5 (4%); 1 patient (<1%) had grade 4, and there was 1 CRS-related death (<1%). Median time to onset of CRS was 1 day (range, 1–12 days) with a median duration of 5 days (range, 1–63 days). For most individuals (52%) CRS could be adequately managed with tocilizumab. CRS was also related to the dose of CAR-T cells; any-grade CRS was observed in 50%, 76% and 96% of patients at doses of 150, 300, and 450×10^6 CAR-Ts, respectively. Grade ⩾3 CRS was not common, affecting 6% of patients at doses of 300 or 450×10^6. Neurotoxicity was also reported in 18% of patients, but there were no reports of grade 4–5. Neurotoxicity typically followed CRS, particularly if CRS appeared early and had a higher intensity. The median time to any neurotoxicity event was 2 days, and its median duration, 3 days. Neurotoxicity was not reported in patients receiving the 150×10^6 dose while it affected 17% and 20% of patients at doses of 300 and 450×10^6 CAR-T cells. Out of 44 patients (34%) who died during the study, 3 (2%) died within 8 weeks after infusion from adverse events considered ide-cel related (bronchopulmonary aspergillosis, gastrointestinal hemorrhage, and CRS). Most deaths in the study ($n=27$) were related to myeloma progression.

Idecabtagene vicleucel ongoing trials

Ide-cel is currently being explored in three additional trials. KARMMA-2 [ClinicalTrials.gov identifier: NCT03601078] is a multicohort phase II trial evaluating the efficacy and safety of ide-cel in refractory MM, including less heavily treated subjects conveying a bad prognosis; that is, MM having progressed within 18 months of frontline treatment, including ASCT (cohort 2a), or not (cohort 2b), or subjects with inadequate response to ASCT (cohort 2c). KARMMA-4 [ClinicalTrials.gov identifier: NCT04196491] is a phase I trial exploring ide-cel in high-risk (R-ISS 3) newly diagnosed patients following standard induction. Finally, KARMMA-3 [ClinicalTrials.gov identifier: NCT03651128] is a phase III trial attempting to enroll approximately 381 subjects with RRMM having received two to four prior lines of treatment and randomize them in a 2:1 ratio to either ide-cel or one of several salvage treatments of choice.

Idecabtagene vicleucel efficacy in the competitive landscape

Patients who are refractory to PIs, IMIDs, and anti-CD38 MoAbs have a dismal prognosis. A recent cohort sudy[11] described the characteristics of these patients and observed an ORR of 31% after anti-CD38 MoAb failure. Responses were typically short-lived, with a median PFS of 3.4 months and a median OS of 9.3 months. Some agents with new mechanisms of action have been explored in the setting of triple-refractory MM, including the recently approved exportin-1 inhibitor selinexor,[63] the peptide–drug conjugate melflufen (melphalan flufenamide)[64] and the ADC belantamab mafodotin.[13] Selinexor achieved a PR or better in 26% of patients; the median DOR was 4.4 months, the median PFS 3.7 months, and the median OS 8.6 months.[63] The ORR of melflufen in triple-refractory MM patients was 26%, with a median DOR of

Table 2. Efficacy and safety profile of new agents in the treatment of advanced relapsed and refractory multiple myeloma.

	Selinexor[63]	Melflufen[64]	Belamaf[13]	Teclistamab[14]	Talquetamab[15]	Ide-cel[16]	Cilta-cel[65]
Efficacy							
ORR, %	26	29	31	69	69	73	97
CR, %	<2	1	8	26	19	33	67
PFS, months	3.7	4.2	2.8	–	–	8.8	77% at 12 months
OS, months	8.6	11.6	13.7	–	–	19.4	88% at 12 months
Safety							
Neutropenia, %	40	82	20	57	47	91	91
Grade ⩾3	21	79	12	46	31	89	91
Thrombocytopenia, %	73	82	24	40	32	63	79
Grade ⩾3	58	76	19	22	13	52	60
CRS, %	–	–	–	55	54	84	95
Grade ⩾3	–	0	3	5	4		
Neurotoxicity, %	–	–	–	5	6	18	21
Grade ⩾3	–	0	2	3	10		
Other	Fatigue 73% GI 72%	–	71%, ocular keratopathy	–	–	–	–

Belamaf, belantamab mafodotin; Cilta-cel, ciltacabtagene autoleucel; CR, complete response; CRS cytokine-release syndrome; GI, gastrointestinal; Ide-cel, idecabtagene vicleucel; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

5.5 months, a median PFS of 4.2 months, and median OS of 11.6 months.[64] The results of belantamab mafodotin, as previously discussed, are in the same range.[13] Although direct comparisons are difficult because patient characteristics differed slightly among these three trials and between these and the KARMMA trial, ide-cel is likely to represent a major step forward in comparison with previously available agents (Table 2). Current data show that TCEs targeting BCMA or other molecules can achieve responses in around two thirds of patients,[14,15] although CR rates appear to be lower than those reported for ide-cel and other CAR-Ts (Table 2); available data come from dose-finding phase I trials, and may prove better in patients at the recommended phase II dose. Additionally, responses may deepen over time with continuous treatment. If TCE results are confirmed in robust trials with a sufficient follow up, they may provide a more convenient alternative to ide-cel or other CAR-Ts, particularly in patients where bridging therapy or off-treatment time of manufacture are not an option.

Finally, other CAR-T products will be available shortly. Ciltacabtagene autoleucel (cilta-cel, previously LCAR-B38M) is an anti-BCMA CAR-T characterized by having two different heavy-chain variable domains which recognize separate epitopes of the BCMA antigen.[66] Its phase I clinical trial with 57 patients obtained an ORR of 88% and a CR rate 68%; additionally, 63% of patients achieved MRD negativity. The median PFS was 15 months.[66] Results of a subsequent phase Ib/II trial (CARTITUDE-1) in 97 patients have been communicated recently.[65] In this analysis cilta-cel obtained an impressive PR and CR rate, 97% and 67%, respectively, and a 12-month PFS and OS of 76.6% and 88.5%, respectively. Orvacabtagene autoleucel (orva-cel), a fully human CAR-T, delivered in a fixed 1:1 CD4/CD8 ratio, also showed interesting results, with a 91% ORR and 39% CR rate but a still-short follow up.[52] Other

CAR-T products are being tested in clinical trials and have reported similar, but still immature, results. Additionally, allo-CAR-Ts are also being explored in the clinical setting;[67] such agents are expected to combine the efficacy of autologous CAR-Ts with the convenience of 'off the shelf' availability. Despite the observation of deep responses in very advanced and refractory patients, there is no apparent plateau in the PFS curves of MM patients treated with CAR-Ts, and consequently, durability of the product may emerge as a key factor in defining the best choice, in terms of efficacy. Current data do not allow determination of whether there will be major differences in terms of efficacy among different CAR-T products.

Idecabtagene vicleucel safety in the competitive landscape

From the safety point of view, anti-BCMAs appear to present less toxicity than anti-CD19 CAR-Ts used in other B-cell malignancies. Ide-cel demonstrated a consistent manageable safety profile in phase I and II trials.[5,16] The CRS was frequent (84% in the phase II trial) but mostly low grade with grade $\geqslant$3 events observed in $\leqslant$6% of patients at all doses. Only two patients in the KARMMA trial experienced CRS grade 4 or 5 (one each). Onset of CRS was within the first week of infusion, mostly (median 1 day), and its median duration was 5–6 days, regardless of grade in less severe cases, but it lasted a median of 11 days in patients with maximum grade $\geqslant$3. Early use of tocilizumab may have prevented most severe forms of CRS. Similarly, neurotoxicity was reported in 18% of patients in the KARMMA trial but half of them had a grade 1 and none grade 4 or 5. All neurotoxic events occurred in the proximity of CRS events, either overlapping with CRS or within the following week. There were no late events, and this may represent a differential characteristic with cilta-cel where delayed-onset neurotoxicity was described in up to 12% of individuals.[65] Management of ide-cel neurotoxicity in the KARMMA trial involved the use of corticoids in 10 patients (43%) and tocilizumab in 3 (13%). The use of corticoids had no apparent impact on the ORR or DOR. CRS and neurotoxicity appear to be more frequent and severe with CAR-Ts than those reported for TCEs. In any case, the applicability of CAR-Ts or TCEs is not likely to be limited, with improved expertise in the management of CRS and neurotoxicity if differences in efficacy with respect to alternatives are confirmed. On the other hand, prolonged neutropenia and thrombocytopenia may affect over a third of patients and may be challenging in some patients. The severity and specific characteristics of long-term immunosuppression after treatment with ide-cel or other CAR-Ts and TCEs remain a matter of concern for both treatment modalities.

Future perspectives

Important challenges need to be addressed in future development of CAR-T-cell strategies in MM. Current limitations are both product related, including lack of expansion/early exhaustion,[68] and disease related, including issues such as BCMA shielding and dynamic BCMA expression after infusion, the development of other survival mechanisms by the malignant cell, and the myeloma-induced alterations of the microenvironment to create an immunosuppressive milieu.[42,69]

Several strategies are under evaluation to prevent escape of MM cells, to minimize a potential immune rejection, and to modify the microenvironment. Combinatorial antigen-recognition approaches may be able to circumvent antigen shielding. The combination of a CAR-T against BCMA with another CAR-T against CD19 has already been explored in early clinical trials.[70] The development of bi-specific CAR-Ts may be even more effective to prevent disease progression associated to loss of BCMA expression. Bicistronic vectors encoding two CARs avoid the challenge of parallel manufacturing separate CAR-T-cell products, while providing superior efficacy. Several CAR-Ts combining receptors against BCMA and GPRC5D,[71] SLAMF7,[72] or CD19[73] are in early development. Also, dual-targeting of BCMA and the transmembrane activator and CAML interactor (TACI) on MM cells has successfully been reported by use of an APRIL-based CAR in mouse models and in *ex vivo* primary myeloma cells, including BCMA-negative MM cells.[74] While targeting more than one antigen has the potential to increase CAR-T-cell efficacy and reduce the risk of antigen scape, it increases the risk of on-target, off-tumor toxicities; therefore, such strategies should be compared in a randomized fashion with standard single-antigen CAR therapy before implementation. Increasing BCMA expression on the plasma cell surface might also improve the efficacy of BCMA CAR-T cells, and preliminary data have shown that GS inhibitors could reduce the cleavage

of BCMA.[41,75] Administration of an oral GS inhibitor with BCMA CAR-T cells is being explored.[76]

Increasing the CAR-T-cell durability is still the most critical factor for improving current results. In an attempt to reduce the proportion of senescent T cells, a recently developed anti-BCMA CAR-T, bb21217, used the same CAR molecule as ide-cel but added a phosphoinositide-3-kinase inhibitor during *ex vivo* culture to enrich the drug product for memory-like T cells. The CRB-402 [ClinicalTrials.gov identifier: NCT03274219] ongoing phase I trial is investigating whether this procedure has a clinically relevant impact on outcomes. The trial design is similar to that of the ide-cel phase I trial, and researchers plan to enroll 74 patients, including 50 in an expansion cohort. The results of the first 46 patients have been communicated recently.[77] The safety profile appears to be similar to those of other CAR-T products, with a slightly delayed onset of CRS (median 3 days). Despite the enrichment procedure being effective, patients with a reported response were 55%, including 18% with CR or better, and the median DOR was 12 months. However, the presence of T-cell markers associated with memory, and the absence of T-cell markers associated with senescence in the product, correlated with peak expansion and DOR, supporting the hypothesis that enrichment for memory-like T cells may result in more durable CAR-T cells and improved clinical outcomes.

Lack of CAR-T-cell persistence is not only dependent on the choice of an optimal co-stimulatory domain or the proportion of CD4/CD8 or memory/effector cells. The targeting moieties of the CAR often display reduced stability and are therefore at risk of oligomerization or clustering, leading to continuous off-target signaling and development of an exhausted T-cell phenotype. Refined targeting moieties, such as small monomeric proteins, might diminish CAR structure related tonic signaling. One such CAR-T-cell product, P-BCMA-101, has already reported early clinical results,[78] Additionally, P-BCMA-101 makes use of the piggyBac^{R} transposon-based deoxyribonucleic acid modification, and it is speculated that viral-free generation of the system may favor the development of a T-stem-cell memory phenotype.[78] The clinical relevance of strategies to specifically engineer products of a desirable T-cell-subset composition remains unclear, as follow-up periods of early trials are still too limited to assess durability of responses.

Finally, immunotherapy may also be critically affected by the worsening immune dysfunction that occurs with disease progression. Quality of CAR-Ts is likely to depend more on the T-cell quality at time of apheresis than on the actual manufacturing process. It is likely that the greatest benefit of these agents will only be seen when incorporated earlier into the treatment strategy. Given that PFS benefit of any conventional treatment triplet in patients suffering early relapses after front line therapy will probably be below 12 months, such patients are a potential target for earlier use of ide-cel. Consolidation of upfront therapy in high-risk disease not achieving immunophenotypic CR is also an adequate target for immunotherapy. The ongoing KARMMA 2, 3 and 4 ide-cel trials are exploring the potential advantage of earlier CAR-T therapy after a lymphocyte apheresis in a less immunocompromised patient. Additionally, the infusion of CAR-Ts while still in response or at biological relapse, may increase safety, maximize efficacy, and reduce the risk of full-blown progression before infusion.

Conclusions

Ide-cel is the first CAR-T product to be approved for the treatment of MM, representing a major advance in the immunotherapeutic approach to the disease and covering a major and emerging clinical need, that of triple-refractory patients. The median PFS of almost 1 year after a single administration, a relatively acceptable safety profile, and the possibility of avoiding continuous treatment in heavily exposed patients may outweigh the convenience of other 'off the shelf' alternatives. Current trials will determine if ide-cel and other CAR-T products should move forward to treat high-risk patients earlier in the course of disease.

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