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Opinion

CAR-T and Bispecific Antibodies: The New Standard for Relapsed and Refractory Multiple Myeloma, or Reserved for Late-Line Salvage Therapy?

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Abstract: The treatment of relapsed and refractory multiple myeloma has improved substantially in the last 5–10 years based on the development and use of several novel classes of drugs and drug combinations. These advances have led to improvements in progression-free and overall survival as well as quality of life. The general tendency has been to advance drugs/combinations that have performed well in advanced disease to the earlier line settings (frontline, first/early relapse). There are several triplet drug combinations that, when used as part of first or early relapse, can provide remission durations of 3 years or longer. More recently, impressive responses have been seen with the use of targeted immunotherapeutics (chimeric antigen receptor T-cells and bispecific antibodies) in heavily pretreated patients with MM. These treatments, however, have been associated with some new and occasionally severe toxicities, including cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, and severe infections, including opportunistic infections and profound cytopenias. These potential toxicities bring into question whether these immune-targeting drugs should remain as late-line therapeutics or whether the high single-agent overall response rates mandate that these agents be used in earlier line settings. Herein, the authors provide a point and counterpoint about the future use of these agents.

Keywords: immunotherapy; relapsed/refractory multiple myeloma; CAR T; bispecific antibodies; T-cell engager

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1. Introduction

Both CAR T-cell therapy and bispecific antibodies have demonstrated deep and durable responses in advanced triple-class exposed relapsed and refractory multiple myeloma (Table 1) [1–3]. This encouraging clinical efficacy has led to the conditional approval of two BCMA-CAR T cell products (cilta-cel and ide-cel) and one BCMA-CD3 bispecific antibody (teclistamab). In all three cases, the approval was based on the results of non-randomized phase 1b/2 clinical trials, and thus randomized evidence against other standard-of-care (SoC) drugs is lacking [1–3].

Table 1. CAR-T cells in MM.

	Phase	Target	Binder and Costim	Age (Range)	Disease Setting	# of Lines	HR Cyto, %	EMD, %	Triple-R, %	CRS: Any Grade, 3/4	Neuro: Any Grade, 3/4	ORR, %	CR/sCR, %	PFS	Ref.
Ide-cel KarMMa (*n* = 128)	II	BCMA	scFv Murine 4-1BB	61 (33–78)	RRMM	6	35	39	84	84/5	18/3	81 ^	39 ^	12.1 ^ m	[1]
Ide-cel KarMMa-3 (*n* = 386)	III			63 (30–81)	2–4 PLT	3	42	24	65	88/4	15/3	71	39	13.3 m	[4]
Cilta-cel CARTITUDE-1 (*n* = 97)	Ib/II	BCMA	VHH, Camelid 4-1BB	61 (56–68)	RRMM	6	24	13	88	95/4	21/9	98	82	34.9 m	[5,6]
Cilta-cel CARTITUDE4 (*n* = 419)	III			61.5 (27–78)	1–3 PLT	2	35	21	14	74.5/1.1	20.5/2.8	85	73	76%@12 m	[7]
ARI0002h (*n* = 60)	I/II	BCMA	scFv Human Synthetic 4-1BB	58 (36–74)	RRMM	3	28	18	NR	90/5	3/0	95	58	15.8 m	[8]
ddBCMA (*n* = 40)	I	BCMA		66 (44–76)	RRMM	4	29	34	100	95/3	18/5	100	76	74%@12 m	[9]
GC012F FasTCAR (*n* = 22)	I	BCMA/ CD19	scFv	59 (43–69)	NDMM	1	32 *	55	0	27/0	0/0	100	95.5	NR	[10]
CC-95266 (*n* = 84)	I	GPRC5D	scFv, Human	63 (39–80)	RRMM	5	44	41	74	76/4	ICANS 10/2 (non-ICANS 11/4)	88	45	NR	[11]

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; EMD, extramedullary disease; HR cyto, high-risk cytogenetics; NA, not available; NR, not reached/not reported; ScFv, single-chain variable fragment; VHH, variable-domain heavy chain; Triple-R, triple-class refractory; CRS, cytokine release syndrome; Neuro, neurologic toxicity; ORR, overall response rate; sCR, stringent complete response; PLT: prior lines of therapy. ^ 450×10^6 CAR T-cells, * 1q21 $\geq$ 4 copies

In addition to novel T-cell redirecting agents such as CAR T-cells or bispecific antibodies (Table 2), other drugs have also been approved for the treatment of triple-class exposed RRMM, such as selinexor [12], melflufen [13], or belantamab mafodotin [14]. Although no head-to-head comparison is available, there are several indirect comparisons published using the matched adjusted comparison methodology that demonstrate the superiority of CAR T-cell therapies (cilta-cel or ide-cel) and teclistamab over the other three approved treatments, suggesting that the BCMA-targeted agents would yield the best clinical outcomes in triple-class exposed RRMM patients and should be prioritized whenever possible [15–17]. Still, an important remaining question is whether these T-cell-redirecting treatments will be the new standard treatment for all relapse MM patients and not just for triple-class exposed patients.

Table 2. Bispecific antibodies.

Bispecific Antibody	**Teclistamab (JNJ6400795) [18]**	**Elranatamab (PF-06863135) [19]**	**Linvoseltamab (REGN5458) [20,21]**	**Talquetamab (JNJ-64407564) [22,23]**		**Cevostamab (GO39775) [24,25]**
Structure/Function	BCMA-CD3	BCMA-CD3	BCMA-CD3	GPRC5D-CD3		FcRH5 X CD3
Treatment	Weekly SC	Weekly SC	Weekly IV	Weekly SC	Bi-weekly SC	Every 3 weeks IV, up to 17 cycles
Patients (*n*; age)	*n* = 165; 64 (33–84)	*n* = 123; 68 (36–89)	*n* = 117; 70 (37–91)	*n* = 143; 67 (46–86)	*n* = 145; 67 (38–84)	*n* = 161; 64 (33–82)
Median prior lines	5	5	5	5	5	6
HR cyto/EMD TCR	26%/17% 78%	25%/32% 97%	36%/14% 74%	31%/23% 74%	29%/26% 69%	40%/21% 85%
ORR/CR (at RP2D) RP2D	63%/39.2% 1.5 mg/kg	61%/35% 76 mg	71%/46% 200 mg	74%/34% 0.4 mg/kg	72%/32% 0.8 mg/kg	57%/8.4% 132–198 mg
PFS	11.3 mos	51@15 mos	69%@12 mos	7.5 mos	11.9 mos	NR
DOR	18.4 mos	71.5@15 mos	78%@12mos	9.3 mos	13 mos	11.5 mos
Median f/u	14.1 mos	14.7 mos	11 mos	18.8 mos	12.7 mos	8.8 mos
CRS (all/Gr3+)	72.1% (0.6%)	58% (0%)	46% (1%)	79% (02.1%)	72.4% (0.7%)	81% (1.2%) → toci prophy: 36% (2.3%)
Infections (all/Gr3+)	76.4% (45%)	70% (40%)	73% (34%)	57% (17%)	51% (12%)	~48% (20%)
Neutropenia (all/Gr3+)	71% (64%)	49% (49%)	42% (40%)	34% (31%)	28% (22%)	~39% (37%)
Anemia Thrombocytopenia (all/Gr3+)	52% (37%) 40% (21%)	49% (37%) 31% (24%)	36% (31%) 18% (6%)	45% (31% 27% (20%)	39% (25%) 27% (17%)	~36% (16%) ~28% (18%)
Neurotoxicity ICANS (all/Gr+) Other	3% (0%) 10% (0%)	3.4%/0% PN 17.1	8% (3%)	10.7% (1.6%)	10.1% (1.8%)	~14% (1%)
Hypogamma (IVIg replacement)	75% (39)%	NR	NR	64% (15%)	68% (13%)	NR

BCMA, B-cell maturation antigen; CD3, cluster determination 3; SC, subcutaneous; IV, intravenous; EMD, extramedullary disease; HR cyto, high-risk cytogenetics; NA, not available; NR, not reached/not reported; TCR, triple-class refractory; ORR, overall response rate; CR, complete response; RP2D, recommended phase 2 dose; PFS, progression-free survival; DOR, duration of response; f/u, follow-up; AEs, adverse events; Gr, grade; CRS, cytokine release syndrome; Neuro, neurologic toxicity.

2. Point: CAR-T and Bispecific Antibodies Are Not Yet the Standard for RRMM

In the last decade, several new agents and combinations have been approved for the management of RRMM. In patients with early relapse, we can achieve high ORR and prolonged PFS using some of the currently approved triplets combining anti-CD38 monoclonal antibodies with second-generation proteasome inhibitors (carfilzomib [K]) or immunomodulatory agents (lenalidomide [R] or pomalidomide [P]) [26–32]. As examples, the PFS with daratumumab (D), lenalidomide, and dexamethasone (DRd) in the POLLUX[13] study was 45 months compared to 35.7 months with isatuximab, carfilzomib, and dexamethasone (IsaKd) in the IKEMA trial [29]. Moreover, in patients experiencing their first relapse, in which the disease was not refractory to lenalidomide, the median PFS was up to 53.3 months with DRd, which is one of the longest so far reported in the relapse setting.

This means that prolonged disease control is achievable with conventional treatments given until disease progression in a significant proportion of patients with RRMM. Whether this efficacy can be challenged with novel immunotherapeutic agents remains unknown. This question is indeed very provocative when we envision a comparison between continuous treatments against single CAR T-cell infusion.

In fact, if we analyze closely the preliminary evidence generated in cohort A from the phase 2 CARTITUDE-2 trial in which 20 patients with 1–3 prior lines and lenalidomide-refractory were treated with cilta-cel, PFS at 15 months was 70% (95% CI, 45.1–85.3%), which is comparable to that reported in the CARTITUDE-1 trial in a much more advanced patient population [3,33]. Therefore, it is still unknown whether outcomes would be improved by using CAR T-cells in an earlier setting as a single infusion.

This question is being addressed in two large phase 3 randomized studies comparing BCMA CAR T-cells vs. SoC triplets at the time of early relapse: the KarMMa-3 (NCT03651128) and CARTITUDE-4 (NCT04181827) trials. In the KarMMa-3 trial, patients with two to four prior lines of therapy, exposed to prior lenalidomide and an anti-CD38 monoclonal antibody were included and randomized between a single ide-cel infusion or the physician's choice of five different SoC triplets [34]. In the CARTITUDE-4, patients receiving one to up to three prior lines of treatment, all lenalidomide-exposed, were included and randomized to cilta-cel or a standard treatment with daratumumab, pomalidomide, dexamethasone (DPd) or pomalidomide, bortezomib, or dexamethasone (PVd). Both studies have now reached their primary endpoint, showing the superior PFS and response rates of one infusion of BCMA-targeting CAR T-cells over conventional drug-based treatment [5,7]. Despite these promising results, several questions remain unanswered since, for example, none of these trials have used DKd or isatuximab-Kd as a control arm.

Eventually, the picture will be different if we use continuous therapy with bispecific antibodies (i.e., teclistamab) in combination with SoC. This is being evaluated in the phase 3 MajesTEC-3 trial (NCT05083169), where teclistamab and daratumumab are being compared to DPd or daratumumaba–bortezomib–dexamethasone (DVd) in patients with one to three prior lines and exposed to prior lenalidomide. However, continuous treatment with T-cell engager therapies may raise other concerns derived from continuous T-cell exhaustion, leading to an increased risk of opportunistic infections and eventually second primary malignancies.

Hence, the safety profile of CAR T-cells and bispecific T-cell engagers is an important aspect to consider if we think of using these drugs widely for all RRMM patients. In fact, patients treated so far in the context of clinical studies were highly selected, representing mainly fit patients without significant comorbidities. However, this will surely evolve as we incorporate these therapies in the real-world setting. Indeed, recent evidence coming from early real-world experience with ide-cel shows that efficacy and safety was comparable to that reported in the KarMMa study, yet 77% would not have been eligible for the clinical trial [35].

Notwithstanding, it is clear that in order to deliver these treatments safely, medical education as well as organization in hospitals are of utmost importance. Additionally, hospitals need to have a minimum structure, including rapid access to the intensive care unit and trained staff available to manage toxicities properly. Acute toxicity in the form of cytokine release syndrome is very common, and although it is usually low-grade, early recognition and treatment is critical to preventing progression to severe forms. Importantly, these therapies have been either so far delivered in the context of clinical trials with a highly selected patient population and well-trained staff or in experienced centers in the real-world setting. On the other hand, neurological complications, albeit in low incidence, can be severe, and again, training for their early recognition is mandatory. Finally, it is also important to prevent and manage long-term toxicities, including infectious complications or second primary malignancies. This is to say that the unprecedented clinical efficacy seen with these agents needs to be balanced with the observed safety profile and adequate patient selection, and proper use in well-trained centers is recommended. We could certainly

envision a future in which we will identify patients likely to benefit from conventional treatments given until disease progression and in which the early use of CARs or bispecifics would lead to better outcomes.

3. Counterpoint: CAR-T and Bispecific Antibodies Will Rapidly Become the Standard for the Treatment of RRMM

In the last 10 years, there have been 10 new drugs approved for the treatment of multiple myeloma, and these drugs have significantly improved survival. The majority of these drugs were conditionally approved after showing activity in the relapsed and refractory setting, with the most active agents then being evaluated in early relapse or as part of frontline therapy. An example of this is the anti-CD38 antibody daratumumab, which was given accelerated approval after showing single-agent response rates of ~30% in RRMM [36]. Daratumumab was then tested in earlier lines of therapy and now has received full approval in combination with many other standard agents in the early relapse and frontline settings [37]. This example highlights the standard path for drug development in MM. We currently have three very active classes of agents to treat MM, immunomodulatory drugs, proteasome inhibitors, and anti-CD38 monoclonal antibodies, and individual drugs from these three classes have dominated the treatment landscape from NDMM to RRMM. Single-agent response rates for all approved MM drugs have generally ranged between 15 and 30%, with a few drugs having been approved with lower single-agent response rates but good activity in combination with other agents. This plethora of drugs has changed the average survival of MM patients but a cure still remains elusive. Thus, we welcome the *immunotherapy era* for the treatment of MM and specifically have optimism for BCMA-directed immunotherapeutics, including chimeric antigen receptor T (CART) cells and bispecific T cell-engaging antibodies (BsAbs).

In the last 2–5 years, we have seen unprecedented single-agent response rates from some of the newer immunotherapies and specifically from BCMA-targeted CART cells and bispecific T cell-engaging antibodies. At the American Society of Clinical Oncology meeting in 2017, Fan et al. presented the initial results from a phase 1 trial (LCAR-38M) utilizing a novel BCMA-targeted CAR T-cell therapy showing an overall response rate of 100% in 19 patients having received three or more prior lines of therapy [38]. This study generated significant enthusiasm for the immunotherapy era of MM, and many companies and academic programs began focusing on BCMA-targeted immune therapeutics. In fact, since then, LCAR-38M was licensed to Janssen and became cilta-cel, and the results from over 10 BCMA-targeted CAR T-cell and bispecific T-cell redirecting antibody trials have been reported, demonstrating amazing single-agent response rates (ORR, range 55–98%) [39]. These are the most active agents to date, with many patients achieving deep responses and reaching minimal residual disease negativity (MRD(-5)). The depth and durability of these responses in RRMM patients are truly unprecedented.

The phase 1b/2 CARTITUDE-1 trial led to the FDA approval of cilta-cel, based on an ORR of 98% with 82.5% of patients achieving sCR and a progression-free survival rate of ~55% at 27 months [3]. The phase 1/2 Majestic 1 study recently reported an ORR of 63% to single-agent Teclistamab (BCMA-CD3-BsAb), with 40% of patients achieving CR and a median duration of response of 18.3 months [2]. These examples are not unique, and we also have other BsAbs targeting other plasma cell surface antigens (GPRC5D, FcHR5, CD38) showing response rates between 53 and 70% in early-phase trials. The impressive overall response rates with novel immunotherapies have propelled these agents to be tested in earlier lines of therapy, including in the frontline setting and in early relapse when T-cells are potentially healthier. These agents have even greater potential to induce deep and durable responses and offer the possibility of a "cure"when used in earlier lines. They may as well offer the important goal of achieving limited duration of therapy (e.g., stopping therapy after sustained MRD(-)) as these goals have not been achievable with the currently available agents.

Use in frontline and early relapsed disease will certainly be contingent upon safety. There are unique side effects associated with immune-activating agents, including cytokine release syndrome, immune effector cell-associated neurotoxicity (ICANS), cytopenias, and infection. Early CART trials have reported high rates of CRS (40–95%), but the majority of events are Gr1/2, with <5% being Gr 3/4 in most trials. Patients require supportive care with anti-pyretics, intravenous fluids, antibiotics, anti-IL-6 therapy (tocilizumab), corticosteroids, and occasionally supplemental oxygen or low-dose vasopressive agents; currently, these are delivered in specialty centers [1,40]. Bispecific antibodies also frequently cause CRS (incidence ~40–75%), and this occurs most commonly following the first few doses and rarely after the first cycle of therapy. The CRS with bispecifics is generally mild (Gr1-2) and often responds rapidly to supportive care, including tocilizumab therapy [2,39]. Although the CRS is manageable, an initial hospital stay is currently required for the initial dosing of bispecific antibodies and CART cells, and the use of these have been limited to centers specialized in their delivery. ICANS is less common, occurring in ~5–25% of patients receiving CART cells and <10% with BsAbs, with the majority of cases being Gr1/2 [1,39,40]. Overall, CRS and ICANS are manageable toxicities and standard guidelines for treating these toxicities are rapidly being developed. The cytopenias also occur frequently with CART cell therapies (>90% occurrence), but are also common with BsAbs and are very manageable with cytokine and blood product support. Infections are common (incidence ~30–75%), after both CART and BsAb therapy and patients require prophylactic medications as well as close monitoring while receiving these therapies. A variety of infections have been reported, including immunocompromised infections (e.g., CMV and parvovirus re-activation pneumocystis, etc.). These patients often required gammaglobulin replacement therapy which continues until B-cell recovery occurr. Overall, the toxicity from these agents is certainly manageable and thus will not limit use in earlier lines of therapy.

4. Conclusions

In summary, the activity of these novel immunotherapies has already led to clinical trials utilizing these agents in early relapse and in NDMM. The myeloma treatment landscape will rapidly change to allow the introduction of these active agents with goals of achieving deeper responses and providing the potential for cure and limited duration of therapy. However, the ideal sequence, combination, and duration of use of these novel therapeutics and how to best incorporate these agents with the current myeloma landscape will be the subject of multiple trials. Also of importance is that more innovation is on the way with the potential to further change/improve the options/choices of treatment. Additional agents include novel CELMoDs, trispecific antibodies, novel cytokine/interleukins, NK-CARs, and NK-cell engagers, amongst others. Novel plasma cell surface targets have and will continue to be developed, and efforts to optimize cellular therapeutics and T-cell engager therapies will continue until *curative* therapy is developed/achieved.

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References

1. Munshi, N.C.; Anderson, L.D., Jr.; Shah, N.; Madduri, D.; Berdeja, J.; Lonial, S.; Raje, N.; Lin, Y.; Siegel, D.; Oriol, A.; et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. *N. Engl. J. Med.* **2021**, *384*, 705–716. [CrossRef] [PubMed]
2. Moreau, P.; Garfall, A.L.; van de Donk, N.W.; Nahi, H.; San-Miguel, J.F.; Oriol, A.; Nooka, A.K.; Martin, T.; Rosinol, L.; Chari, A.; et al. Teclistamab in Relapsed or Refractory Multiple Myeloma. *N. Engl. J. Med.* **2022**, *387*, 495–505. [CrossRef]

3. Martin, T.; Usmani, S.Z.; Berdeja, J.G.; Agha, M.; Cohen, A.D.; Hari, P.; Avigan, D.; Deol, A.; Htut, M.; Lesokhin, A.; et al. Ciltacabtagene Autoleucel, an Anti-B-cell Maturation Antigen Chimeric Antigen Receptor T-Cell Therapy, for Relapsed/Refractory Multiple Myeloma: CARTITUDE-1 2-Year Follow-Up. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2022**, *41*, 1265. [CrossRef] [PubMed]
4. Rodriguez-Otero, P.; Ailawadhi, S.; Arnulf, B.; Patel, K.; Cavo, M.; Nooka, A.K.; Manier, S.; Callander, N.; Costa, L.J.; Vij, R.; et al. Ide-cel or standard regimens in relapsed and refractory multiple myeloma. *N. Engl. J. Med.* **2023**, *388*, 1002–1014. [CrossRef] [PubMed]
5. Berdeja, J.G.; Madduri, D.; Usmani, S.Z.; Jakubowiak, A.; Agha, M.; Cohen, A.D.; Stewart, A.K.; Hari, P.; Htut, M.; Lesokhin, A.; et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): A phase 1b/2 open-label study. *Lancet* **2021**, *398*, 314–324. [CrossRef] [PubMed]
6. Jagganath, S.; Jackson, C.C.; Schecter, J.M.; Lenvia, N.; Sun, H.; Akram, M.; Patel, N.; Martin, T.G. Cilta-cel, a BCMA targeted CAR-T therapy for patients with multiple myeloma. *Expert Opin. Biol. Ther.* **2024**. online ahead of print. [CrossRef] [PubMed]
7. San-Miguel, J.; Dhakal, B.; Yong, K.; Spencer, A.; Anguille, S.; Mateos, M.V.; Fernández de Larrea, C.; Martínez-López, J.; Moreau, P.; Touzeau, C.; et al. Cilta-cel or standard care in lenalidomide-refractory multiple myeloma. *N. Engl. J. Med.* **2023**, *389*, 335–347. [CrossRef] [PubMed]
8. Oliver-Caldes, A.; Gonzalez-Calle, V.; Cabañas, V.; Lopez-Muñoz, N.; Otero, P.R.; Reguera, J.L.; Español-Rego, M.; Inoges, S.; Zabaleta, A.; Corral, L.L.; et al. ARI0002h (Cesnicabtagene Autoleucel), an Academic Point-of-Care B-Cell Maturation Antigen (BCMA)-Directed Chimeric Antigen Receptor (CAR) T-Cell Strategy: Activity and Safety after Fractionated Initial Therapy and Booster Dose in 60 Patients with Relapsed/Refractory Multiple Myeloma. *Blood* **2023**, *142*, 1026.
9. Frigault, M.; Rosenblatt, J.; Dhakal, B.; Raje, N.; Cook, D.; Gaballa, M.R.; Emmanuel-Alejandro, E.; Nissen, D.; Cornwell, C.; Banerjee, K.; et al. Phase 1 Study of CART-Ddbcma for the Treatment of Patients with Relapsed and/or Refractory Multiple Myeloma: Results from at Least 1-Year Follow-up in All Patients. *Blood* **2023**, *142*, 1023. [CrossRef]
10. Du, J.; Qiang, W.; Lu, J.; Jia, Y.; He, H.; Liu, J.; Guo, P.; Yang, Y.; Feng, Z.; Jin, L.; et al. Updated results of a phase I open-label single-arm study of dual Targeting BCMA and CD19 Fastcar-T cells (GC012F) as first-line therapy for transplant-eligible newly diagnosed high-risk multiple myeloma. *Blood* **2023**, *142*, 1022. [CrossRef]
11. Bal, S.; Htut, M.; Nadeem, O.; Anderson Jr, L.D.; Koçoğlu, H.; Gregory, T.; Rossi, A.C.; Martin, T.; Egan, D.N.; Costa, L.; et al. BMS-986393 (CC-95266), a G Protein-Coupled Receptor Class C Group 5 Member D (GPRC5D)-Targeted Chimeric Antigen Receptor (CAR) T-Cell Therapy for Relapsed/Refractory Multiple Myeloma (RRMM): Updated Results from a Phase 1 Study. *Blood* **2023**, *142*, 219. [CrossRef]
12. Vogl, D.T.; Dingli, D.; Cornell, R.F.; Huff, C.A.; Jagannath, S.; Bhutani, D.; Zonder, J.; Baz, R.; Nooka, A.; Richter, J.; et al. Selective Inhibition of Nuclear Export With Oral Selinexor for Treatment of Relapsed or Refractory Multiple Myeloma. *J. Clin. Oncol.* **2018**, *36*, 859. [CrossRef] [PubMed]
13. Richardson, P.G.; Oriol, A.; Larocca, A.; Blade, J.; Cavo, M.; Rodriguez-Otero, P.; Leleu, X.; Nadeem, O.; Hiemenz, J.W.; Hassoun, H.; et al. Melflufen and Dexamethasone in Heavily Pretreated Relapsed and Refractory Multiple Myeloma. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2021**, *39*, 757–767. [CrossRef]
14. Lonial, S.; Lee, H.C.; Badros, A.; Trudel, S.; Nooka, A.K.; Chari, A.; Abdallah, A.-O.; Callander, N.; Lendvai, N.; Sborov, D.; et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): A two-arm, randomised, open-label, phase 2 study. *Lancet Oncol.* **2020**, *21*, 207–221. [CrossRef]
15. Weisel, K.; Krishnan, A.; Schecter, J.M.; Vogel, M.; Jackson, C.C.; Deraedt, W.; Yeh, T.-M.; Banerjee, A.; Yalniz, F.; Nesheiwat, T.; et al. Matching-Adjusted Indirect Treatment Comparison to Assess the Comparative Efficacy of Ciltacabtagene Autoleucel in CARTITUDE-1 Versus Belantamab Mafodotin in DREAMM-2, Selinexor-Dexamethasone in STORM Part 2, and Melphalan Flufenamide-Dexamethasone in HORIZON for the Treatment of Patients With Triple-Class Exposed Relapsed or Refractory Multiple Myeloma. *Clin. Lymphoma Myeloma Leuk.* **2022**, *22*, 690–701. [CrossRef]
16. Rodriguez-Otero, P.; Ayers, D.; Cope, S.; Davies, F.E.; Delforge, M.; Mojebi, A.; Jansen, J.P.; Weisel, K.; Hege, K.; Dhanasiri, S. Matching adjusted indirect comparisons of efficacy outcomes for idecabtagene vicleucel (ide-cel, bb2121) versus selinexor + dexamethasone and belantamab mafodotin in relapsed and refractory multiple myeloma. *Leuk. Lymphoma* **2021**, *62*, 2482–2491. [CrossRef] [PubMed]
17. Bahlis, N.J.; Usmani, S.Z.; Rosiñol, L.; Krishnan, A.Y.; Nooka, A.K.; Rocafiguera, A.O.; Delforge, M.; Garfall, A.L.; van de Donk, N.W.; Rodríguez-Otero, P.; et al. Matching-adjusted indirect comparison (MAIC) of teclistamab (tec) versus selinexor-dexamethasone (sel-dex) for the treatment of patients (pts) with triple-class exposed (TCE) relapsed/refractory multiple myeloma (RRMM). *J. Clin. Oncol.* **2022**, *40* (Suppl. S16), e20028. [CrossRef]
18. Lesokhin, A.; Tomasson, M.; Arnulf, B.; Bahlis, N.J.; Prince, H.M.; Niesvizky, R.; Rodríguez-Otero, P.; Martinez-Lopez, J.; Koehne, G.; Touzeau, C.; et al. Elranatamab in relapsed or refractory multiple myeloma: Phase 2 MagnetisMM-3. *Trial Nat. Med.* **2023**, *29*, 2259–2267. [CrossRef]
19. Jagannath, S.; Richter, J.; Dhodapkar, M.V.; Hoffman, J.E.; Lee, H.C.; Suvannasankha, A.; Shah, M.R.; Lentzsch, S.; Zonder, J.A.; Baz, R.; et al. Linvoseltamab, a B-cell maturation antigen-targeted T-cell-engaging biscpcific antibody induces deep and durable responses in patients with relapsed or refractory multiple myeloma including difficult-to-treat subgroups. In Proceedings of the 115th Annual Meeting of the American Association for Cancer Research, San Diego, CA, USA, 5–10 April 2024.

20. Lee, H.C.; Bumma, N.; Richter, J.R.; Dhodapkar, M.V.; Hoffman, J.E.; Suvannasankha, A.; Zonder, J.A.; Shah, M.R.; Lentzsch, S.; Maly, J.J.; et al. LINKER-MM1 study: Linvoseltamab (REGN5458) in patients with relapsed/refractory multiple myeloma. *J. Clin. Oncol.* **2023**, *41*, 8006. [CrossRef]
21. Chari, A.; Minnema, M.; Berdeja, J.; Oriol, A.; Van de Donk, N.; Rodríguez-Otero, P.; Askari, E.; Mateous, M.V.; Costa, L.; Caers, J.; et al. Talquetamab, a T-cell-redirecting GPRC5D bispecific antibody for multiple myeloma. *N. Engl. J. Med.* **2022**, *387*, 2232–2244. [CrossRef]
22. Chari, A.; Touzeau, C.; Schinke, C.; Minnema, M.; Berdeja, J.; Oriol, A.; Van de Donk, N.; Rodríguez-Otero, P.; Askari, E.; Mateous, M.V.; et al. Talquetamab, a G Protein-Coupled Receptor Family C Group 5 Member D × CD3 Bispecific Antibody, in Patients With Relapsed/Refractory Multiple Myeloma: Phase 1/2 Results From MonumenTAL-1. *Blood* **2022**, *140* (Suppl. S1), 384–387. [CrossRef]
23. Trudel, S.; Cohen, A.D.; Krishnan, A.Y.; Fonseca, R.; Spencer, A.; Berdeja, J.G.; Lesokhin, A.; Forsberg, P.A.; Laubach, J.P.; Costa, L.J.; et al. Cevostamab monotherapy continues to show clinically meaningful activity and manageable safety in patients with heavily pre-treated relapsed/refractory multiple myeloma (RRMM): Updated results from an ongoing phase I study. *Blood* **2021**, *138* (Suppl. S1), 157. [CrossRef]
24. Trudel, S.; Bahlis, N.J.; Spencer, A.; Kaedbey, R.; Rodriguez Otero, P.; Harrison, S.J.; Wong, C.; Goodman, G.R.; Nakamura, R.; Choeurng, V.; et al. Pretreatment with tocilizumab prior to the CD3 bispecific cevostamab in patients with relapsed/refractory multiple myeloma (RRMM) showed a marked reduction in cytokine release syndrome incidence and severity. *Blood* **2022**, *140* (Suppl. S1), 1363–1365. [CrossRef]
25. Dimopoulos, M.; Quach, H.; Mateos, M.-V.; Landgren, O.; Leleu, X.; Siegel, D.; Weisel, K.; Yang, H.; Klippel, Z.; Zahlten-Kumeli, A.; et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): Results from a randomised, multicentre, open-label, phase 3 study. *Lancet* **2020**, *396*, 186–197. [CrossRef] [PubMed]
26. Martin, T.; Mikhael, J.; Hajek, R.; Kim, K.; Suzuki, K.; Hulin, C.; Garg, M.; Quach, H.; Sia, H.; George, A.; et al. Depth of Response and Response Kinetics of Isatuximab Plus Carfilzomib and Dexamethasone in Relapsed Multiple Myeloma: Ikema Interim Analysis. *Blood* **2020**, *136* (Suppl. S1), 7–8. [CrossRef]
27. Moreau, P.; Dimopoulos, M.-A.; Mikhael, J.; Yong, K.; Capra, M.; Facon, T.; Hajek, R.; Baker, R.; Kim, K.; Martinez, G.; et al. Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): A multicentre, open-label, randomised phase 3 trial. *Lancet* **2021**, *397*, 2361–2371. [CrossRef] [PubMed]
28. Kaufman, J.L.; Usmani, S.Z.; San-Miguel, J.; Bahlis, N.; White, D.J.; Benboubker, L.; Cook, G.; Leiba, M.; Ho, P.J.; Kim, K.; et al. Four-Year Follow-up of the Phase 3 Pollux Study of Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) Alone in Relapsed or Refractory Multiple Myeloma (RRMM). *Blood* **2019**, *134* (Suppl. S1), 1866. [CrossRef]
29. Attal, M.; Richardson, P.G.; Rajkumar, S.V.; San-Miguel, J.; Beksac, M.; Spicka, I.; Leleu, X.; Schjesvold, F.; Moreau, P.; Dimopoulos, M.A.; et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): A randomised, multicentre, open-label, phase 3 study. *Lancet* **2019**, *394*, 2096–2107. [CrossRef] [PubMed]
30. Dimopoulos, M.A.; Terpos, E.; Boccadoro, M.; Delimpasi, S.; Beksac, M.; Katodritou, E.; Moreau, P.; Baldini, L.; Symeonidis, A.; Bila, J.; et al. Apollo: Phase 3 Randomized Study of Subcutaneous Daratumumab Plus Pomalidomide and Dexamethasone (D-Pd) Versus Pomalidomide and Dexamethasone (Pd) Alone in Patients (Pts) with Relapsed/Refractory Multiple Myeloma (RRMM). *Blood* **2020**, *136* (Suppl. S1), 5–6. [CrossRef]
31. Cohen, Y.C.; Cohen, A.D.; Delforge, M.; Hillengass, J.; Goldschmidt, H.; Weisel, K.; Raab, M.-S.; Scheid, C.; Schecter, J.M.; De Braganca, K.C.; et al. Efficacy and Safety of Ciltacabtagene Autoleucel (Cilta-cel), a B-Cell Maturation Antigen (BCMA)-Directed Chimeric Antigen Receptor (CAR) T-Cell Therapy, in Lenalidomide-Refractory Patients with Progressive Multiple Myeloma after 1–3 Prior Lines of Therap. *Blood* **2021**, *138* (Suppl. S1), 3866. [CrossRef]
32. Delforge, M.; Baz, R.C.; Cavo, M.; Callander, N.S.; Ghobadi, A.; Rodriguez-Otero, P.; Mateos, M.-V.; Massaro, M.; Ding, L.; Patel, P.; et al. KarMMa-3: A Phase 3 Study of Idecabtagene Vicleucel (ide-cel, bb2121), a BCMA-Directed CAR T Cell Therapy Vs Standard Regimens in Relapsed and Refractory Multiple Myeloma. *Blood* **2020**, *136*, 24–25. [CrossRef]
33. Sidana, S.; Ahmed, N.; Akhtar, O.S.; Heim, M.; Brazauskas, R.; Hansen, D.K.; Ferreri, C.; Freeman, C.L.L.; Afrough, A.; Anderson , L.D.; et al. Abstract: Real-world results of Idecabtagene vicleucel. In Proceedings of the IMS Annual Meeting, Los Angeles, CA, USA, 25–27 September 2022.
34. Usmani, S.Z.; Nahi, H.; Plesner, T.; Weiss, B.M.; Bahlis, N.J.; Belch, A.; Voorhees, P.M.; Laubach, J.P.; van de Donk, N.W.C.J.; Ahmadi, T.; et al. Daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma: Final results from the phase 2 GEN501 and SIRIUS trials. *Lancet Hematol.* **2020**, *7*, e447–e455. [CrossRef] [PubMed]
35. Nooka, A.K.; Kaufman, J.L.; Hofmeister, C.C.; Joseph, N.S.; Heffner, T.L.; Gupta, V.A.; Sullivan, H.C.; Neish, A.S.; Dhodapkar, M.V.; Lonial, S. Daratumumab in multiple myeloma. *Cancer* **2019**, *125*, 2364–2382. [CrossRef] [PubMed]
36. Zhao, W.-H.; Liu, J.; Wang, B.-Y.; Chen, Y.-X.; Cao, X.-M.; Yang, Y.; Zhang, Y.-L.; Wang, F.-X.; Zhang, P.-Y.; Lei, B.; et al. A phase 1, open-label study of LCAR-B38M, a chimeric antigen receptor T cell therapy directed against B cell maturation antigen, in patients with relapsed or refractory multiple myeloma. *J. Hematol. Oncol.* **2018**, *11*, 141. [CrossRef] [PubMed]

37. Shah, N.; Chari, A.; Scott, E.; Mezzi, K.; Usmani, S.Z. B-cell maturation antigen (BCMA) in multiple myeloma: Rationale for targeting and current therapeutic approaches. *Leukemia* **2020**, *34*, 985–1005. [CrossRef]
38. Krejci, M.; Adam, Z.; Krejci, M.; Pour, L.; Sandecká, V.; Stork, M. CAR-T cells for the treatment of relapsed/refractory multiple myeloma in 2022: Efficacy and toxicity. *Neoplasma* **2022**, *69*, 1008–1018. [CrossRef] [PubMed]
39. Cho, S.-F.; Yeh, T.-J.; Anderson, K.C.; Tai, Y.-T. Bispecific antibodies in multiple myeloma treatment: A journey in progress. *Front. Oncol.* **2022**, *12*, 1032775. [CrossRef]
40. Cohen, A.D.; Parekh, S.; Santomasso, B.D.; Pérez-Larraya, J.G.; van de Donk, N.W.C.J.; Arnulf, B.; Mateos, M.-V.; Lendvai, N.; Jackson, C.C.; De Braganca, K.C.; et al. Incidence and management of CAR-T neurotoxicity in patients with multiple myeloma treated with ciltacabtagene autoleucel in CARTITUDE studies. *Blood Cancer J.* **2022**, *12*, 32. [CrossRef]