Total Cost of Care and Adverse Effects Assessment of Bispecific T-cell Engagers and Chimeric Antigen Receptor T-cell Therapies for Relapsed Refractory Follicular Lymphoma

S. Ndujiuba, PharmD, BCOP[1]; A. Wilson, PharmD[1]; D. Eckwright, PharmD, MHI[1]; A. Kim, PharmD, BCOP[1]. [1]Prime Therapeutics LLC, Eagan, MN, United States

Background

- The incidence of follicular lymphoma (FL) is approximately 2.4 cases per 100,000 people per year and is commonly diagnosed in people ages 65–74.[1] FL is the second most common subtype of slow-growing non-Hodgkin lymphoma (NHL) and accounts for about 30% of newly diagnosed NHL cases.[2] Unfortunately, FL is difficult to cure, with most patients experiencing disease relapses.[3]
- Currently for FL treatment, 3 chimeric antigen receptor T-cell (CAR T) products are US Food and Drug Administration (FDA) approved, with the first axicabtagene ciloleucel (Yescarta) approved in 2021, and 2 bispecific T-cell engagers (BiTEs), starting with mosunetuzumab (Lunsumio) in 2022.[4]
- CAR T and BiTEs are both approved in the third-line relapsed refractory follicular lymphoma (RRFL) setting. The treatment landscape is marked by a debate about which one to use first.[1,5]
- Unlike other hematologic cancers, high response rate, durable response, low toxicity, and avoidance of lymphodepleting chemotherapy make BiTEs preferred over CAR T in many RRFL cases.[5,6] In addition, BiTEs provide ease of access due to off-the-shelf availability, increased potential for outpatient administration, and lower rates of serious side effects like cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).[5-7] These attributes allow for BiTEs' widespread use and potentially lower cost.
- In a survey of RRFL patients and FL treating providers, even though progression-free survival (PFS) was the most important factor for both, they would accept lower PFS for decreased adverse events (AEs).[8]
- In this study, we identified the potential total cost of care (TCOC) and side effect differences between BiTE and CAR T therapy using real-world data.

Objective

Our objective is to compare the 12-month TCOC and AE incidence for patients treated with CAR T versus BiTE therapy in RRFL.

Methods

- This retrospective, observational cohort study analyzed integrated medical and pharmacy claims from 17 million commercial, 1.4 million Medicaid, and 950,000 Medicare members across the United States, covering the period from December 1, 2021, to March 31, 2024.
- Study inclusion was limited to members newly initiating BiTE or CAR T therapy for RRFL, defined as no BiTE or CAR T claims in the 6-month pre-index period. Index drugs included mosunetuzumab (BiTE) and axicabtagene ciloleucel, tisagenlecleucel, and lisocabtagene maraleucel (CAR Ts). Members were required to have continuous enrollment 6 months before and after the index date.
- Claims were identified using product-specific drug codes (HCPCS, GPI, NDC, ICD-10-PCS) and ICD-10 diagnosis codes. AEs, including CRS and ICANS, were identified using ICD-10 codes (D89.83, T80.82, G90.20) and tocilizumab-specific drug codes.
- TCOC was assessed using all member claims and categorized into clinically relevant groups:
  - Index Therapy: mosunetuzumab (BiTE); axicabtagene ciloleucel, tisagenlecleucel, lisocabtagene maraleucel (CAR Ts)
  - RRFL Treatment: alkylating agents, anthracyclines, anti-CD19/CD20/CD79b monoclonal antibodies, BTK inhibitors, immunomodulators, PD-1 inhibitors, proteasome inhibitors, vinca alkaloids
  - Lymphodepletion and CAR T Preparation: fludarabine and/or cyclophosphamide within 45 days prior to CAR T administration
  - Supportive Care: immune globulin, erythropoiesis-stimulating agents, granulocyte-colony stimulating factors, low-molecular-weight heparin, steroids
  - AE: claims for CRS and ICANS using ICD-10 and drug codes
  - RRFL Other: all other claims with RRFL ICD-10 codes not included above
  - Other: all remaining non-RRFL claims
- Baseline characteristics assessed included age, sex, rural-urban status commuting area (RUCA), and insurance type. Nonparametric and association tests were used to evaluate the relationship between the index drug and outcomes.
- Epcoritamab-bysp (Epkinly), a BiTE therapy, was approved after the study period, on June 26, 2025, and therefore was not included.

Table 1
Baseline Characteristics

	BiTE Cohort (N=30)		CAR T Cohort (N=31)	
	Mean/%	S/D Count	Mean/%	SD/Count
Line of business				
Commercial	50%	15	71%	22
Medicare	50%	15	29%	9
Age				
	66	12.9	61	8.5
Gender				
Female	33%	10	48%	15
Male	67%	20	50%	16
Member RUCA				
Rual	13%	4	10%	3
Suburban	13%	4	16%	5
Urban	73%	22	74%	23

BiTE = bispecific T-cell engager, CAR T = chimeric antigen receptor T-cell, RUCA = rural-urban commuting area

Figure 1
Site of Care at Index Date

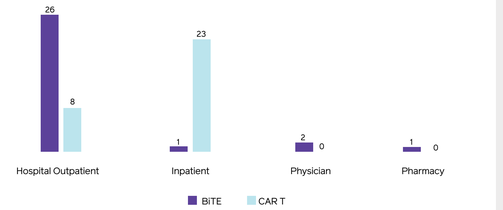

Figure 2
Average Allowed Amount by Category and Line of Business

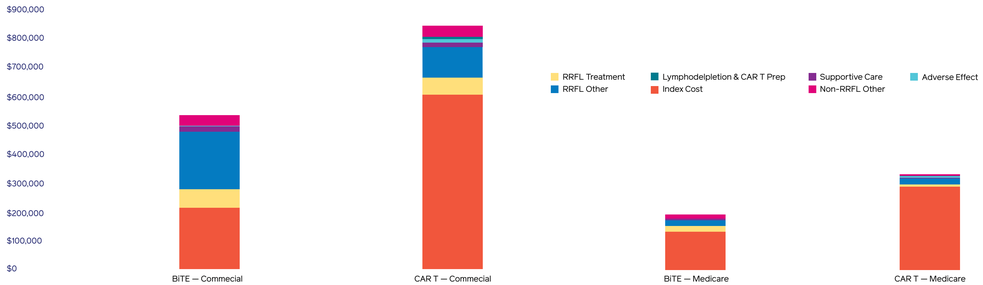

Table 2
Members with Adverse Effects of Interest

Cohort	At Least 1 AE	CRS	ICANS	Other Immune Effector Toxicity
BiTE (N=7)	23%	7	1	0
CAR T (N=16)	52%	12	8	4

The percentage is a count of distinct members.
The CRS, ICANS, and Other Immune Effector Toxicity is a claims count.

Table 3
Non-Index Relapsed Refractory Follicular Lymphoma Drug Utilization Post Index

	BiTE	CAR T	Odds Ratio	Test Statistic	P-Value	95% CI
Members with ≥1 non-index RRFL treatment	6	3	2.33	1.12	0.3	0.53-10.35
Member-drug claims	15	7				
Distinct drugs	8	6				

Reference group: BiTE cohort

Results

- A total of 30 BiTE and 31 CAR T members met all study-inclusion criteria.
- Only 1 case was identified in Medicaid, which was removed from the analysis.
- The mean age across cohorts was 63 years, 41% were female, 61% had commercial insurance, and 74% resided in urban areas.
- No statistically significant differences in baseline characteristics were observed between cohorts (a = 0.05).
- The CAR T cohort had significantly higher average TCOC compared to the BiTE cohort ($702K vs. $372K; P < 0.05).
- Index drug costs were significantly higher in the CAR T cohort ($521K vs. $183K; P < 0.05) and accounted for 74% of TCOC compared to 49% in the BiTE cohort.
- AE costs were also significantly higher in the CAR T cohort ($9K vs. <$500; P < 0.05).
- Most BiTE cohort members (87%) initiated index therapy in a hospital outpatient setting, while most CAR T members (74%) received therapy in an inpatient setting.
- AEs occurred in 52% of CAR T members and 23% of BiTE members, with the CAR T cohort being 3.5 times more likely to experience an AE compared to the BiTE cohort (OR = 3.5; P = 0.03; 95% CI: 1.17–10.54).
- There were no cases of switching between BiTE and CAR T in the 6-month post period.
- There were no significant differences in the proportion of members who received other RRFL treatments post index.

Conclusion

- The findings of this study describe the real-world utilization of a BiTE and CAR T therapies for RRFL treatment from December 2021 through March 2024.
- BiTEs utilization was similar to CAR T but it demonstrated a lower average total cost and lower CRS and ICANS rates compared to CAR T.
- Access data demonstrated the greatest access in urban areas and an opportunity to shift CAR T therapy from inpatient to hospital outpatient settings.
- Real-world findings support existing clinical literature indicating that BiTE therapies are associated with fewer side effects and may offer a lower TCOC, positioning them as a viable alternative to CAR T therapy.

Limitations

- BiTE therapies are chronic, but this study only evaluated the first 6 months of treatment; cost of care may increase over time for members who continue therapy, as mosunetuzumab can be given for 8 to 17 cycles based on response. Post cycle 1, the dose for each cycle is administered once every 3 weeks.
- Inpatient claims may follow varied billing practices, which can complicate the capture of inpatient drug costs and influence index drug cost estimates for both CAR T and BiTE therapies.
- AEs were identified using ICD-10 codes, which may underestimate real-world incidence due to inconsistent provider coding of side effects.
- Administrative pharmacy and medical claims data may be miscoded and rely on assumptions about members' actual drug use and diagnoses.
- The study population was limited to commercially insured and Medicare members; findings may not be generalizable to the Medicaid population.

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2900 Ames Crossing Road, Eagan, MN 55121
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Simone Ndujiuba
Simone.Ndujiuba@PrimeTherapeutics.com