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BCMA-targeted CAR-T cell therapies in relapsed and/or refractory multiple myeloma: latest updates from 2023 ASCO Annual Meeting

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Abstract

Treatment of relapsed and/or refractory multiple myeloma (RRMM) utilizing the novel therapeutic target of the B-cell maturation antigen (BCMA) has demonstrated incredible results, leading to regulatory approval of BCMA-targeted chimeric antigen receptor (CAR)-T cell therapies in RRMM. With now two approved BCMA-targeted CAR-T cell therapies, investigators globally are working to build off and improve upon BCMA-targeted therapies. We discuss long-term data from the pivotal study that led to CAR-T approval, a phase 3 trial supporting their use in earlier lines, and novel manufacturing platforms to decrease vein-to-vein time. We highlight five key abstracts from the 2023 ASCO Annual Meeting that showcase these exciting updates in BCMA-directed CAR-T cell therapies in RRMM.

Keywords CAR-T, BCMA, MM

To the editor

B-cell maturation antigen (BCMA)-targeted chimeric antigen receptor (CAR)-T cell therapy revolutionized treatment of relapsed and/or refractory multiple myeloma (RRMM) [1–4]. The deep and durable responses with manageable safety profiles led to US Food and Drug Administration regulatory approval of idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel) in 2021 and 2022, respectively. We summarized the important updates in BCMA CAR-T therapies for RRMM from the 2023 ASCO Annual Meeting.

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Approved BCMA-targeted CAR-T cell therapy in RRMM

Long-terms results of BCMA-targeted CAR-T trials were reported at ASCO 2023. Dr. Mi reported the ≥ 5-year follow-up data from LEGEND-2 [5], the first-in-human phase 1 study of LCAR-B38M CAR-T conducted in China, the longest follow-up for any BCMA-targeted therapy study (Table 1). Overall response rate (ORR), complete remission (CR) rate, and median progression free survival (PFS) were unchanged compared to prior reports [4]. At 65.4 months median follow-up, median overall survival (OS) was 55.8 months and 18% of patients with RRMM were alive and disease-free. Those without progressive disease were more likely to be less heavily pre-treated and have good performance status [5]. No new toxicities were reported since 48-month follow-up [4], which previously showed 9.5% grade ≥ 3 cytokine release syndrome (CRS) and one reversible grade 1 immune effector cell-associated neurotoxicity syndrome (ICANS) event (Table 2).

Dr. Lin reported the final results of CARTITUDE-1 [6], a phase 1b/2 study of cilta-cel in heavily pretreated (median 6 lines of therapy) patients with

Table 1 Properties of BCMA-targeted CAR-T cell therapies in MM

Author	Agent	Clinical Trial Identifier	Phase	Target	Co-stimulatory domain/ signaling domain	Mechanism	scFV	Cell source	References
Munshi et al.	ide-cel	NCT03361748	2	BCMA	4-1BB/CD3ζ	CAR-T	Chimeric mouse	Autologous	[1]
Mi et al.	cilta-cel	NCT03758417	2	Dual-binding BCMA	4-1BB/CD3ζ	CAR-T	Chimeric llama	Autologous	[3]
Mi et al.	LCAR-B38M CAR-T	NCT03090659	1	Dual-binding BCMA	4-1BB/CD3ζ	CAR-T	Chimeric llama	Autologous	[4, 5]
Lin et al.	cilta-cel	NCT03548207	1b/2	Dual-binding BCMA	4-1BB/CD3ζ	CAR-T	Chimeric llama	Autologous	[2, 6]
Rodriguez-Otero et al.	ide-cel	NCT03651128	3	BCMA	4-1BB/CD3ζ	CAR-T	Chimeric mouse	Autologous	[7]
Dhakal et al.	cilta-cel	NCT04181827	3	Dual-binding BCMA	4-1BB/CD3ζ	CAR-T	Chimeric llama	Autologous	[8, 9]
Sperling et al.	PHE885	NCT04318327	1	BCMA	4-1BB/CD3ζ	CAR-T	Human	Autologous	[10]
Du et al.	GC012F	NCT04236011; NCT04182581	1	BCMA/CD19	4-1BB/CD3ζ	CAR-T	Not specified	Autologous	[11]

BCMA B-cell maturation antigen, *CAR* chimeric antigen receptor, *scFV* single-chain variable fragment, *cilta-cel* ciltacabtagene autoleucel, *ide-cel* idecabtagene vicleucel

RRMM (Table 1). Median PFS was an unprecedented 34.9 months, a benefit not seen with any other therapy in this setting. At 3-year follow-up, an estimated 62.9% of patients were alive and almost half remained in remission. No new CRS or ICANS reported (Table 2). Patients will continue to be followed for safety and survival in the 15-y CARTINUE long-term study (NCT05201781; MMY4002).

Moving BCMA-targeted CAR-T cell therapy into earlier lines

With the groundbreaking approvals of BCMA-targeted CAR-T cell therapies for RRMM, KarMMa-3 [7] and CARTITUDE-4 [8, 9] showed promise in moving these therapies into earlier lines. The phase 3 KArMMa-3 trial of ide-cel [7] in patients with 2–4 prior lines of therapy showed a 51% reduction in risk of disease progression or death versus standard of care (SOC) with a similar toxicity profile compared to previous reports with no new safety signals detected.

Dr. Dhakal presented the phase 3, randomized, controlled trial of cilta-cel [8, 9] in patients with 1–3 prior lines of therapy who were lenalidomide refractory. Cilta-cel reduced the risk of disease progression or death versus SOC by 74%, with benefits seen across all subgroups. Cilta-cel also improved ORR, rate of CR or better, and overall minimal residual disease (MRD) negativity. The side effects with cilta-cel were manageable with appropriate supportive care, and overall lower incidence and severity of CRS, ICANS, cytopenia, and other neurotoxicities were observed compared to CARTITUDE-1 (Table 2). These results are suggestive of the cilta-cel being a new standard of care for patients with lenalidomide-refractory myeloma, after the first relapse. Use in earlier LOTs is currently under evaluation in CARTITUDE-5 (NCT04923893) and Emagine/CARTITUDE-6 (EMN28; NCT05257083).

Shorter manufacturing for BCMA-targeted CAR-T cell therapy

Several trials are utilizing novel platforms to decrease vein-to-vein time. Dr. Sperling presented the updated phase 1 results of PHE885, a BCMA-targeted CAR-T cell therapy in RRMM (Table 1) [10]. Utilization of a novel T-Charge™ platform allows for < 2-day manufacturing, with a median of 16 days from apheresis to lymphodepletion. PHE885 achieved 100% ORR at active doses with 10% grade 3 CRS and 6% grade 3 neurotoxicity (Table 2). A phase 2 study in RRMM is currently enrolling patients (NCT05172596).

Dr. Qiang presented the phase 1 results of BCMA/CD19 dual-targeting FasT CAR-T GC012F in RRMM (Table 1) [11]. The FasTCAR platform allows for 22–26 h manufacturing. In a predominately high-risk population, ORR was 93.1% with 100% MRD negativity and a median PFS of 38 months (Table 2). GC012F phase 1b/2 trials are starting in the USA and China (NCT05850234).

In conclusion, as highlighted in Tables 1 and 2, the 2023 ASCO Annual Meeting provided many innovations surrounding BCMA-targeted CAR-T cell therapy in RRMM. Translating these impressive clinical trial results, real-world access for patients will be essential.

Table 2 Outcomes of BCMA-targeted CAR-T cell clinical trials in MM

Author	Agent	Clinical Trial Identifier	Patients (n)	Medium number of prior LOT (range)	ISS Stage 3	High-risk cytogenetics (%)	ORR (%)	≥CR (%)	Median PFS (months)	Median OS (months)	Hazard Ratio for Disease Progression or Death	Grade ≥3 CRS (%)	Grade ≥3 Neurotoxicity (%)	References
Munshi et al.	Ide-cel	NCT03361748	128	6 (3–16)	16.0%	35.0	73.0	33.0	8.8	Immature	–	5.0	3.0	[1]
Mi et al.	Cilta-cel	NCT03758417	48	4 (3–9)	18.8%	43.8	89.6	77.1	Not reached	Not reached	–	35.4	0.0	[3]
Mi et al.	LCAR-B38M CAR-T	NCT03090659	74	3 (1–9)	28.4%	35.7	87.8	73.0	18	55.8	–	9.5	0.0	[4, 5]
Lin et al.	Cilta-cel	NCT03548207	97	6 (4–8)	14.0%	24.0	97.9	82.5	34.9	Not reached	–	5.2	12.4	[2, 6]
Rodriguez-Otero et al.*	Ide-cel	NCT03651128	254	3 (2–4)	12.0%	42.0	71.0	39.0	13.3	Immature	0.49	5.0	3.0	[7]
Dhakal et al.*	cilta-cel	NCT04181827	208	2 (1–3)	5.8%	59.4	84.6	73.1	Not reached	Immature	0.26	1.1	2.8	[8, 9]
Sperling et al.	PHE885	NCT04318327	50	4 (2–10)	54%†	36.0	98.0	41.0	–	–	–	10.0	6.0	[10]
Du et al.	GC012F	NCT04236011; NCT04182581	29	5 (2–9)	–	90.0	93.1	82.8	38	–	–	7.0	0.0	[11]

BCMA B-cell maturation antigen, *CAR* chimeric antigen receptor, *cilta-cel* ciltacabtagene autoleucel, *ide-cel* idecabtagene vicleucel, *LOT* lines of treatment, *ORR* overall response rate, ≥*CR* complete response or better, *PFS* progression free survival, *OS* overall survival, *CRS* cytokine release syndrome

*Data only for CAR-T arm

† ISS Stage 2/3

–, not assessed by study

Abbreviations

BCMA	B-cell maturation antigen
CAR	Chimeric antigen receptor
RRMM	Relapsed and/or refractory multiple myeloma
Ide-cel	Idecabtagene vicleucel
Cilta-cel	Ciltacabtagene autoleucel
ORR	Overall response rate
CR	Complete remission
PFS	Progression free survival
OS	Overall survival
CRS	Cytokine release syndrome
ICANS	Immune effector cell-associated neurotoxicity
SOC	Standard of care

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This is not applicable for this summary.

Author contributions
JFW designed the study, drafted the manuscript, and prepared the tables. JFW and BD participated in the process of drafting and revising the manuscript. JFW and BD read and approved the final manuscript.

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Availability of data and materials
The material supporting the conclusion of this study has been included within the article.

Declarations

Ethics approval and consent to participate
This is not applicable for this summary.

Consent for publication
This is not applicable for this summary.

Competing interests
The authors declare no competing interests.

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