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BCMA-targeted therapies for multiple myeloma: latest updates from 2024 ASH annual meeting

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Abstract
B-cell maturation antigen (BCMA) is currently the most extensively explored target for multiple myeloma (MM). BCMA-targeted therapies such as antibody-drug conjugate (ADC), bispecific antibodies (BsAbs), chimeric antigen receptor T(CAR-T) cell have shown promising therapeutic prospects in MM. We have summarized the latest reports on the three types of drugs for MM at the 2024 ASH Annual Meeting.

Keywords BCMA-targeted therapies, Multiple myeloma, ASH 2024

To the editor

In recent years, BCMA-targeted drugs have greatly improved the prognosis of patients with relapsed/refractory multiple myeloma (R/RMM) [1]. Researchers are also exploring the possibility of applying these drugs to newly diagnosed multiple myeloma (NDMM). We have summarized the latest reports on antibody-drug conjugates (ADC), bispecific antibodies (BsAbs), and chimeric antigen receptor T(CAR-T) cell therapy for MM at the ASH 2024 Annual Meeting.

Belantamab mafodotin

Belantamab mafodotin (belamaf) was the first BCMA-targeted ADC approved by the US Food and Drug Administration(FDA), but it was withdrawn from the US market due to the failure of DREAMM-3, a phase 3 clinical trial, to meet its clinical endpoint. However, in recent years, efforts have been made to explore new clinical trial data to support the drug's return to the market. Hungria et al. reported the results of DREAMM-7, a phase 3 trial comparing the efficacy of belamaf, bortezomib and dexamethasone (BVd) and daratumumab, bortezomib and dexamethasone (DVd) [2]. A total of 494 patients were included and randomly divided in a 1:1 ratio. The patients in the belamaf treatment group had significantly longer progression free survival (PFS) than the control group (36.6 months vs. 13.4 months), and also had a higher rate of complete response (CR). At the same time, they found that patients in the belamaf treatment group were more likely to achieve minimal residual disease (MRD) negativity and maintain deep remission [3]. Another study analyzed R/R MM who were at first relapse after 1 prior line of therapy (LOT) in DREAMM-8 trial, which compared the efficacy of belamaf + pomalidomide + dexamethasone(BPd) and

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Table 1 The characteristics of BCMA-targeted therapies regimen

Product	Target	Research design	Indication	Type	Clinical trial name	Clinical trial identifier	Refs.
Belantamab mafodotin	BCMA	BVd vs. DVd	R/R MM	ADC	DREAMM-7	NCT04246047	[2–3]
		BPd vs. PVd	R/R MM		DREAMM-8	NCT04484623	[4]
		Belantamab mafodotin + VRd	NDMM		DREAMM-9	NCT04091126	[5]
Teclistamab	BCMA x CD3	teclistamab + DP	R/R MM	BsAb	MajesTEC-2 TRIMM-2	NCT04722146 NCT04108195	[6]
		teclistamab + lenalidomide/teclistamab alone	NDMM		MajesTEC-4/EMN30	NCT04722146	[7]
		teclistamab + DRd/teclistamab + DVRd	NDMM		MajesTEC-5	NCT05695508	[8]
Cilta-cel	BCMA	Cilta-cel vs. SoC	R/R MM	CAR-T	CARTITUDE-4	NCT04181827	[9]
Anito-cel	BCMA	monotherapy	R/R MM	CAR-T	NA	NCT04155749	[10]
		monotherapy	R/R MM		iMMagine-1	NCT05396885	[11]

R/R: relapsed/refractory; BCMA, b-cell maturation antigen; MM: multiple myeloma; ADC: antibody-drug conjugate; BsAbs: bispecific antibody, CAR-T: chimeric antigen receptor T cell; NDMM: newly diagnosed multiple myeloma; Cilta-cel: ciltacabtagene autoleucel; Anito-cel: anitocabtagene autoleucel; SoC: standard of care; BVd: belantamab mafodotin, bortezomib and dexamethasone; DVd: daratumumab, bortezomib and dexamethasone; BPd: belantamab mafodotin, pomalidomide and dexamethasone; PVd: pomalidomide, bortezomib and dexamethasone; VRd: bortezomib, lenalidomide and dexamethasone; DP: daratumumab and pomalidomide; DRd: daratumumab, lenalidomide and dexamethasone; DVRd: daratumumab, bortezomib, lenalidomide and dexamethasone; NR: not reached

pomalidomide + bortezomib + dexamethasone(PVd). The BPd group showed a longer PFS (NR vs. 13.1 months) compared to the control group [4]. And a higher proportion of patients achieve CR and MRD negativity. Usmani et al. updated the results of the DREAMM-9 trial, which was a phase I dose optimization trial evaluating the efficacy of belamaf plus bortezomib, lenalidomide, and dexamethasone (VRd) in autologous stem cell transplant (ASCT)-ineligible NDMM [5]. 108 patients were divided into 8 cohorts (C1-8) and received different doses and dosing intervals. belamaf plus VRd produced efficient tumor responses in all cohorts.The overall response rate (ORR) was 90%.

Teclistamab

Teclistamab is an FDA-approved BsAb targeting BCMA and CD3. The safety and efficacy data from R/RMM treated with teclistamab in combination with daratumumab and pomalidomide (tec DP) in two phase 1b studies, MajesTEC-2 and TRIMM-2, have been updated [6].After a median follow-up of 25.8 months, the ORR was 88.5%. The patients with cytokine release syndrome (CRS) were all ≤ grade 2, and only one patient had experienced immune effector cell-associated neurotoxicity syndrome (ICANS), which was only grade 1.The results of another phase 3 MajesTEC-4/EMN30 trial showed that teclistamab alone or in combination with lenalidomide was effective as maintenance therapy for NDMM after ASCT [7].The assessable patients were all in MRD negative CR and did not experience ICANS or high-grade CRS. Raab et al. reported the comprehensive results of the induction therapy phase of MajesTEC-5, a phase 2 trial evaluating the efficacy of a combination therapy based on teclistamab in NDMM [8]. After three cycles of treatment, all patients achieved MRD negativity after induction therapy with teclistamab combined with daratumumab, bortezomib, lenalidomide and dexamethasone(DVRd) or DRd, and no patients developed ICANS or ≥ grade 3 CRS.

BCMA CAR-T cell pruducts

The latest results of the phase 3 CARTITUDE-4 trial have been announced, which compared the efficacy differences between Ciltacabtagene Autoleucel (cilta-cel) and standard of care(SoC) in R/RMM [9].At a median follow-up of 34 months, the MRD negative rate of evaluable patients receiving cilta-cel treatment was 89%, compared to 38% in the SoC.In addition, 44% of patients in the cilta-cel group can be assessed as having sustained MRD negative and ≥ CR for at least 12 months, compared to only 8% in the SoC. Bishop et al. reported the latest phase I clinical trial results of Anitocabtagene Autoleucel (anito-cel), in which 38 R/RMM received anito-cel treatment [10]. After a median follow-up of 34 months, the ORR was 100%,the rate of CR/sCR was 79%, and 89% of patients achieved MRD negativity. 36 patients developed CRS, including 1 case with grade 3.The preliminary results of the iMMagine-1 trial have also been reported, which was a phase 2 study of anito-cel for R/RMM [11]. After a median follow-up of 10.3 months, patients had 95% ORR with a CR/sCR rate of 62%. Among the 39 patients eligible for MRD assessment,92% of them achieved MRD negativity. Only 2% of patients experience severe CRS or ICANS.

ASH 2024 presented the prospects and progress of BCMA-targeted therapies for the treatment of MM as summarized in Tables 1 and 2. These exciting clinical trial results bring hope to MM patients, and further research is still ongoing.

Table 2 Outcomes of clinical trials of BCMA-targeted therapies in MM from ASH 2024

References	[2–3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]	[11]
Product	Belantamab mafodotin	Belantamab mafodotin	Belantamab mafodotin	Teclistamab	Teclistamab	Teclistamab	Cital-cel	Anito-cel	Anito-cel
Clinical trial name	DREAMM-7	DREAMM-8	DREAMM-9	MajesTEC-2 TRIMM-2	MajesTEC-4/EMN30	MajesTEC-5	CARTITUDE-4	NA	iMMagine-1
Research design	BVd vs. DVd	BPd vs. PVd	Belantamab mafodotin +VRd	teclisamab + DP	teclistamab + lenalidomide /teclistamab alone	teclistamab + DRd/ teclistamab + DVRd	Cilta-cel vs. SoC	monotherapy	monotherapy
Medium number of prior LOT	NA	1	0	2	NA	0	NA	4	4
High-risk cytogenetics (%)	28	NA	NA	NA	NA	NA	NA	29	NA
Phase	III	III	I	Ib	III	II	III	I	II
Patients (n)	243 vs. 251	82 vs. 77	108	27	94	49	208 vs. 211	38	58
ORR(%)	90.0	NA	90.0	88.5	NA	NA	NA	100.0	95.0
CR(%)	28.6	46.0 vs. 23.0	NA	61.5	100.0	NA	57.0 vs. 12.0	79.0	62.0
mFU(months)	28.2	21.5 vs. 19.8	NA	25.8	14.4,5.0 and 4.9	NA	33.6	34.0	10.3
Survival(months)	mPFS: (36.6 vs. 13.4) mDOR: (35.6 vs. 17.8)	mPFS: (NR vs. 18.5) mDOR: (NR vs. 13.8)	NA	mPFS: 26.5 mDOR: NR	NA	NA	mPFS: NR vs. 37.8 mOS: NR vs. NR	NA	mPFS: NR mOS: NR
MRD negativity(%)	25.0 vs. 10.0	33.0 vs. 5.0	VGPR+:10.0–83.0 CR+:0.0–75.0	NA	100.0	100.0	89.0 vs. 38.0	89.0	92.0
Grade ≥ 3 CRS(%)	NA	NA	NA	0.0	0.0	0.0	0.0	3.0	2.0
Grade ≥ 3 ICANS(%)	NA	NA	NA	0.0	0.0	0.0	0.0	5.0	2.0
Clinical trial identifier	NCT04246047	NCT04484623	NCT04091126	NCT04722146 NCT04108195	NCT04722146	NCT05695508	NCT04181827	NCT04155749	NCT05396885

ORR: overall response rate; CR: complete response; LOT: line of therapy; mFU: median follow-up; mPFS: median progression-free survival; mOS: median overall survival; mDOR: median duration of response; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome; NR: not reached; NA, not available; Cilta-cel: ciltacabtagene autoleucel; Anito-cel: anitocabtagene autoleucel; SoC: standard of care; BVd: belantamab mafodotin, bortezomib and dexamethasone; DVd: daratumumab, bortezomib and dexamethasone; BPd: belantamab mafodotin, pomalidomide and dexamethasone; PVd: pomalidomide, bortezomib and dexamethasone; VRd: bortezomib, lenalidomide and dexamethasone; DP: daratumumab and pomalidomide; DRd: daratumumab, lenalidomide and dexamethasone; DVRd: daratumumab, bortezomib, lenalidomide and dexamethasone

Abbreviations

BCMA	B cell maturation antigen
ASH	American Society of Hematology
ADC	Antibody-drug conjugat
BsAbs	Bispecific antibodies
CAR	Chimeric antigen receptor
R/RMM	Relapsed/refractory multiple myeloma
NDMM	Newly diagnosed multiple myeloma
FDA	Food and drug administration
PFS	Progression free survival
CR	Complete response
MRD	Minimal residual disease
LOT	Line of therapy
ASCT	Autologous stem cell transplantation
ORR	Overall response rate
CRS	Cytokine release syndrome
ICANS	Immune effector cell-associated neurotoxicity syndrome
Cilta-cel	Ciltacabtagene autoleucel
SoC	Standard of care
Anito-cel	Anitocabtagene autoleucel

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Author contributions
ZX and HL designed the study. HZ and HX drafted the manuscript. WZ, CL and RP prepared the tables. All authors participated in the process of drafting and revising the manuscript. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable for this summary.

Consent for publication
Not applicable for this summary.

Competing interests
The authors declare no competing interests.

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