Teclistamab *versus* B-cell maturation antigen-targeting chimeric antigen receptor T-cell therapy in multiple myeloma: a comparative effectiveness analysis

Despite recent advances in the treatment of multiple myeloma, relapse remains common and incurable, with patients exposed to three classes of treatment having a 12-month progression-free survival of 19.9% and an overall survival of 51.8%.[1] Two B-cell maturation antigen (BCMA) chimeric antigen receptor (CAR) T-cell therapies, ciltacabtagene autoleucel (cilta-cel) and idecabtagene vicleucel (ide-cel), were initially approved by the Food and Drug Administration for patients with relapsed and refractory MM who have received four or more lines of therapy. The label has been revised, and cilta-cel is now approved for use after one line of therapy and ide-cel for triple-class-exposed myeloma patients.[2-4] Similarly, BCMA bispecifics such as teclistamab and elranatamab have received accelerated Food and Drug Administration approval for relapsed and refractory myeloma after four or more lines of therapy and are currently being investigated for use in earlier lines of treatment.[5,6] While BCMA-directed therapies are becoming a staple in myeloma, there are currently no prospective or retrospective studies that compare BCMA bispecific and CAR T-cell therapies. To fill this gap, we performed comparative effectiveness analyses between BCMA CAR T-cell therapy and a BCMA bispecific – teclistamab – using information in a large de-identified database.

We conducted a propensity score-matched retrospective cohort study utilizing the TriNetX US Collaborative Network.[7,8] This network is a collaborative electronic healthcare record database that contains the records of over 100 million patients from more than 60 healthcare organizations in the USA. The TriNetX database complies with the General Data Protection Regulation and Health Insurance Portability & Accountability Act (HIPPA).[7] Several institutional review boards approved the use of this database and granted a waiver of informed consent, as the platform contains only aggregated data and no individual-level information.[7] It provides real-time data, including patients' demographics, diagnoses based on the International Classification of Diseases 10th Revision Codes (ICD-10), medications prescribed, procedures conducted, and laboratory tests.[7]

From within the database, we extracted patients aged 18 to 90 years old diagnosed with MM and administered CAR T-cell therapy (ide-cel or cilta-cel) or teclistamab between January 2021 and January 2024. We excluded patients who received both CAR T cells and teclistamab. The patients were divided into two cohorts: (i) those who received CAR T cells and (ii) those who received teclistamab. The two cohorts were propensity score-matched in a 1:1 ratio by using the greedy nearest-neighbor matching method with preselected characteristics, including demographics, underlying disease, and type of previously administered MM therapy, applying a caliper width of 0.1. The index date was set as the first date of either CAR T-cell or teclistamab administration. Standardized mean differences were utilized to assess whether the two cohorts were well balanced, with a standardized mean difference less than 0.2 indicative of a small difference.[9] Survival and Cox-regression analyses were conducted, and the hazard ratio (HR) and 95% confidence interval (95% CI) of each prespecified outcome were calculated with a P value of <0.05 considered statistically significant. All analyses were conducted using data available up to August 31, 2024, from 65 healthcare organizations in the USA, utilizing the TriNetX in-built function and RStudio (R4.4.1).

We assessed all-cause mortality, cytokine release syndrome (CRS), and immune effector cell-associated neurotoxicity syndrome (ICANS) during a 12-month follow-up. Additionally, we measured and compared sepsis, pneumonia, and urinary tract infection rates. We set joint pain as a falsification outcome to assess possible unmatched biases and confounders. The ICD-10 and TriNetX codes used to extract these data are summarized in *Online Supplementary Table S1*.

We included 427 patients in the CAR T-cell cohort (294 ide-cel users and 133 cilta-cel users) and 517 patients in the teclistamab cohort. Before propensity score matching, the CAR T-cell cohort demonstrated lower risk features than the teclistamab cohort. The CAR T-cell cohort had a lower mean age (64.1 *vs*. 68.7 years), lower serum β_2 microglobulin concentration (4.1 *vs*. 5.2 mg/L), lower serum lactate dehydrogenase concentration (234.3 *vs*. 272.4 U/L), and higher serum albumin level (3.6 *vs*. 3.5 mg/dL). Additionally, the CAR T-cell cohort included more white patients (74.7% *vs*. 58.8%). After matching, each cohort consisted of 262 patients. The matched two cohorts had a similar mean age (65.8 *vs*. 65.9 years) and similar levels of serum β_2 microglobulin (5.0 *vs*. 4.3 mg/L), serum lactate dehydrogenase (230.1 *vs*. 249.5 U/L), and serum albumin (3.6 *vs*. 3.6 mg/dL) (Table 1).

Compared to the teclistamab cohort, the CAR T-cell cohort had a lower risk of all-cause mortality at 3 months (HR=0.36, 95% CI: 0.20-0.65), 6 months (HR=0.51, 95%

CI: 0.32-0.81), and 1 year (HR=0.53, 95% CI: 0.35-0.78) of follow-up (Figure 1A). The CAR T-cell cohort had a higher risk of CRS (1-month HR=1.47, 95% CI: 1.10-1.97; 1-year HR=1.40, 95% CI: 1.06-1.84) (Figure 1B). Most cases of CRS were diagnosed within 1 month of therapy initiation, with 108 out of 120 CRS cases in the CAR T-cell cohort and 76 out of 88 CRS cases in the teclistamab cohort occurring within the first month of therapy. The risk of ICANS was similar with the two therapies (1-month HR=1.27, 95% CI: 0.80-2.01; 1-year HR=1.12, 95% CI: 0.74-1.69), with most cases also diagnosed within 1 month of therapy initiation (41 out of 49 in the CAR T-cell cohort and 32 out of 42 in the teclistamab cohort) (Figure 1C). Additionally, the CAR T-cell cohort had a lower risk of infection compared to the teclistamab cohort, with the risk of pneumonia being significantly lower that of the teclistamab cohort (HR=0.61, 95% CI: 0.41-0.91) but no significant differences in the risks of sepsis and urinary tract infection (Table 2). The rates of the falsification outcome, joint pain, were similar in the two cohorts at

Table 1. Baseline characteristics of the patients who received B-cell maturation antigen chimeric antigen receptor T-cell therapy and those treated with teclistamab, before and after propensity score matching.

Characteristics	Before propensity score matching			After propensity score matching		
	CAR T-cell user N=427	Teclistamab user N=517	SMD	CAR T-cell user N=262	Teclistamab user N=262	SMD
Demographics						
Age at index in years, mean ± SD	64.1±8.9	68.7±9.9	0.48	65.8±8.1	65.9±10.2	0.01
Female, N (%)	180 (42.2)	242 (46.8)	0.09	113 (43.1)	117 (44.7)	0.03
Male, N (%)	247 (57.8)	241 (46.6)	0.23	149 (56.9)	145 (55.3)	0.03
Asian, N (%)	10 (2.3)	15 (2.9)	0.04	10 (3.8)	10 (3.8)	<0.01
Black or African American, N (%)	76 (17.8)	107 (20.7)	0.07	52 (19.8)	47 (17.9)	0.05
Hispanic or Latino, N (%)	17 (4.0)	30 (5.8)	0.08	10 (3.8)	14 (5.3)	0.07
White, N (%)	319 (74.7)	304 (58.8)	0.34	184 (70.2)	186 (71.0)	0.02
Laboratory values, mean ± SD						
Hemoglobin, g/dL	10.4±2.0	9.9±2.0	0.26	10.3±1.9	10.3±2.0	0.04
Serum albumin, g/dL	3.6±0.5	3.5±0.6	0.25	3.6±0.5	3.6±0.5	0.06
Serum β_2-microglobulin, mg/L	4.1±6.7	5.2±4.5	0.2	5.0±8.3	4.3±4.4	0.1
Serum creatinine, mg/dL	1.0±1.1	1.4±1.2	0.3	1.1±1.4	1.3±1.1	0.13
Serum lactate dehydrogenase, U/L	234.3±197.6	272.4±424.6	0.11	230.1±207.7	249.5±189.8	0.1
Body mass index, kg/m^2	28.3±5.8	27.7±5.8	0.1	28.1±5.9	27.9±6.0	0.02
Treatment for multiple myeloma, N (%)						
Autologous stem cell transplantation	167 (39.1)	152 (29.4)	0.21	102 (38.9)	93 (35.5)	0.07
Dexamethasone	371 (86.9)	499 (96.5)	0.35	248 (94.7)	248 (94.7)	<0.01
Lenalidomide	212 (49.6)	299 (57.8)	0.16	148 (56.5)	147 (56.1)	0.01
Thalidomide	52 (12.2)	60 (11.6)	0.02	37 (14.1)	36 (13.7)	0.01
Bortezomib	163 (38.2)	234 (45.3)	0.14	105 (40.1)	105 (40.1)	<0.01
Ixazomib	49 (11.5)	82 (15.9)	0.13	32 (12.2)	33 (12.6)	0.01
Carfilzomib	131 (30.7)	183 (35.4)	0.1	82 (31.3)	87 (33.2)	0.04
Pomalidomide	215 (50.4)	288 (55.7)	0.11	145 (55.3)	145 (55.3)	<0.01
Daratumumab	166 (38.9)	206 (39.8)	0.02	101 (38.6)	101 (38.6)	<0.01
Underlying comorbidities, N (%)						
Anemia, unspecified	240 (56.2)	322 (62.3)	0.12	156 (59.5)	147 (56.1)	0.07
Neutropenia	276 (64.6)	294 (56.9)	0.16	165 (63.0)	157 (59.9)	0.06
Immunodeficiency, unspecified	158 (37.0)	223 (43.1)	0.13	108 (41.2)	106 (40.5)	0.02
Type 2 diabetes mellitus	98 (23.0)	145 (28.0)	0.12	62 (23.7)	59 (22.5)	0.03
Malnutrition	85 (19.9)	130 (25.1)	0.13	51 (19.5)	57 (21.8)	0.06
Hypertensive diseases	265 (62.1)	395 (76.4)	0.31	178 (67.9)	178 (67.9)	<0.01
Ischemic heart diseases	100 (23.4)	151 (29.2)	0.13	64 (24.4)	67 (25.6)	0.03
Heart failure	81 (19.0)	133 (25.7)	0.16	57 (21.8)	49 (18.7)	0.08
Cerebral infarction	16 (3.7)	28 (5.4)	0.08	12 (4.6)	14 (5.3)	0.04
Chronic lower respiratory tract diseases	98 (23.0)	121 (23.4)	0.01	62 (23.7)	62 (23.7)	<0.01
Diseases of liver	66 (15.5)	79 (15.3)	<0.01	39 (14.9)	42 (16.0)	0.03
Systemic connective tissue disorders	17 (4.0)	32 (6.2)	0.1	10 (3.8)	16 (6.1)	0.11
Disorder of continuity of bone	131 (30.7)	177 (34.2)	0.08	89 (34.0)	90 (34.4)	0.01

The TriNetX database does not report exact values for sample sizes less than 10 to protect identity. Laboratory values reported were from the most recent results before initiating either of the therapies. CAR T-cell: chimeric antigen receptor T-cell; SMD: standardized mean difference; SD: standard deviation.

the 1-year follow-up (HR=0.94, 95% CI: 0.68-1.31).
The CAR T-cell cohort was further divided into ide-cel and cilta-cel cohorts and then compared to the teclistamab cohort after propensity score matching. Compared to the teclistamab cohort, the ide-cel cohort showed a lower risk of all-cause mortality at the 1-year follow-up (HR=0.53, 95% CI: 0.34-0.81). The risk of CRS was higher in the ide-cel cohort (HR=1.39, 95% CI: 1.03-1.87), and

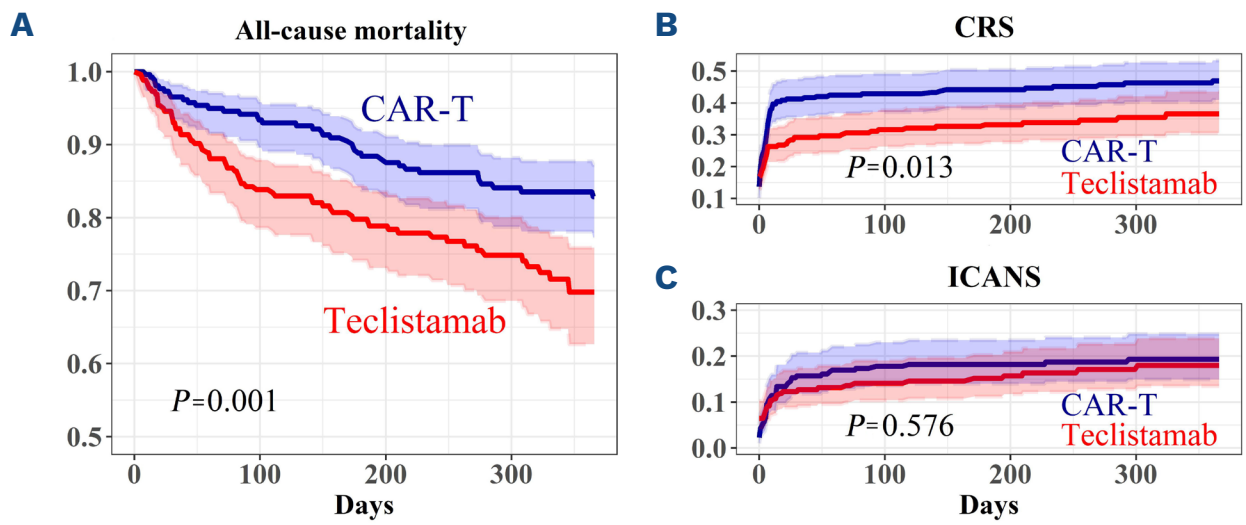

Figure 1. Kaplan-Meier survival curve for all-cause mortality, cytokine release syndrome, and immune effector cell-associated neurotoxicity syndrome comparing the chimeric antigen receptor T-cell user cohort with the teclistamab cohort after propensity score matching. (A) All-cause mortality. (B) Cytokine release syndrome. (C) Immune effector cell-associated neurotoxicity syndrome. All-cause mortality for chimeric antigen receptor T-cell recipients *versus* teclistamab recipients (hazard ratio [HR], 95% confidence interval [95% CI], N dead/N in cohort) at 1 month: HR=0.55 (95% CI: 0.24-1.24), 9/262 *vs*. 16/262; at 3 months: HR=0.36 (95% CI: 0.20-0.65), 15/262 *vs*. 39/262; at 6 months: HR=0.51 (95% CI: 0.32-0.81), 28/262 *vs*. 49/262; and at 12 months: HR=0.53 (95% CI: 0.35-0.78), 40/262 *vs*. 64/262. CAR-T: chimeric antigen receptor T-cell therapy; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome.

Table 2. One-year comparison of all-cause mortality, cytokine release syndrome, and immune effector cell-associated neurotoxicity syndrome between the B-cell maturation antigen chimeric antigen receptor T-cell and teclistamab cohorts after propensity score matching.

Outcomes	BCMA CAR T-cell users		Teclistamab users		Hazard ratio (95% CI)	*P* log-rank
	Pts at risk, N	Cases, N	Pts at risk, N	Cases, N		
CAR T-cell cohort, total						
All-cause mortality	262	40	262	64	0.53 (0.35-0.78)	0.001
CRS	262	120	262	88	1.40 (1.06-1.84)	0.013
ICANS	262	49	262	42	1.12 (0.74-1.69)	0.576
Sepsis	262	27	262	33	0.72 (0.44-1.21)	0.212
Pneumonia	262	44	262	58	0.61 (0.41-0.91)	0.013
Urinary tract infection	262	23	262	27	0.72 (0.41-1.25)	0.242
Idecabtagene vicleucel cohort						
All-cause mortality	214	34	214	54	0.53 (0.34-0.81)	0.003
CRS	214	104	214	76	1.39 (1.03-1.87)	0.024
ICANS	214	34	214	43	0.74 (0.47-1.17)	0.194
Sepsis	214	23	214	35	0.56 (0.33-0.95)	0.030
Pneumonia	214	29	214	51	0.43 (0.27-0.69)	<0.001
Urinary tract infection	214	17	214	26	0.52 (0.28-0.95)	0.031
Ciltacabtagene autoleucel cohort						
All-cause mortality	101	9	101	24	0.38 (0.18-0.80)	0.007
CRS	101	48	101	33	1.52 (0.97-2.37)	0.051
ICANS	101	23	101	17	1.35 (0.72-2.53)	0.338
Sepsis	101	12	101	15	0.76 (0.35-1.61)	0.467
Pneumonia	101	22	101	23	0.86 (0.48-1.55)	0.621
Urinary tract infection	101	12	101	10	1.11 (0.48-2.58)	0.802

BCMA: B-cell maturation antigen; CAR: chimeric antigen receptor; Pts: patients; 95% CI: 95% confidence interval; CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome.

the risk of ICANS remained similar in the two cohorts (HR=0.74, 95% CI: 0.47-1.17). Similar results were observed when cilta-cel was compared to teclistamab for all-cause mortality (HR=0.38, 95% CI: 0.18-0.80), CRS (HR=1.52, 95% CI: 0.97-2.37), and ICANS (HR=1.35, 95% CI: 0.72-2.53), although the difference for CRS was not statistically significant (Table 2).

Our study results align with those of a recent meta-analysis[10] showing that CAR T-cell therapy produced superior complete response (0.54 *vs*. 0.35) and overall response (0.83 *vs*. 0.65) rates compared to those produced by bispecifics, although with a higher risk of CRS (0.83 *vs*. 0.59). However, the meta-analysis was limited by high heterogeneity (I^2 ~ 90%), whereas our study offers a real-world perspective with overall survival comparisons. Our findings are also consistent with results from pivotal trials in relapsed and refractory MM. For example, the reported outcomes in the KarMMa-3 trial[3,11] (ide-cel) were a median overall survival of 41.4 months, overall response rate of 71%, CRS rate of 80% (5% grade ≥3), and neurotoxicity rate of 15%. Patients in the MajesTEC-1 trial[5] (teclistamab) showed a median overall survival of 22.2 months, 63% overall response rate, 72.1% incidence of CRS (0.6% grade ≥3), and 14.5% incidence of neurotoxicity. In the CARTITUDE-1 trial[12] (cilta-cel) the median overall survival had not been reached, with a 97% overall response rate, 95% CRS rate (5% grade ≥3), and 15% incidence of neurotoxicity. Additionally, our study found a lower, though non-significant, risk of infections in the CAR T-cell cohort, consistent with recent research comparing infection risks between receipients of CAR T-cell and bispecific therapies.[13]

Our study should be interpreted with caution because of several limitations. First, the observed improved survival in the CAR T-cell cohort could be attributed to multiple factors, including greater treatment efficacy, differences in disease aggressiveness (as patients with more severe disease may have received bispecifics), and healthcare disparities.[14,15] Additionally, manufacturing delays for CAR T-cell therapy and the potential exclusion of severely ill patients who may not ultimately receive treatment could introduce a selection bias. Furthermore, by excluding patients who received both therapies, our study did not account for those who switched between treatments or used bispecifics as bridging therapy. However, multiple studies have demonstrated the superior efficacy of CAR T-cell therapy, aligning with our findings. Second, we were unable to risk-stratify MM because of the lack of information on cytogenetics, fluorescence *in situ* hybridization, and mutations. We also could not determine how many patients were enrolled in clinical trials, assess Eastern Cooperative Oncology Group performance status, evaluate conventional endpoints such as progression-free survival or response rate, or determine the time to treatment switch or prior therapy lines, as these data were unavailable. However, we utilized the propensity score matching and falsification outcome methods to minimize confounding factors. Additionally, we matched the previously used MM medications, and most patients were likely to have been exposed to three classes of medication. Third, reliance on ICD-10 and TriNetX codes may introduce biases due to misdiagnosis, miscoding, or the inability to accurately assess the severity of toxicities; however, these biases are likely similar across the CAR T-cell and teclistamab cohorts, minimizing their impact on risk estimation. Lastly, our analysis was limited to teclistamab, as insufficient data were available for other BCMA bispecifics, such as elranatamab and linvoseltamab. Despite its limitations, our study lays a strong foundation for further research with more granular data and a broader population.

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Disclosures

No conflicts of interest to disclose.

Contributions

JS and AKM conceived and designed the study and drafted the manuscript. YCha and JS acquired, analyzed or interpreted the

data. YCha and JS performed the statistical analysis. AKM and TP provided supervision. All the authors reviewed the manuscript.

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Data-sharing statement

This study utilizes de-identified, stratified, population-level aggregate data generated by the TriNetX platform. Due to the privacy of the data, we did not use patient-level data and, therefore, they cannot be shared.

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