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Review Article

Bispecific Antibodies and CAR T in Multiple Myeloma: Appropriate Selection of Patients and Sequencing

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Abstract. T-cell redirecting therapies (TCR) marked a step forward in the treatment of relapsed/refractory multiple myeloma (RRMM). These agents, represented by chimeric antigen receptor (CAR) T-cells and bispecific antibodies (BsAbs), proved to ameliorate the prognosis of difficult-to-treat patients in pivotal clinical trials, leading to their introduction into clinical practice. Both strategies rely on recruiting patients' T-cells against specific tumor antigens, with B-cell maturation antigen (BCMA) and G-protein coupled receptor group C family 5 member D (GPRC5D) being the targets most extensively studied. Nevertheless, most of these regimens under the current label do not hesitate in a clear plateau of survival curves, thus raising the scenario of patients receiving more than one TCR agent in sequence. Also, they differ in their toxicity profiles and administration features. Consequently, the appropriate application of these agents mandates a careful selection of the right treatment for the right patient, with the ultimate intent of optimizing patient outcomes. In this respect, practical considerations regarding tumor- and patient-specific features are of high importance. Tailored clinical trials and analysis of real-word experiences are also crucial to produce evidence-based recommendations. Likewise, pre-clinical research is critical for the conceptualization of treatment algorithms potentially driven by immunological clues and knowledge of mechanisms of resistance. In this review we aim at providing practical guidance for defining the most appropriate treatment sequencing and determining the selection of patients for each treatment.

Keywords: Multiple Myeloma; T-cell redirecting therapies; CAR-T; Bispecific Antibodies; Patient selection; Treatment sequencing.

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Introduction. The treatment landscape of multiple myeloma (MM) is evolving rapidly.[1] Notably, the amelioration of the first and subsequent lines of therapy, based on the combination of agents with different anti-myeloma activity, has led to a substantial improvement in survival rates, with estimated median overall survival (mOS) of 10 years or more.[2-4]

Nevertheless, the relapsing nature of the disease imposes continuous treatment exposure, and virtually all patients develop subsequent refractoriness to previously effective drugs.[5] Noteworthy, the prognostic scenario of patients who are refractory to an anti-CD38 antibody, an immunomodulatory agent (IMiD), and a proteasome inhibitor (PI) (namely triple-class refractory MM) is particularly poor, with estimated OS rates of less than one year.[6-8]

In this setting, immune-based therapies aimed at redirecting patients' T-cells against specific tumor antigens proved to be effective, leading to the introduction of chimeric antigen receptor (CAR) T-cells and bispecific antibodies (BsAbs) into clinical practice.[9-15] Although conceptually similar, these two strategies differ in a range of features, so that accurate selection of the right patient for the appropriate treatment at the proper time is mandatory.[16] Moreover, the overlapping regulatory indications of CAR T-cells and BsAbs, coupled with the inherent development of resistance by different biological mechanisms, pose the issue of sequencing more than one immune-based therapy after another, with the intent of maximizing efficacy.[17] In this article, we will briefly review the main results from the most relevant registrational trials, as well as promising combination strategies and new agents under advanced investigation. Henceforth, we will dedicate a special focus to the current body of knowledge regarding patient selection and treatment sequencing with these cutting-edge therapies.

CAR T-Cell Therapy in Multiple Myeloma. CAR T-cells are autologous T-cells transduced with a lentiviral or retroviral vector that carries a gene encoding for a CAR. This latter consists of an extracellular targeting domain without Major Histocompatibility Complex (MHC) restriction, usually derived from a single-chain variable fragment (scFv) of a monoclonal antibody; the extracellular domain is linked to an intracellular signaling domain that includes a CD3ζ activation domain and a co-stimulatory domain (mainly 4-1BB). After transduction, these cells are expanded and then re-infused into patients, upon lymphodepleting chemotherapy. Once infused, CAR T-cells engage with the tumoral antigens independently of human leukocyte antigen (HLA), release cytokines, lyse target cells, and proliferate in vivo through the action of the co-stimulatory domain.[18,19] Thus far, the main targets explored with available constructs include the B-cell maturation antigen (BCMA) and the G protein–coupled receptor class C group 5 member D (GPRC5D). Other products designed to recognize further antigens that can be targeted either alone or in combination with B-cell

Table 1. Pivotal CAR T-cells trials –Efficacy.

	Ide-cel		Cilta-cel		Anito-cel	MCARH109	Arlo-cel
Trial	KarMMa [9]	KarMMa-3 (11)(20)	CARTITUDE-1 (10)(21)	CARTITUDE-4 (12)	NCT04155749 (25)	NCT04555551 (27)(28)	NCT04674813 (30)
Pts, n°	128	254	97	208	40	17	84
Median age (range), ys	61 (33-78)	63 (30-81)	61 (56-68)	61.5 (27-78)	66 (44-76)	59 (37-76)	63 (39-80)
Median previous LOT (range), n°	6 (3-16)	3 (2-4)	6 (4-8)	2 (1-3)	4 (3-16)	6 (4-14)	5 (3-15)
Triple-class refractory pts, %	84	65	88	14	100	94	76
Penta-refractory pts, %	26	6	42	1	68	NA (penta-exposed 100)	35
ORR, %	73	71	97	84	100	71	87
≥ VGPR, %	52	61	94	81	92	58	NA
≥ CR, %	33	44	82	73	79	41	NA
MRD-negative, %	26	22	57	89	62	47	26
Median DOR, mos	10.7	16.6	33.9	NR (84% at 12 mos)	NA	8.6	NA
Median PFS, mos	8.8	13.8	34.9	NR (75% at 12 mos)	NR (52% at 27 mos)	NA	14.5
Median OS, mos	19.4	41.4	NR (63% at 36 mos)	NR (84% at 12 mos)	NR (78% at 27 mos)	NR (59% at 3 ys)	NA

Abbreviations: pts = patients; n° = number; ys = years; LOT = line(s) of therapy; ORR = overall response rate; VGPR = very good partial response; CR = complete response; MRD = minimal residual disease; DOR = duration of response; mos = months; NA = not available; NR = not reached; PFS = progression-free survival; OS = overall survival.

maturation antigen (BCMA) are under development. The efficacy results of the most relevant CAR T-cells trials are summarized in **Table 1**.

Idecabtagene vicleucel. Idecabtagene vicleucel (ide-cel) is a BCMA-directed, second-generation CAR T-cell construct.

Ide-cel was first explored in patients exposed to at least 3 previous lines of therapy in the phase II KarMMa trial (NCT03361748). Overall response rate (ORR) was 73%; 52% of patients obtained a very good partial response (VGPR), or better. Median progression-free survival (mPFS) was 8.8 months (mos) and mOS was 19.4 mos.[9]

Subsequently, the phase III KarMMa-3 trial (NCT03651128) enrolled patients exposed to two to four previous lines of therapy, who were randomized to receive either ide-cel or standard of care (SOC) therapy (including daratumumab plus either bortezomib-dexamethasone, or pomalidomide-dexamethasone [DPd], elotuzumab-pomalidomide-dexamethasone [elo-Pd], ixazomib-lenalidomide-dexamethasone, or carfilzomib-dexamethasone [Kd]). ORR was 71% for ide-cel vs 42% for SOC; CR rate was 44% vs 6%, respectively. Ide-cel demonstrated a PFS benefit with a mPFS of 13.8 mos vs 4.4 mos. Instead, no OS benefit was shown, with a mOS of 41.4 mos and 37.9 mos, respectively. In this sense, however, it should be underscored that cross-over to experimental therapy was permitted in this trial. Indeed, 56% of patients received ide-cel as subsequent therapy, after progressing with SOC. When adjusting for crossover, the ide-cel arm portended a trend toward superior OS when compared to the SOC arm (mOS 41.4 mos vs 23.4 mos, respectively).[11,20]

Based on these results, ide-cel is approved by the European Medicines Agency (EMA) and the Food and Drugs Administration (FDA) for the treatment of adult patients with relapsed and refractory multiple myeloma (RRMM) who have received at least two prior therapies, including an IMiD, a PI, and an anti-CD38 antibody, and who have demonstrated disease progression on the last therapy.

Ciltacabtagene autoleucel. Ciltacabtagene autoleucel (cilta-cel) is a CAR-T agent expressing two BCMA-targeting single-domain antibodies designed to confer high avidity.[10]

CARTITUDE-1 (NCT03548207) is a phase Ib/II study that explored cilta-cel for patients previously exposed to at least 3 lines of therapy or double refractory to a PI and an IMiD. ORR was 97.9%, with a stringent complete response (sCR) rate of 82.5%. At 27 mos, PFS was 54.9% and OS 70.4%. At a subsequent update, mPFS for the cilta-cel arm was 34.9 mos.[10,21,22]

Considering the results of the CARTITUDE-1 trial, the phase III CARTITUDE-4 trial (NCT04181827) was designed to compare cilta-cel vs SOC therapies (i.e., pomalidomide-bortezomib-dexamethasone [PVd] or DPd, at physician's discretion) in patients exposed to 1-3 prior lines of treatment and who were refractory to lenalidomide. Efficacy results at 3 years follow-up showed an ORR of 84.6% in the cilta-cel arm vs 67.3% in the SOC arm, with ≥VGPR being 81.2% vs 45.5% and ≥CR 76.9% vs 24.2%, respectively. PFS was significantly better in the cilta-cel arm (mPFS not reached [NR] vs 11.8 mos; PFS at 30 mos 59.4% vs 25.7%). An OS advantage at 30 mos was also showed (76.4% vs 63.8%, respectively). Consistently, minimal residual disease (MRD) negativity rates with a minimal sensitivity of 10^{-5} were superior in the cilta-cel arm (62% vs 18.5%, respectively), in an intention-to-treat analysis.[12,23]

Currently, cilta-cel is approved by FDA and EMA for the treatment of adult RRMM patients who have received at least one prior therapy, including IMiD and a PI, have demonstrated disease progression on the last therapy, and are refractory to lenalidomide.

A controlled and randomized head-to-head comparison between ide-cel and cilta-cel is still lacking. However, a retrospective, multicenter analysis of 586 patients treated with either cilta-cel or ide-cel was recently conducted. The two cohorts were well-balanced and represented different baseline characteristics evenly. Cilta-cel was proven to confer better efficacy in terms of response rates, PFS, and OS in most of the patient subpopulations, though associated with a more burdensome toxicity profile in terms of high-grade CRS, delayed neurotoxicity, and infections.[24]

Anitocabtagene autoleucel. Anitocabtagene autoleucel (anito-cel, previously known as CART-ddBCMA) is an anti-BCMA CAR T-cell construct modeled to express a D-domain binder between the CD8 hinge-region and the transmembrane domain. The D-domain is of synthetic and non-antibody origin, facilitating the transduction of activation signals, while reducing tonic signaling. In the iMMagine-1 phase I/II trial (NCT05396885), patients exposed to at least three previous line of therapy and to at least a PI, an IMiD, and an anti-CD38 antibody, received anito-cel, with a dose-finding approach. Collectively, ORR was 100%, CR rate 76%, while 24-mos-PFS was 56%. MRD negativity with a minimum sensitivity of 10^{-5} was reached in 89% of all evaluable patients.[25] Furthermore, a phase III, randomized, registrational trial (iMMagine-3, NCT06413498) is ongoing to confront anito-cel vs SOC therapies (i.e., PVd, DPd, Kd, or daratumumab plus Kd) in patients with RRMM previously exposed to 1-3 lines of therapy and at least to an anti-CD38 and an IMiD.[26]

Anti GPRC5D CAR T-cells therapy. MCARH109 is a CAR T-cell construct with a GPRC5D single-chain

variable fragment. MCARH109 safety and efficacy were explored in a phase I trial (NCT04555551) that enrolled triple-class exposed patients with RRMM with 3 or more previous lines of treatment. Interestingly, 59% of patients were exposed to a prior anti-BCMA therapy and 47% to a prior CAR T-cell therapy. ORR was 71% in the whole population, 70% in BCMA-exposed patients, and 75% in BCMA CAR T-cells treated patients.[27,28]

Arlocabtagene autoleucel (arlo-cel) (CC-95266, formerly BMS-986393) is another GPRC5D-targeting autologous CAR T-cell agent. Preliminary data from a phase I trial (NCT04674813) enrolling triple-class exposed patients with three or more previous lines of treatment (49% of whom had received a prior BCMA-targeted therapy, including a BCMA-directed CAR T-cells therapy in 38% of them) showed efficacy and a favorable safety profile. At almost 15 mos median follow-up, ORR was 87% (38% CR) in the whole population and 79% in patients previously treated with anti BCMA therapy, while mPFS was 14.5 mos. Also, long-term safety data revealed a manageable profile, supporting BMS-986393 as a potential treatment for RRMM and further research (e.g., the ongoing phase II QUINTESSENTIAL study, NCT06297226).[29,30] Interestingly, preliminary data from patients with 1-3 prior lines of therapy including a PI and an IMiD are also encouraging, with high rates of response that deepened over time and no new safety concerns, though the follow-up is still limited.[31] Moreover, a phase III, randomized, registrational clinical trial (QUINTESSENTIAL-2, NCT06615479) is ongoing to confront arlo-cel vs SOC therapies in patients with lenalidomide-refractory RRMM exposed to 1-3 lines of therapies including an anti-CD38, a Pi and an IMiD.

Bispecific Antibodies in Multiple Myeloma. BsAbs are monoclonal antibodies designed with two fragment antigen-binding (Fab) arms capable of creating an immune synapsis between T-cell receptor (CD3) and a tumor cell antigen, thus leading to T-cells activation without MHC restriction. As of today, almost all BsAbs contain a fragment-crystallizable (Fc) domain that adds stability, increases the half-life of the molecule and induces T-cell- and complement-dependent cytotoxicity.[32] At present, BsAbs targeting BCMA, GPRC5D and the Fc receptor-like 5 (FcRL5) have demonstrated remarkable clinical activity in triple-class refractory patients, granting approval to some of these products, while several newer agents are under study. The efficacy results of the most relevant BsAbs trials are summarized in **Table 2**.

Teclistamab. Teclistamab (Tec) is a subcutaneous BsAb that simultaneously targets CD3 on T-cells and BCMA on myeloma cells.
Tec safety and efficacy were evaluated in the phase I/II trial MajesTEC-1 (NCT04557098) that enrolled triple-exposed RRMM patients. The ORR was 63%; CR or better rates were 46.1%. mPFS was 11.4 mos and mOS was 22.2 mos. At a median follow-up of 30.4 mos,PFS for patients in CR was estimated to be 61%. [13,33]

Tec is being investigated alone or in combination with daratumumab in a phase III randomized clinical trial (MajesTEC-3, NCT05083169) against SOC

Table 2. Pivotal BsAbs trials – Efficacy

Trial	Teclistamab	Elranatamab	Linvoseltamab	Talquetamab		Cevostamab
	MajesTEC-1 (13,33)	MagnetisMM-3 (14,35)	LINKER-MM1 (37)	MonumenTAL-1 (15) (39)		CAMMA-2 (41)
				400 µg QW	800 µg Q2W	
Pts, n°	165	123	117	143	154	167
Median age (range), ys	64 (33-84)	68 (36-89)	70 (37-91)	62 (46-80)	64 (47-84)	66 (40-90)
Median previous LOT (range), n°	5 (2-14)	5 (2-22)	5 (2-16)	6 (2-14)	5 (2-17)	6 (2-18)
Triple-class refractory pts, %	78	97	82	74	69	96
Penta-refractory pts, %	30	42	28	29	23	74
ORR, %	63	61	71	74	70	43
≥ VGPR, %	59	56	63	59	59	26
≥ CR, %	46	37	50	33	40	13
MRD-negative, %	29	21	22	NA	NA	NA
Median DOR, mos	24	NR (67% at 24 mos)	29.4	9.5	17.5	10.4
Median PFS, mos	11.4	17.2	NR (70% a 12 mos)	7.5	11.2	NA
Median OS, mos	22.2	24.6	31.4	NA	NA	NA

Abbreviations: pts = patients; n° = number; ys = years; LOT = line(s) of therapy; ORR = overall response rate; VGPR = very good partial response; CR = complete response; MRD = minimal residual disease; DOR = duration of response; mos = months; NA = not available; NR = not reached; PFS = progression-free survival; OS = overall survival.

therapies (i.e., DPd or DVd, as per investigator's choice) in patients with RRMM exposed to 1-3 lines of therapy including an IMiD and a PI.[34]

At present, Tec is approved by EMA as monotherapy in patients with RRMM who have received at least three prior therapies, including an IMiD, a PI, and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy. FDA approval includes patients previously exposed to four prior lines of therapies.

Elranatamab. Elranatamab (Elra) is a subcutaneous humanized BsAb that targets both BCMA and CD3.

Elra has been studied in the MagnetisMM-1 phase I trial (NCT03269136) and subsequently in the phase II MagnetisMM-3 trial (NCT04649359) that enrolled triple-class exposed RRMM patients. After a median follow-up of about 28 mos, the ORR was 61.0%, with 37.4% CR or better. Median PFS and OS were 17.2 mos and 24.6 mos, respectively. The probability of maintaining a response at 24 mos was estimated to be 87.9% for patients in CR or better.[14,35]

At present, Elra is being investigated alone or in combination with daratumumab in a phase III randomized clinical trial (MagnetisMM-5, NCT05020236) against SOC (i.e, DPd) in RRMM patients who have received at least 1 prior line of therapy including lenalidomide and a PI.[36]

Elra is currently approved by FDA and EMA as monotherapy for the treatment of adult patients with RRMM, who have received at least three prior therapies, including an IMiD, a PI, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

Linvoseltamab. Linvoseltamab (REGN5458) is an intravenous fully human BCMAxCD3 BsAb designed to have minimal immunogenicity together with favorable molecular stability and pharmacokinetic properties.[37]

The phase I-II LINKER-MM1 (NCT03761108) trial showed encouraging results, with 70.9% ORR, 63.2% ≥VGPR, and 49.6% ≥CR in patients who received the full dose of 200 mg. 12-mos PFS and OS were 70.0% and 75.3% respectively.[37] Currently, an open-label, randomized phase III trial, LINKER-MM3 (NCT05730036), is evaluating safety and efficacy of linvoseltamab monotherapy compared with SOC (i.e, elo-Pd) in RRMM patients.

To date, linvoseltamab is not approved by regulatory agencies.

Talquetamab. Talquetamab (Tal) is a subcutaneous bispecific immunoglobulin G4 (IgG4) antibody that targets GPRC5D with a scaffold designed to minimize Fc-receptor binding to both GPRC5D and CD3.

Tal has been evaluated in the phase I/II trial MonumenTAL-1 study (NCT03399799/NCT04634552) enrolling triple-exposed patients with ≥3 previous lines of therapy.[15] In the 0.8 mg/kg every other week (Q2W) cohort, ORR was 69.5%; ≥VGPR and ≥CR rates were 59.1% and 40.3%, respectively. Median PFS was 11.2 mos.[38,39]

Moreover, Tal is being investigated in combination with daratumumab with or without pomalidomide in a phase III, randomized, clinical trial (MonumenTAL-3, NCT05455320) against SOC (i.e, DPd) in patients with RRMM exposed to at least 1 prior line and at least to an IMiD and a PI.[40]

Tal is approved by EMA as monotherapy at the dose of 0.4 mg/kg weekly or 0.8 mg/kg Q2W for the treatment of patients with RRMM, who have received at least 3 prior lines of therapy, including an IMiD, a PI, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy. FDA approved Tal for the treatment of patients with RRMM, who have received at least 4 prior lines of therapy.

Cevostamab. Cevostamab is an intravenous IgG1-based T-cell-engaging BsAb that targets FcRH5 on myeloma cells and CD3 on T cells.[41]

The ongoing open-label, multicenter phase I/II trial CAMMA-2 (CO43476; NCT05535244) is evaluating cevostamab in triple-class refractory RRMM patients who had previously received anti-BCMA agents for whom no established therapy was available, appropriate, or tolerable. Interestingly, 57% of patients had received ≥1 prior BCMA targeted therapy and 24% of them had received ≥1 prior BsAb. ORR was 43.1%, VGPR o better was 25.7%. ORR was 30.2% in patients with ≥1 prior BCMA-targeted therapy and 60.6% in those without. ORR was 30.0% in patients with ≥1 prior BsAb, 33.3% with ≥1 prior CAR T-cell, and 41.2% with ≥1 prior antibody-drug conjugate (ADC).[41]

To date, cevostamab is not approved by regulatory agencies.

BsAbs and CAR T-Cells: Toxicity Profile. CAR T-cells and BsAbs share a similar toxicity profile, arising from the production of inflammatory cytokines. Thus far, the most relevant safety alerts are represented by cytokine realizing syndrome (CRS) and immune effector cells associated neurotoxicity syndrome (ICANS), though other common and equally distinctive toxicities associated to these promising immunotherapies are emerging, including cytopenias and infections.

CRS is a systemic inflammatory reaction presenting with fever and possibly with hypotension and hypoxemia that might require intensive life support.[42] After few days from CAR-T cell infusion, CRS is common (84-95%), with some G3/4 events (4-5%). [9,10] BsAbs are associated with a slightly lower CRS rate (75-79%), while G3

events are exceedingly rare. The onset occurs mainly during the step-up dosing and at the first full dose.[13-15,37,41]

ICANS is a neurotoxic syndrome with a poorly understood pathophysiology in which disruption of the brain blood barrier and various pro-inflammatory cytokines might have a role.[43] ICANS typically manifests as a toxic encephalopathy presenting with word-finding difficulty, confusion, dysphasia, aphasia, impaired fine motor skills, and somnolence. More severe cases are characterized by seizures, motor weakness, cerebral oedema, and coma. In the anti-BCMA CAR T-cells setting, the incidence of neurotoxic events is 18-21% with some G3/4 events (3-9%).[9-12] Furthermore, cilta-cel portended a characteristic Parkinson-like syndrome, affecting 6% of patients in CARTITUDE-1 and 1 patient in CARTITUDE-4, together with cranial nerve palsy in 9% of patients in the latter study.[10,12] As anti-GPRC5D CAR T-cells are under development, one safety signal in terms of neurotoxicity is the association with some cases of cerebellar ataxia.[28,30] Meanwhile, BsAbs are associated with very low rate of ICANS (3-13%), all being grade 1 or 2. Of note, in the MagnetisMM-3 trial, 17% and 13% of patients developed motor dysfunction or sensory neuropathy, respectively.[13-15,37,41]

Beyond these well-known side effects, infections are common in patients affected by MM, especially under treatment.[44] In the context of CAR T-cells trials, the rate of infection ranged between 58% and 69%, G3/4 being 20-22%. However, it is important to highlight that in the KarMMa-3 and CARTITUDE-4 trials, the incidence of infections was similar between the experimental and the SOC arms.[9-12,20,21] Similarly, anti-BCMA BsAbs are also burdened by a high incidence of infections (74-79%), G3/4 ranging from 35% to 55%, with some mortality signals.[33,45] Notably, this risk can be effectively mitigated with intravenous immunoglobulin (IVIG) supplementation and schedule modifications from weekly (QW) to Q2W.[33,46] Of note, the rate of infections is lower with non-BCMA BsAbs. Indeed, high-grade events are much rarer, and no grade 5 infections are reported: overall, infections range between 60-70%, with G3/4 around 20-22%.[38,39,47]

Cytopenias are frequent and their incidence is higher in patients treated with CAR T-cells, as compared to BsAbs. In particular, G3/4 neutropenia is reported in 90% of patients treated with CAR T-cells, in 65% of patients treated with anti-BCMA BsAbs, and in 30% of patients treated with non-anti-BCMA BsAbs, whereas G3/4 thrombocytopenia affected about 55% of patients treated with CAR T-cells and 20% of patients treated with BsAbs.[9,21,29,31,33,37,38,41,45] Noticeably, cytopenias during BsAbs therapy is often quickly reversible with dose delays and growth factor support. Instead, prolonged cytopenias after CAR T-cell therapy were reported, configuring a specific entity denominated immune effector cell-associated hematotoxicity (ICAHT).[48] ICAHT is characterized by cytopenia persisting long after the resolution of clinical CRS. It correlates with tumor and inflammatory burden, as deciphered by the dedicated risk-score CAR-HEMATOTOX, and its occurrence portends decreased survival.[49,50]

In addition, secondary primary malignancies (SPMs) are reported after CAR T-cells therapies and the FDA has published a warning about the risk of development of T-cell lymphomas.[51] In MM CAR T-cells trials these data do not appear to be confirmed with the current follow up. In the KarMMa-3 study, the incidence per 100 patient-years of SPMs was comparable between the ide-cel and SOC (3.6 vs 4.1 respectively). No SPMs of T-cell origin was reported in the ide-cel arm. In the CARTITUDE-4 trial, the incidence of SPM was 4.3% in cilta-cel arm and 6.7% in SOC, while one peripheral T-cell lymphoma was reported.[12,20]

Furthermore, owing to target expression on keratinized tissues, anti-GPRC5D TCR are affected by on target/off tumor toxicities in particular skin related (73%), nail related (53%), dysgeusia (71%) and weight loss (≥10% from baseline) (34%). Additionally, the anti-GPRC5D CAR-T cells trials reported few cases of cerebellar ataxia (MCARH109: 2/17 patients; arlo-cel: 2/70 patients).[27-29,39]

In response to the emergence of these adverse events, the International Myeloma Working Group (IMWG) has issued specific recommendations on the prevention and management of these TCR toxicities.[52,53]

The toxicity profile of the most relevant TCR agents is summarized in **Table 3**.

Challenges of the Immunotherapy Era: Patient Selection and the Need for Sequential Treatments. The efficacy leveraged by TCR agents, as described in the previous sections, marked a step forward in the previously difficult-to-treat triple-class-refractory MM scenario.[54] Importantly, such efficacy is foreseen to be fostered by moving these therapies in earlier line settings, or by combination strategies.[55,56] However, several aspects need to be weighted in order to maximize their action, since a definitive curative intent is mostly far from being met for the majority of the patients.

First of all, it is conceivable that the first TCR agent a patient receives will be the one benefiting the most; thus, it needs to be carefully selected. In this sense, clinical (both patient- and tumor-wise) and logistical aspects ought to be considered. Moreover, treatment selection should account for the potential need of sequential exposure to different TCR therapies, whose efficacy may be mutually influenced. Indeed, the critical themes of interest in sequencing TCR treatments are the features of prior TCR exposure, the mechanisms of

Table 3. Relevant toxicities of CAR T-cells and BsAbs.

	Ide-cel (9,11,20)	Cilta-cel (10,12,21)	Anito-cel (25)	MCARH109 (27)	Arlo-cel (29,30)	Teclistamab (13,33)	Elranatamab (14,45)	Linvoseltamab (37)	Talquetamab (15,38,39)	Cevostamab (41)
CRS (G ≥ 3), %	84-88 (4-5)	95-76 (1-5)	84 (1)	88 (6)	82 (79)	72 (1)	58 (0)	46 (1)	77-80 (35-23)	74 (2)
ICANS (G ≥ 3), %	15-18 (3)	7-17 (2)	9 (2)	6 (6)	10 (2)	3 (0)	5 (0)	8 (3)	11 (0)	13 (2)
Parkinson-like syndrome (G ≥ 3), %	/	1-6 (NA)	/	/	/	/	/	/	/	/
Cranial nerve palsy (G ≥ 3), %	/	9 (1)	/	/	/	/	/	/	/	/
Cerebellar ataxia (G ≥ 3), %	/	/	/	12 (12)	3 (NA)	/	/	/	/	/
Peripheral neuropathy (G ≥ 3), %	/	/	/	/	/	/	30 (1)	/	/	/
Anemia (G ≥ 3), %	58-70 (45-60)	54-81 (36-68)	(26)	88 (41)	31 (NA)	55 (38)	49 (37)	39 (31)	43-60 (23-30)	23 (18)
Neutropenia (G ≥ 3), %	91 (79-89)	90-96 (90-95)	(62)	100 (100)	69 (NA)	72 (65)	49 (49)	43 (42)	36-67 (32-60)	31 (28)
Thrombocytopenia (G ≥ 3), %	54-63 (42-52)	54-79 (41-60)	(26)	88 (65)	30 (NA)	42 (23)	31 (24)	NA	23-37 (11-23)	/
Infections (G ≥ 3), %	56-69 (22)	58-62 (20-27)	/	18 (12)	50 (17)	79 (55)	70 (49)	74 (38)	61-70 (20-22)	54 (22)
SPMs (G ≥ 3), %	3.6 per 100 pts/ys	4	/	/	/	/	/	/	/	/
Skin related toxicities (G ≥ 3), %	/	/	/	18 (0)	30 (0)	/	/	/	57-73 (2)	/
Nail related toxicities (G ≥ 3), %	/	/	/	65 (0)	19 (0)	/	/	/	53-55 (2)	/
Dysgeusia (G ≥ 3), %	/	/	/	12 (0)	31 (0)	/	/	/	71-72 (NA)	/

Abbreviations: CRS = cytokine release syndrome; G = grade; ICANS = immune effector cell-associated neurotoxicity syndrome; SPMs = second primary malignancies; pts = patients; ys = years; NA = not available.

resistance causing the failure of previous agents (possibly implied in the efficacy of subsequent lines), evidence from clinical trials, and real-life observations regarding the effectiveness of specific sequencing models. Thus, patient selections and sequencing of TCRs are the subject of intensive research and clinical review. Recently, in-depth recommendations from the IMWG were published.[57]

Patient selection: practical and clinical aspects of interest. The choice of the first TCR agent a patient is receiving should integrate both patient- and tumor-specific aspects, alongside with logistical implications.[16,17,57] Importantly, the first limitation of CAR T-cells therapy is the time imposed by the manufacturing process (i.e., the time running between leukapheresis and infusion of the product, conceptually addressed as *vein-to-vein* period). Additionally, a *brain-to-vein* period is also implied, i.e., the time between the physician's referral and access to an accredited tertiary center capable of ensuring CAR T-cells administration.[57] As brain-to-vein and vein-to-vein periods are highly variable in their duration, with the present technology of CAR T-cells manufacturing and spread of CAR T-cells centers in western countries, they are estimable in 1-2 months.[16,58-60] In this sense, tumor progression pace should be indolent (or efficiently controlled) enough to bridge the patient through the process, without running into clinical deterioration or development of uncontrollable progression.[16,17,57] In fact, efficacy of CAR T-cells was demonstrated to be potentially hampered by the extent of tumor burden, which ultimately also affects morbidity in terms of CRS and ICANS.[21,61-64] Brain-to-vein durations and referral limitations could be lessened by more efficient manufacturing technologies, increased number of facilities accredited for CAR T-cells administration in the national territory, and manufacturing of academic-driven products.[65-67] In this regard, it must be remembered that up to 10-20% of referred patients could not receive the CAR T-cell product after apheresis due to uncontrolled disease progression, or manufacturing failure.[58-60]

Expectedly, the types of therapy a patient receives through the CAR T-cells process are of great importance. Specifically, the therapy potentially needed after first referral is addressed to as *holding therapy*, whose purpose should be to impede further tumor progression without interfering with the manufacturing process and CAR T-cells anti-tumor capacity.[16,17,57] Possibly, it should be based on agents to which the patient is not refractory or recently exposed, and drugs negatively

interfering with lymphocytes' biology, such as alkylators, should be avoided.[68] In this setting, an interesting scenario is represented by the possibility of fostering lymphocytes' fitness in terms of those qualities demonstrated to positively impact the efficacy of CAR-T constructs, such as ratios of naïve and memory T-cells.[69,70] Interestingly, is has been proposed that IMiDs are capable to increase T-cell fitness in terms of proliferation and persistence potential.[71,72] With the same rationale, CELMoDs (Cereblon E3 Ligase Modulators) are being investigated with the purpose of improving the quality of T-cell response before and after TCRs.[73,74] Then, therapy is to be held two to four weeks before leukapheresis itself, as suggested by the IMWG committee, even though robust evidence is lacking.[57]

On the other hand, the therapy potentially needed after leukapheresis and before product infusion (i.e., during *vein-to-vein* time) is referred to as *bridging therapy*.[57] It should impede further tumor progression and possibly reduce its burden. Under these terms, cytotoxic therapy as debulking solution could be used, although it has been demonstrated to correlate with inferior outcomes.[75] In addition, it has been shown that overall response to bridging therapy correlates with treatment outcome. However, bridging therapy itself portends shorter survival, especially when ineffective, possibly as a surrogate of a more aggressive disease.[76,77] Also, quite differently from the holding therapy, it is captivating that bridging strategies based on BsAbs are soon to be further investigated, with the rationale that they might be implicated in the amelioration of T-cell repertoire in terms of memory and persistence. In this regard, growing interest in the use of talquetamab is emerging.[78,79] The IMWG committee recommended a two-week washout of bridging therapy before CAR T-cells infusion.[57]

By contrast, BsAbs inherently represents an off-the-shelf strategy that is not hampered by manufacturing time and is less limited by reduced accessibility. Thus, when dealing with tumor progressions that require immediate intervention, it seems rational to prefer BsAbs. Nevertheless, it should be stressed that even BsAbs demonstrated less efficacy in high tumor burden diseases, variably represented by extramedullary disease, elevated soluble BCMA and bone marrow plasma-cells percentage.[13,14]

Another key aspect to be considered in patient selection concerns the specific toxicity profiles of TCRs. Frail patients are usually not deemed eligible for CAR T-cells, upon the assumption of insufficient organ function to cope with the burdensome impact of CRS, ICANS, and prolonged cytopenia.[16,17] This adds to the real-life awareness of an increased incidence of high-grade events in the frail population.[80,81] Even though robust standardization is lacking, patients are usually screened for eligibility to CAR-T therapies based on pre-immunotherapy frailty scores. Interestingly, it must be noted that real-life experiences with CAR-T administrations showed equal efficacy and safety for patients not meeting inclusion criteria in registrational trials, underpinning their feasibility in less selected patients.[58-60] On the other hand, the lower incidence of severe CRS, ICANS and prolonged cytopenia portended by BsAbs makes them a potentially better option for frail patients,[17,57] though the inherent infectious risk warrants prudence when referring a patient with a history of recurrent and/or severe infections.[82]

CAR T-cells and BsAbs also differ in terms of logistical burden on health-care facilities, caregivers, and patients themselves.[16,17,50] While CAR T-cells require a complex organization in terms of accessibility, administration, and early management of toxicities, it is indeed a one-shot therapy. As a result, patients could undergo prolonged periods of remission, with reduced access to the hospital and ancillary therapies. In this sense, improved quality of life leading to significant and meaningful improvements in relevant symptoms, fatigue, physical functioning, and overall health status has been demonstrated in both ide-cel and cilta-cel trials, underscoring the favorable impact of such a strategy on patient's well-being.[83,84] Additionally, such a treatment-free interval could possibly leverage the recovery of T-cells, which could be eventually beneficial in a potential subsequent TCR therapy at relapse.[85,86] At the same time, BsAbs do not require access to a tertiary center, although the schedule of administration until-remission, alongside the need for supportive therapies to prevent infectious complications, requires frequent and facilitated access to the hospitals. Thus, though BsAbs were also proved to be beneficial in terms of improved patients' quality of life in registrational trials, this may be impacted by the burden of continuous therapy.[87-89]

Sequencing of T-cell redirecting therapies. CAR T-cells and BsAbs have marked a paradigm shift in the treatment of RRMM. However, they still lack curative potential in most cases, especially in the late line setting they were approved for in the first instance.[90-92]

Intense threads of clinical research are also ongoing to boost their beneficial effects, in terms of earlier line positioning and combinatorial strategies.[12,20,34,36,40,93-96] As such, when referring a patient to a TCR agent, the treating physician should foresee the chance of prescribing more than one strategy after another. This raises the issue of finding an optimal sequencing model, ultimately intended to enhance the activity of a single agent by virtue of previous exposure to TCRs. Therefore, the adoption of an ideal sequencing requires an adequate understanding of the mechanisms of resistance.[86,97]

In this regard, CAR T-cells and BsAbs share some mechanisms of resistance while differing in others. For instance, they are both impacted in their functioning by

detrimental tumor specific aspects, such as high-risk cytogenetics, elevated ferritin, extramedullary disease, plasma cells leukemia, or elevated soluble BCMA.[13-15,21,98,99] They are also accustomed by microenvironment-driven resistance in terms of immunosuppressive effect of myeloid derive stromal cells (MDSC), increased regulatory T cells (T-regs) and inhibitory cytokine's pattern.[100-102] Furthermore, an important mechanism of resistance is represented by persisting or acquired exhaustion of T-cell functioning, especially in regard of loss of naïve and memory repertoire.[103-105] In these terms, BsAbs and CAR T-cells do differ, given the persisting T-cell activation fostered by the first as compared to the time-limited anti-tumor effect of the second, raising the chance for a fixed duration schedule of BsAbs, with the intent of limiting immune system exploitation.[106,107] The different treatment pressure also makes sense for the diverse emerging of resisting clones. In fact, while antigen loss represents a rare event after CART therapies, in relation to their time-limited effect, it is described to account for about 50% of relapses after exposure to BsAbs.[86,108] Moreover, agents targeting different antigens may develop specific pattern of resistance, being complete antigen downregulation specific of GPRC5D, while BCMA more often undergoes epitopes mutation, in light of their respective different role in plasma-cells biology.[27,86,108,109] It is also believed that selective and persisting treatment pressure gives rise to resistant clones by favoring the emerge of acquired mechanism of resistance, rather than the selection of pre-existing resistant sub-clones, underpinning the importance of surveillance of clone populations during treatment.[110]

In addition to an in-depth comprehension of the mechanisms of resistance, the collection of robust clinical data with the final intent of deciphering the efficacy and feasibility of specific sequencing models is of crucial importance. Conceptually, real-life analyses have shown that sequencing TCRs is feasible and outperforms other treatment modalities, with the chance of prolonged disease control in difficult-to-treat patients. In a retrospective US cohort of 79 CAR T-cells-treated patients, 35 received a TCR agent at any given timepoint after CAR T-cells. The ORR was 91.4%, mPFS of salvaged patients was 9.1 mos and OS was not reached at 21 mos of follow-up.[111] Similarly, a retrospective cohort of 58 BsAbs-treated patients (49 with anti-GPRC5D, 9 with anti-BCMA agents) showed promising outcomes with subsequent TCR exposure (19 patients: 10 BsAbs, 9 CAR T-cells). ORR, PFS and OS were 84%, 28.9 mos and not reached, respectively.[112] Both studies showed consistently worse outcomes in conventionally treated cohorts. The efficacy results of the most relevant sequencing models are summarized in **Table 4**.

1-BsAbs after CAR T-cells therapies. CAR T-cell therapy was developed for patients affected by RRMM before the availability of BsAbs. As such, a sufficient amount of data is available from registrational trials and real-life observations regarding the CAR T-cells followed by a BsAb sequencing model.

Tec was studied in patients previously exposed to BCMA-targeted treatment in the cohort C of MajesTEC-1 trial. The ORR was 52.5%, the mPFS was 4.5 mos and the mOS 15.5 mos. Efficacy was similar in patients with prior BCMA-targeted ADC and CAR T-cells.[113] Also, studies in the MagnetisMM program (MM-1, MM-3, MM-9) enrolled patients treated with prior BCMA-directed therapies. In CAR T-cells pre-treated patients, the ORR was 52%, and mPFS in the whole population was 4.8 mos.[114]

Data arising from real-life experience of patients treated with Tec or Elra confirmed the evidence derived from clinical trials. Nevertheless, while ORR seems independent from prior anti-BCMA CAR T-cell exposure, the PFS is consistently lower in patients previously treated with an anti-BCMA CAR-T therapy. All in all, it is not clear whether the time elapsing between CAR-T cell infusion and the subsequent therapy with an anti-BCMA BsAb may affect ORR and PFS.[115,116]

MonumelTAL-1 trial showed good efficacy of Tal in patients previously exposed to anti BCMA CAR-T, validating the principle of changing the target. Particularly, in the subgroup of patients previously exposed to CART cell therapy, an ORR of 72% and a median duration of response (mDoR) of 12.3 mos were noticed. Furthermore, the ORR was comparable in patients who received CAR-T as immediate prior line vs any prior line of therapy before Tal (75.9% vs 71.4%, respectively).[117] The few real life experiences available when Tal was used after an anti-BCMA CAR T-cell therapy confirmed the good rate of response (with ORR of 72-78%) obtained in the MonumelTAL-1 trial.[118,119]

The CAMMA 2 study included the cohort A1 where cevostamab was given to patients exposed to a prior anti-BCMA targeting ADC or CAR T, showing an encouraging ORR of 73% in the group with prior CAR T.[120]

Overall, data arising for selected cohorts of pivotal trials and from real life experiences show good efficacy of BsAbs in patients relapsed after an anti-BCMA CAR T-cell therapy, especially using a BsAb with a different target. Biological insights could possibly rely on the prolonged off-therapy period, that poses the chance for immunological reconstitution of T-cells populations, eventually hesitating in a better performance of BsAbs-based therapies.[85,86,116]

2-Sequential CAR T-cells therapies. Data regarding the sequential use of more than a CAR T-cell product after

another are limited. In this sense, the re-infusion of both ide-cel and cilta-cel at subsequent relapse was studied in

Table 4. Selected studies exploring sequencing of TCR.

	Previous TCR	Subsequent TCR	ORR, %	Median DOR, mos	Median PFS, mos	Median OS, mos
MajesTEC-1 cohort C [113]	BCMA CAR-T	teclistamab	53	14.4	4.4	14.9
MagnetisMM pooled analysis [114]	BCMA CAR-T	elranatamab	52	79% at 9 mos	4.8 (all pts)	60% at 9 mos (all pts)
Real-life [115]	BCMA CAR-T	teclistamab	33	NR (all pts)	1.8	NR (all pts)
Real-life [116]	BCMA CAR-T	Anti-BCMA BsAbs	60	4.4	3.6	NA
MonumenTAL-1 prior TCR [117]	BCMA CAR-T	talquetamab	73	12.3	NA	NA
Real-Life [118]	BCMA CAR-T	talquetamab	72	NA	42% at 6 mos (all pts)	75% at 6 mos (all pts)
Real-Life [119]	BCMA CAR-T	talquetamab	78	NA	NA	NA
CAMMA 2 cohort A1 [120]	BCMA CAR-T	cevostamab	73	NA	NA	NA
KarMMa [9]	ide-cel	ide-cel	21	NA	1	NA
CARTITUDE-1 [21]	cilta-cel	cilta-cel	0 (3 pts infused)	/	/	/
Real-life [121]	BCMA CAR-T	ide-cel	100	NR	NR	NA
Real-life [58]	BCMA-TT	cilta-cel	70	NA	13.6	79% at 12 mo
NCT04555551[28]	BCMA CAR-T	MCARH109	75	NA	NA	NA
CC-95266-MM-001 [30]	BCMA-TT	arlo-cel	79	NA	NA	NA
CARTITUDE-2 Cohort C [122]	BCMA BsAbs	cilta-cel	57	8.2	5.3	NA
Real-life [121]	BCMA BsAbs	ide-cel	86	2.8	2.8	NA
MonumenTAL-1 [123]	talquetamab	CAR-T	67	NA	NA	NA
Real-life [124]	GPRC5D TCR	BCMA CAR-T	75	NA	7.1	NA
Real-life [125]	BsAbs	BCMA CAR-T	75	NA	9.6	NA
MonumenTAL-1 [123]	talquetamab	BsAbs	44	NA	NA	NA
Real-Life [118]	BsAbs	talquetamab	59	NA	42% at 6 mos (all pts)	75% at 6 mos (all pts)
Real-Life [119]	BsAbs	talquetamab	50	NA	NA	NA

Abbreviations: TCR = T-cell redirecting therapy; ORR = overall response rate; DOR = duration of response; mos = months; PFS = progression-free survival; OS =overall survival; BCMA = B-cell maturation antigen; CAR = chimeric antigen receptor; NR = not reached; BsAbs = bispecific antibodies; NA = not available; BCMA-TT = BCMA targeted therapy; pts = patients; n° = number; ys = years; GPRC5D = G protein–coupled receptor class C group 5 member D.

restricted cohorts of the KarMMa-1 and CARTITUDE-1 trials, however with unsatisfactory results.[9,21] Efficacy of a different CAR T-cells product targeting the same antigen (e.g., ide-cel after cilta-cel, or vice-versa) was evaluated in some retrospective real-life series, again with inconsistent results.[58,121] In this regards, the IMWG committee consensus suggests the referral to a second anti-BCMA CAR T-cells agent only in the instance of a reasonably prolonged response to the first.[57]

Meanwhile, data on sequential anti-GPRC5D CAR T-cells after an anti-BCMA product are more compelling, with the assumption that shifting the target could counteract the occurrence of BCMA-mutated clones, as pre-clinically described.[86] In this respect, MCARH109 and arlo-cel showed promising response rates in patients previously treated with anti-BCMA CAR T, with ORR of 75-78%, despite the limitation of low numbers, and missing survival data.[27,29]

3-CAR T-cells after BsAbs therapies. CAR-T therapies preceded the introduction of BsAbs, both in clinical research and practice availability. Nevertheless, they might be used after a BsAb when the latter was given first within a clinical trial context or for more convenient availability. Altogether, prospective evidence and real-life data are scarce in this setting.

Cilta-cel was experimented in cohort C of the CARTITUDE-2 trial designed for patients previously exposed to anti-BCMA agents. As a result, patients who received previous BsAbs showed reduced ORR, mDOR and mPFS (57.1%, 8.2 mos, 5.3 mos respectively).[122] Similarly, a retrospective cohorts collected by the US

Myeloma CAR T consortium focused on efficacy of ide-cel in patients previously exposed to an anti-BCMA BsAb. While ORR was 74%, comparable with other real-life observations, the 2.8 mos mPFS revealed to be undermining.[121] Interestingly, both studies showed better efficacy in terms of ORR when CAR T-cells therapies were given after prolonged amount of time from the last BsAb exposure.

On the contrary, patients who progressed under Tal within the MONUMENTAL-1 trial were showed to respond well to a subsequent anti-BCMA CAR-T agent (ORR 78%).[123] Similarly, a single center retrospective study focusing on Tal-resistant patients revealed acceptable efficacy when an anti-BCMA CAR T was given as subsequent therapy, with ORR and mPFS of 75% and 7.07 mos, respectively.[124] However, it should be reminded that both studies were limited by little numbers. In addition, a German retrospective study showed encouraging results when anti-BCMA CAR T-cells agents were given after bridging therapies with BsAbs (either Tal or Tec); on the contrary, the outcome of patients exposed to BsABs before apheresis were consistently worst, especially with prolonged exposure to teclistamab.[125]

Altogether, there is sufficient evidence to discourage anti-BCMA CAR T-cells therapy in patients progressing under BsAbs directed against the same target. The outcomes of this sequencing model predict better results when more time elapsed between the last exposure to BsAbs and CAR T-cells therapy, and when the target antigen is switched. As previously noted, data regarding BsAbs as bridging therapy after apheresis and before CAR T-cells infusion are biologically and clinically compelling.[78,79] Also, it should be reminded that the IMWG committee consensus recommends a washout period of at least 4-weeks between the last dose of BsAbs and apheretic procedures.[57]

4-Sequential BsAbs therapies. The possibility of sequencing two BsAb agents can be relevant for patients not eligible for CAR T-cells therapy and in clinical settings where access to CAR T-cells is logistically difficult.

Some evidence concerning this sequencing model emerged from the MonumelTAL-1 trial, in which 25 enrolled patients were previously exposed to a BsAb agent (23/25 anti-BCMA): the ORR was 52.2% and mDoR was 6.5 mos, both inferior as compared to patients previously exposed to BCMA-directed CAR T-cells or ADC agents. Specifically, the ORR was lower in patients who had received a BsAb as the immediate preceding line than any prior line of therapy before Tal (28.6% vs 61.1%, respectively); of note, the distance between the last dose of prior BsAb and Tal seemed to correlate with ORR.[123] Biologically, this evidence may be related to the T-cell exhaustion found in patients treated with continuous BsAb exposure, as opposed to the restoration of the T-cell repertoire when being off-therapy pressure.[105,106,126]

Some experiences of patients treated with Tal and previously exposed to anti-BCMA BsAbs are available from real-life settings. Consistently with MonumenTal-1 trial data, the ORRs reported in patients previously treated with BsAbs are inferior as compared to patients priorly exposed to CAR T-cells.[118,119]

In conclusion, the few available evidence suggests that the sequencing of two BsAbs is feasible but limited by inferior efficacy if compared to BsAbs administered after CAR T-cells therapy.[57]

Conclusions and Future Directions. The treatment landscape of RRMM has been revolutionized by the introduction of CAR T-cells and BsAbs. A learning curve regarding their best use is underway, specifically in terms of patient selection and sequencing models. In fact, it is becoming increasingly apparent that the efficacy, toxicity, and logistical profile of each drug must be properly tailored to both patients- and tumor- features, in order to maximize efficacy. Moreover, given the persisting relapsing pattern of RRMM, even when adequately controlled by TCRs, the use of sequential TCRs is common, freeing up the need for evidence-based characterization of feasible sequencing models, both in terms of safety and efficacy.[16,17,57]

The current bulk of evidence enlightens that, whenever possible, the utilization of a CAR T-cell agent should be prioritized.[16,17,57] Indeed, though the initial burden on patients and health-care facilities represents a barrier to their access, CAR T-cells therapies hinder the chance of a prolonged treatment-free interval, with possible improvements in patients' quality of life. Therefore, patients should be referred to accredited centers in a timely manner, so that the manufacturing process is addressed without uncontrolled clinical progression and possibly with the chance of effective holding and bridging strategies.[16,17,57] In this regard, CAR T-cells referral should be avoided in case of rapidly progressing and clinically impactful diseases, given the well documented association of tumor burden with increased toxicities and reduced efficacy.[16,17,57] Also, judicious evaluation of patient comorbidities is necessary, given the potential burden of CRS, ICANS, prolonged cytopenias, and risk of infections, albeit real-life cohorts showed that CAR T-cells can be safely infused in patients not meeting the inclusion criteria of registrational trials in terms of comorbidities profiles, including renal impairment.[57,58,127]

On the other hand, BsAbs should be the first TCR option when dealing with features not suitable for a safe and effective referral to a CAR T-cells program. Indeed, rapidly progressing tumors might benefit from a timely initiation of therapy with off-the-shelf drugs, such as

BsAbs. In addition, the reduced risk of clinically meaningful CRS, ICANS and prolonged cytopenias suggest the use of BsAbs in frail patients, though the infectious risk, the continuous schedule of administration, and the need for supportive therapies (e.g., for IVIG administration) must be carefully weighted.[16,17,57]

Of note, when patients relapse after a first TCR-exposure, treatment with another TCR agent is advised, as real-life observations have demonstrated that this is the most effective way to prolong survival.[111,112] Currently, the utilization of CAR T-cells first and then of BsAbs against a different target at the eventual relapse represents the most widely validated sequencing model within clinical trials and from real-life experiences, and should be prioritized whenever possible.[57,111-120]

Overall, the TCRs scenario is evolving rapidly, with many strands of clinical research currently underway. Allogeneic and in vivo-generated CAR T-cells are being studied, raising the chance to make this strategy a nearly off-the-shelf one, thereby reducing the burden of manufacturing times and slots availability.[128,129] Meanwhile, fixed-durations, earlier positioning and combination strategies in BsAbs are also promising, with the intent of enhancing their efficacy while reducing toxicity profiles.[34,36,40,95,96,130,131] Moreover, dual-targeting CAR T-cells and trispecific agents (i.e., constructs capable of redirecting T-cells against two tumor antigens at once) are being investigated, with the premise of enhanced efficacy and safety.[132,133]

In addition, the anticipation of TCRs in the treatment algorithm of MM is being investigated and possibly represents the most promising evolution in the use of TCRs. Indeed, more effective and safer anti-tumor activity in contexts of reduced tumor burden and fitter T-cells repertoires is emerging from pre-clinical evidence with a solid rational, and further confirmed by clinical observations.[20,21,69,70,102] Concomitantly, randomized clinical trials are currently evaluating the use of CAR T-cells as consolidation strategies after induction phases, both in transplant-eligible and ineligible patients,[134,135] while other studies are aimed at exploring a fixed-duration schedule as a maintenance strategy with BsAbs.[136,137]

Collectively, the ever-increasing number of patients eligible for TCR therapies should come with a rationalization of health-care resources to assure these therapies as a standard-of-care treatments. Importantly, in this regards, evidence of their use in out-patient setting are being collected.[138,139] Indeed, the possibly residual tumor burden along with fixed-duration schedules are foreseen to dramatically reduce the present load of toxicities and, therefore, the need for onerous supportive therapies, thereby granting a broader access to these therapies. As a consequence, it is conceivable that the current patient selection and sequencing of therapies as we know them will progressively change, possibly eliminating the present area of uncertainty and leading to further improvement in patient outcome.

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