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SYSTEMATIC REVIEW

A Systematic Literature Review of the Economic and Healthcare Resource Utilization Burden of Relapsed/Refractory Follicular Lymphoma

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Abstract

Objective To quantify the economic or healthcare resource utilization (HCRU) burden and examine the value of interventions for relapsed or refractory (R/R) follicular lymphoma (FL).

Methods The PubMed and Embase databases were searched for full-text studies and conference abstracts published between 1 January 2019 and 31 December 2023 that reported either the economic or HCRU burden of R/R FL or reported the results of health economic models assessing interventions for R/R FL. A supplemental manual search was also undertaken to identify conference abstracts that may not have been indexed in the primary databases. A data extraction sheet was used to develop evidence tables.

Results A total of 30 records were included spanning 11 retrospective or prospective studies, 11 cost-effectiveness evaluations, and 8 other economic models. Costs and HCRU generally tended to increase as the line of therapy increased, reaching over US$400,000 annually in later lines. Costs associated with recently approved chimeric antigen receptor T-cell therapy (CAR-T) ranged from US$450,000 to over US$700,000 per patient. Economic models evaluating novel therapies, such as CAR-T, tazemetostat, and mosunetuzumab, estimated they would generally be cost-effective and have minimal budget impact or cost-savings. However, these models noted considerable assumptions regarding treatment duration and discontinuation. Real-world costs and resource use for newly approved therapies including CAR-Ts and bispecifics were limited.

Conclusions The burden of R/R FL is substantial and increases as patients progress. Considerable gaps exist for the real-world impact of novel therapies, including CAR-Ts and bispecifics, on the economic burden and will need to be studied to properly assess their value.

Key Points for Decision Makers

As patients with R/R FL progress through treatment lines their economic and healthcare resource utilization burden generally increases.

A lack of real-world economic and healthcare resource utilization data for newly approved treatments has led to a considerable gap in assessing the value of these therapies to stakeholders.

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1 Introduction

Follicular lymphoma (FL) is the most common indolent non-Hodgkin's lymphoma (NHL) and is responsible for about 20% of all lymphoma cases in the USA [1]. Patients are often diagnosed with advanced disease, which is associated with an increase in mortality rate [2]. While some patients with FL may not immediately require treatment, the decision to treat is often based on the presence of symptoms [3, 4]. FL is treatable, but not curable, and patients will often relapse after a period of remission and become refractory to treatment [5]. As patients progress through treatment lines, the length of remission generally decreases, as does quality of life, while the economic burden increases [6–9].

There is currently no gold standard regimen or treatment sequence for patients with R/R FL. Chemoimmunotherapy regimens and lenalidomide + rituximab (R2) are included as preferred regimens in the second-line (2L) setting in the

National Comprehensive Cancer Network (NCCN) Guidelines [10]. Third-line (3L) and subsequent therapy preferred regimens include mosunetuzumab, axicabtagene ciloleucel (axi-cel), and tisagenlecleucel (tisa-cel). Tazemetostat, and zanubrutinib + obinutuzumab are included as other recommended agents.

Recently approved therapies by the US Food and Drug Administration (FDA) include the EZH2 inhibitor tazemetostat and anti-CD19 chimeric antigen receptor T-cell therapies (CAR-T) including axi-cel and tisa-cel, as well as the bispecifics mosunetuzumab and epcoritamab [11–15]. These therapies have shown significant promise in clinical trials and expand the treatment options for patients with R/R progressing to later lines of treatment [16–19]. Zanubrutinib, a Bruton tyrosine kinase inhibitor (BTKi) received accelerated approval in R/R FL by the FDA in March 2024. Each of these classes of therapies represents a unique approach to treatment, with differences not only in efficacy and safety but also production, delivery, administration setting, and duration of therapy. The differences in economic and healthcare resource utilization (HCRU) outcomes will be a critical component in quantifying the value of these therapies to patients and health systems.

Given the rapidly changing treatment landscape, the objective of this study was to report the current economic and HCRU burden associated with FL treatments and R/R FL patients regardless of treatment, as well as health economic models of treatments. The findings of this review will be used to inform future research to identify unmet needs in this patient population and assess the impact of new therapies on patients and health systems.

2 Methods

A systematic literature review adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards was undertaken. This study was not registered.

2.1 Search Strategy

The Medline (PubMed) and Embase databases were used to identify: (1) retrospective and prospective studies evaluating the economic and HCRU burden of patients with R/R FL, and (2) health economic models evaluating interventions for patients with R/R FL. Search terms and combinations are available in the supporting information (Supplementary Table S1).

Studies included in the databases and published between 1 January 2019 and 31 December 2023, were considered in the search. Only English-language studies were included, although there were no geographic limitations or filters used, and both full-text manuscripts and conference abstracts were included. A supplemental hand search using Google Scholar and the American Society of Hematology (ASH) conference abstract databases was undertaken to identify studies published between 2019 and 2023 that may not have been indexed in the primary databases.

2.2 Study Selection

The records of the studies identified in the Medline and Embase databases were combined, and duplicates were removed to include only unique records. Two independent reviewers screened the study titles and abstracts in the first phase of the review. Studies passing the initial screening had their full text retrieved, or in the case of abstracts, an attempt to retrieve the poster/presentation was made. Two independent reviewers then screened the remaining studies in the final round of review. In both phases of screening, a final decision for any disagreements between the initial two independent reviewers was made by a third independent reviewer.

Studies must have included patients with R/R FL (2L or later) and outcomes related to costs or HCRU. Retrospective and prospective studies were included, as well as health economic models, provided they included the R/R FL patient population and costs/HCRU outcomes. Studies including transformed FL patients with R/R FL were excluded, as were studies including a mixed cohort of treatment-naïve and R/R FL patients if separate results were not available for the patients with R/R FL. In addition, studies of broader NHL populations, that include patients with FL, were excluded if they did not report results separately for patients with R/R FL. The studies without R/R FL results reported independently were excluded owing to differences in the underlying etiology of disease, treatment strategies and patterns, and outcomes, which make them incomparable.

In cases where the same study was published in a conference abstract and as a peer-reviewed manuscript, the peer-reviewed manuscript was included for data extraction.

2.3 Data Extraction

A data extraction sheet was developed in Microsoft Excel. Prospective and retrospective studies had the study design, data source(s), setting, analysis time period, patient population description, treatment regimens (when available), line of therapy, outcomes, and results extracted. Health economic models had the model type, patient population, clinical data source(s), economic data source(s), utility data source(s) comparators, outcomes, and results extracted. The currency and year of costs were also extracted for studies with cost

outcomes. This review only analyzed the data available in the included studies. Any missing or unclear data were ignored.

Study quality for prospective and retrospective non-randomized cohort or case-control studies was assessed using the Newcastle–Ottawa Scale [20]. The Drummond checklist was used to assess the study quality of economic evaluations [21].

3 Results

A total of 30 records were included in this review after screening (Fig. 1) [22–51]. The records detailed 11 retrospective or prospective studies (Table 1), 11 cost-effectiveness evaluations (Table 2), and eight other models including budget impact and other cost-modeling studies (Table 3).

3.1 Cost and HCRU Burden of R/R FL

There were eight studies identified that reported the cost and/or HCRU of R/R FL agnostic of specific treatment regimens (Table 1) [23, 29, 30, 35, 36, 41, 46, 49]. Six of the studies were conducted in the USA [23, 30, 36, 41, 46, 49], one in Italy [29], and one in Canada [35].

The study in Canada retrospectively evaluated the annual cost of 285 patients with FL relapsing after R-based chemotherapy [35]. In the first year after relapse, costs (2019 CAD) were 52,474 CAD, followed by 17,039 CAD in year 2, and 13,637 CAD in year 3. The retrospective analysis of patients with R/R FL initiating 3L treatment in Italy reported a similar trend for years 1 and 2 post-therapy initiation, with a decrease in mean total healthcare costs of €21,081 to €10,249 [29]. However, costs increased to €22,230 in the third year after initiation of 3L therapy. The study reported similar reductions between year 1 and year 2 mean healthcare costs, and then an increase in year 3 costs for patients ultimately receiving three, four, or five or more lines of therapy.

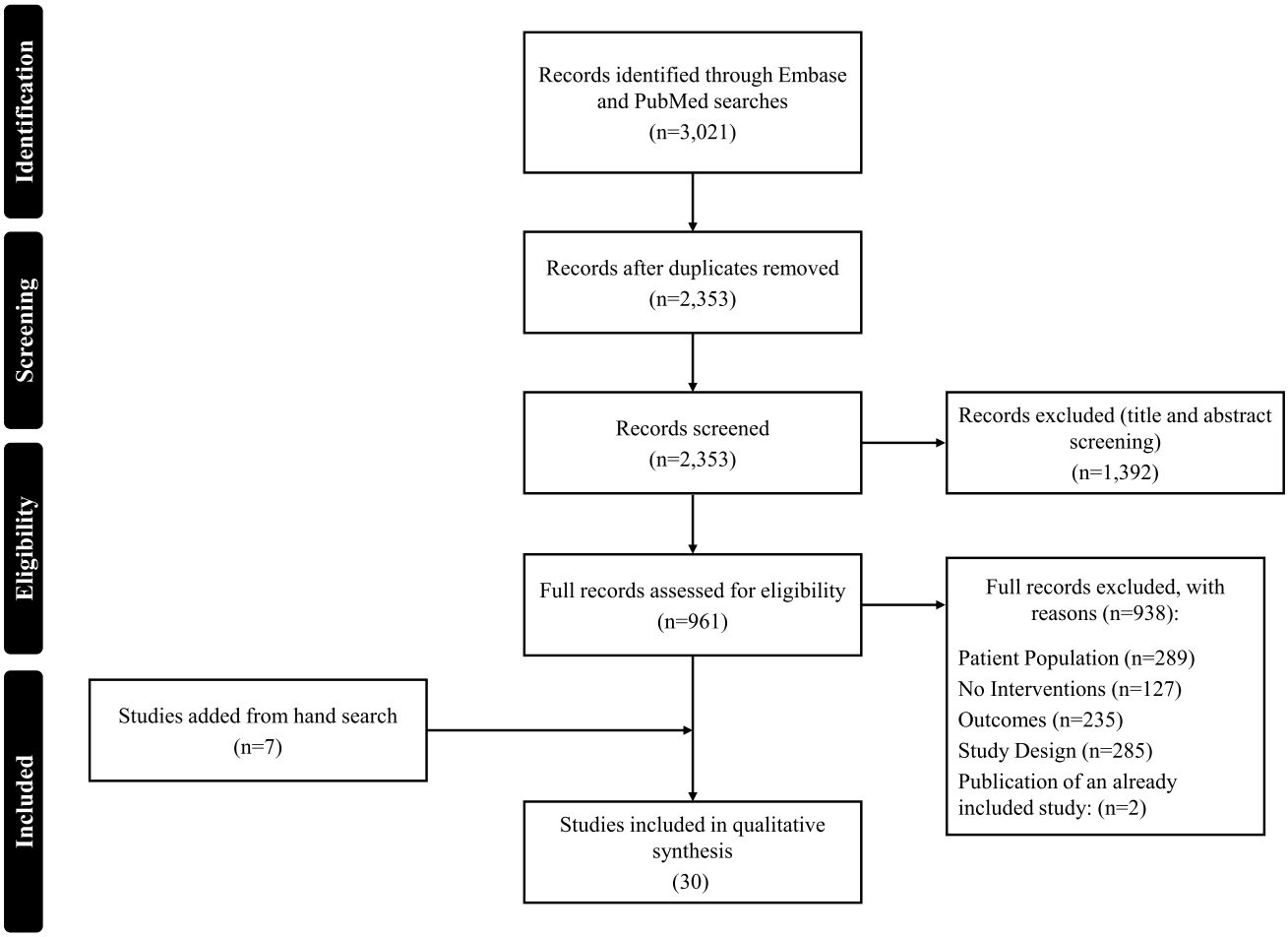

Fig. 1 Study flow diagram

Table 1 Summary of retrospective and prospective studies evaluating costs and/or healthcare resource utilization

Study|references	Publication type	Study type	Data source(s)	Setting(s)	Time period	Costs (year)	Patient population	Regimen(s)	Treatment line	Outcome	Results
Chan et al. 2023|[24]	Abstract	Retrospective	Medicare and commercial insurance claims	USA	1 January 2016–31 December 2022	USD (N/S)	R/R FL after two or more treatment lines	CAR-T (n = 305)	Third-line and later	Medicare (commercial) costs post-CAR-T PPPM, mean	$7513 ($5169)
								SoC (n = 4367)	Third-line	Medicare (commercial) costs PPPM, mean	$8860 ($6297)
									Sixth-line	Medicare (commercial) costs PPPM, mean	$10,060 ($8612)
Bains Chawla et al. 2023|[23]	Poster	Retrospective	IQVIA PharMetrics® Plus	USA	1 January 2011–30 September 2020	USD (N/S)	FL and aged ≥ 66 years at Dx who initiated 3L (n = 410)	No specific regimen / mixed	Second-line (n = 410)	≥ 1 Inpatient admission	19%
										≥ 1 ED visit	28%
										Total all-cause healthcare costs PMPM, mean	$17,767
									Third-line (n = 410)	≥1 Inpatient admission	31%
										≥ 1 ED visit	41%
										Total all-cause healthcare costs (PMPM), mean	$18,266
Di et al. 2022|[26]	Abstract	Retrospective	BCBS axis database	USA	January 2018–June 2021	USD (2018)	R/R FL	CAR-T (n = 6)	Not specified	Costs 41 days prior to 154 days after CAR-T, mean	$743,100
Ferreri et al. 2023|[29]	Manuscript	Retrospective	Administrative databases	Italy	1 January 2015–30 June 2021	Euros (N/S)	Patients with R/R FL with ≥ 3 lines of therapy (n = 2434)	No specific regimen/ mixed	Third-line and after	Hospitalizations, mean	Year 1: 1.6 Year 2: 0.9 Year 3: 2.1
										Total costs, mean	Year 1: €21,081 Year 2: €10,249 Year 3: €22,230
							Patients with R/R FL with three lines of therapy (n = 1318)			Total costs, mean	Year 1: €18,961 Year 2: €6117 Year 3: €23,964

Table 1 (continued)

Study|references	Publication type	Study type	Data source(s)	Setting(s)	Time period	Costs (year)	Patient population	Regimen(s)	Treatment line	Outcome	Results
							Patients with R/R FL with four lines of therapy (n = 494)			Total costs, mean	Year 1: €21,514 Year 2: €8362 Year 3: €27,556
							Patients with R/R FL with ≥ 5 lines of therapy (n = 622)			Total costs, mean	Year 1: €19,208 Year 2: €11,781 Year 3: €20,307
Fowler et al. 2020|[30]	Manuscript	Retrospective	MarketScan®	USA	1 January 2010–31 December 2013	USD (2018)	FL	No specific regimen/ mixed	Second-line (n = 180)	Total all-cause healthcare costs (annual), mean	$125,586
										Total FL-related healthcare costs (annual), mean	$29,460
										All-cause hospitalization (annual), % (mean) [mean LoS]	31.1% (0.5) [2.1]
										All-cause ER visits (annual), % (mean)	51.7% (0.7)
									Third-line (n = 51)	Total all-cause healthcare costs (annual), mean	$239,216
										Total FL-related healthcare costs (annual), mean	$103,387
										All-cause hospitalization (annual), % (mean) [mean LoS]	37.3% (0.5) [3.2]
										All-cause ER visits (annual), % (mean)	49.0% (1.1)

Table 1 (continued)

Study/references	Publication type	Study type	Data source(s)	Setting(s)	Time period	Costs (year)	Patient population	Regimen(s)	Treatment line	Outcome	Results
									Fourth-line ($n = 21$)	total all-cause healthcare costs (annual), mean	$370,597
										Total FL-related healthcare costs (annual), mean	$309,103
										All-cause hospitalization (annual), % (mean) [mean LoS]	47.6% (0.7) [3.7]
										All-cause ER visits (annual), % (mean)	52.4% (0.7)
									Fifth-line ($n = 11$)	Total all-cause healthcare costs (annual), mean	$424,758
										Total FL-related healthcare costs (annual), mean	$85,748
										All-cause hospitalization (annual), % (mean) [mean LoS]	50.0% (0.2) [3.1]
										All-cause ER visits (annual), % (mean)	50.0% (0.9)

Table 1 (continued)

Study/references	Publication type	Study type	Data source(s)	Setting(s)	Time period	Costs (year)	Patient population	Regimen(s)	Treatment line	Outcome	Results
Fowler et al. 2023l[31]	Manuscript	Prospective	ELARA Clinical Trial	International	As of 3 August 2021	USD (2020)	R/R FL After two or more treatment lines (n = 97)	Tisa-cel inpatient administration (n = 80)	Third-line and later	Hospitalizations, %	100%
										Duration of hospitalization, median (mean)	13.0 days (14.3)
										Length of hospital stay, median (mean)	12.5 days (13.8)
										Overall hospitalization costs per patient, mean	$40,054
								Tisa-cel outpatient administration (n = 17)	Third-line and later	Hospitalizations, %	59%
										Duration of hospitalization, median (mean)	5.0 days (5.0)
										Length of hospital stay, median (mean)	4.5 days (4.3)
										Overall hospitalization costs per patient, mean	$7477
Kuruvilla et al. 2023l[35]	Manuscript	Retrospective	Institute for Clinical and Evaluative Sciences	Ontario, Canada	1 January 2005–31 December 2018	CAD (2020)	FL and Relapse After R-chemotherapy (n = 285)	No specific regimen/ mixed	Post relapse	Annual costs post relapse	Year 1: $52,473.61 Year 2: $17,039.29 Year 3: $13,637.22
Leslie et al. 2022l[36]	Manuscript	Retrospective	MarketScan®	USA	1 January 2005–29 February 2020	USD (2020)	FL with early treatment failure of first-line chemoimmunotherapy (n = 644)	No specific regimen/ mixed	Fourth-line and later	All-cause total costs PPPM	$28,420
										Oncology care model episode (first 6 months of line)	$31,092

Table 1 (continued)

Study|references	Publication type	Study type	Data source(s)	Setting(s)	Time period	Costs (year)	Patient population	Regimen(s)	Treatment line	Outcome	Results
Matasar et al. 2021|[41]	Abstract	Retrospective	IQVIA PharMetrics® Plus	USA	1 January 2011–30 September 2020	USD (2020)	R/R FL after two or more treatment lines (n = 100)	No specific regimen / mixed (n = 100)	Third-line and later	All-cause inpatient hospitalizations (annual), mean	0.8
										All-cause number of days in hospital (annual), mean	5.2
										All-cause ER visits (annual), mean	0.9
										Total all-cause costs (annual), mean	$193,207
										Total FL-related costs (annual), mean	$159,815
								oral PI3Kis (n = 45)		Total all-cause costs (annual), mean	$163,108
										Total FL-related costs (annual), mean	$131,208
								Anti-CD20 MoAb Mono (n = 19)		Total all-cause costs (annual), mean	$121,561
										Total FL-related costs (annual), mean	$105,061
								Chemoimmunotherapy (n = 18)		Total all-cause costs (annual), mean	$252,654
										Total FL-related costs (annual), mean	$214,631
Saunder et al. 2023|[46]	Abstract	Retrospective	MarketScan®	USA	January 2015–June 2021	USD (2022)	R/R FL with POD24 (n = 1043)	No specific regimen/ mixed	Second-line	Total all-cause costs PPPM, mean	$11,972
									Third-line	Total all-cause costs PPPM, mean	$12,872

Table 1 (continued)

Study|references	Publication type	Study type	Data source(s)	Setting(s)	Time period	Costs (year)	Patient population	Regimen(s)	Treatment line	Outcome	Results
Saunders et al. 2023|[48]	Abstract	USA	R/R FL After ≥ 2 treatment lines	TRANSCEND-FL	N/R	USD (2023)	R/R FL After one or more treatment lines	Liso-cel	Second-line and later	Median cost of CRS-only	Grade 1: $20,306 Grade 2: $28,441 Grade 3: $32,706
										Median LoS of CRS-only	Grade 1: 3 Grade 2: 5 Grade 3: 3
										Median cost of NEs only	Grade 1: $25,605 Grade 3: $48,739
										Median LoS of NEs only	Grade 1: 5 Grade 3: 8
										Median cost non-concurrent CRS and NEs	Grade < 2: $32,125
										Median LoS non-concurrent CRS and NEs	Grade < 2: 5.5
										Median cost concurrent CRS and NEs	Grade < 2: $42,000 Grade 3: $50,400
										Median LoS concurrent CRS and NEs	Grade < 2: 6.5 Grade 3: 5.5

Table 1 (continued)

Study|references	Publication type	Study type	Data source(s)	Setting(s)	Time period	Costs (year)	Patient population	Regimen(s)	Treatment line	Outcome	Results
Shah et al. 2023|[49]	Poster	Retrospective	Symphony Integrated Dataverse	USA	1 January 2019–31 March 2023	USD (N/S)	FL	No specific regimen/ mixed	Second-line (n = 3061)	All-cause hospitalizations (PPPM), mean	0.79
										FL-related hospitalizations (PPPM), mean	0.18
									Third-line (n = 952)	All-cause hospitalizations (PPPM), mean	1.94
										FL-related hospitalizations (PPPM), mean	0.36
									Fourth-line (n = 263)	All-cause hospitalizations (PPPM), mean	1.85
										FL-related hospitalizations (PPPM), mean	0.45

N/S, not specified

Table 2 Summary of R/R FL cost-effectiveness models

Study/reference	Publication type	Setting	Perspective	Model type	Patient population	Clinical data source	Economic data sources	Costs (year)	Utilities and sources	Cost-effectiveness threshold	Comparators	Outcomes	Results
Erdogan-Ciftci et al. 2019|[28]	Abstract	Turkey	Turkish healthcare payer	Partitioned-survival	R/R FL	GADOLIN Trial	SSI Health Implementation Notification Lists	TRY (N/S)	Values: N/R Source: N/R	3 × GDP per capita (170.000TRY / QALY)	G+B versus B	ICER (TRY per QALY)	G+B versus B: 76.427/ QALY
Lin et al. 2023|[37]	Abstract	USA	US payer	Markov	R/R FL	ZUMA-5 (axi-cel), ELARA (tisa-cel) and GO29781 (mosunetuzumab)	N/R	USD (N/S)	Values: N/R Source: N/R	US$150,000/ QALY	Mosunetuzumab versus axi-cel	Total costs	Mosunetuzumab: $611,851 Axi-cel: $702,380 Incremental: − $90,529
												QALYs	Mosunetuzumab: 3.68 Axi-cel: 3.70 Incremental: − 0.02
												ICER	Axi-cel versus mosunetuzumab: less costly, less effective

Table 2 (continued)

Study|reference	Publication type	Setting	Perspective	Model type	Patient population	Clinical data source	Economic data sources	Costs (year)	Utilities and sources	Cost-effectiveness threshold	Comparators	Outcomes	Results
											Mosunetuzumab versus tisa-cel	Total costs	Mosunetuzumab: $611,851 Tisa-cel: $728,459 Incremental: $116,608
												QALYs	Mosunetuzumab: 3.68 Tisa-cel: 3.62 Incremental: 0.06
												ICER	Mosunetuzumab versus tisa-cel: dominant
Ma et al. 2023|[39]	Manuscript	China	Payers	Markov	R/R FL	GADOLIN trial + literature	Literature + patient and physician surveys	CNY (2022)	Values: PFS: on treatment = 0.807 PFS: off treatment = 0.822 PPS = 0.758 Source: literature	3 × GDP per capita (¥257,094/QALY)	O+B−O versus B-mono	Total costs	O+B−O: ¥541,179 B-mono: ¥420,891 Incremental: ¥120,288
												QALYs	O+B−O: 5.100 B-mono: 3.535 Incremental: 1.565
												ICER	O+B−O versus B-mono: ¥76,859

Table 2 (continued)

Study/reference	Publication type	Setting	Perspective	Model type	Patient population	Clinical data source	Economic data sources	Costs (year)	Utilities and sources	Cost-effectiveness threshold	Comparators	Outcomes	Results
											O+B−O versus BR	Total costs	O+B−O: ¥541,179 BR: ¥490,208 Incremental: ¥50,971
												QALYs	O+B−O: 5.100 BR: 3.770 Incremental: 1.330
												ICER	O+B−O versus BR: ¥38,331
											O+B−O versus R2	Total costs	O+B−O: ¥541,179 R2: ¥763,394 Incremental: −¥171,244
												QALYs	O+B−O: 5.100 R2: 5.005 Incremental: 0.095
												ICER	O+B−O versus R2: dominant

Table 2 (continued)

Study/reference	Publication type	Setting	Perspective	Model type	Patient population	Clinical data source	Economic data sources	Costs (year)	Utilities and sources	Cost-effectiveness threshold	Comparators	Outcomes	Results
											O+B−O versus R-mono	Total costs	O+B−O: ¥541,179 R-mono: ¥475,440 Incremental: ¥65,739
												QALYs	O+B−O: 5.100 R-mono: 4.350 Incremental: 0.750
												ICER	O+B−O versus R-mono: ¥87,620
											O+B−O versus L-mono	Total costs	O+B−O: ¥541,179 L-mono: ¥600,147 Incremental: −¥58,968
												QALYs	O+B−O: 5.100 L-mono: 4.486 Incremental: 0.614
												ICER	O+B−O versus L-mono: dominant

Table 2 (continued)

Study/reference	Publication type	Setting	Perspective	Model type	Patient population	Clinical data source	Economic data sources	Costs (year)	Utilities and sources	Cost-effectiveness threshold	Comparators	Outcomes	Results
											O+B−O versus R-CHOP	Total costs	O+B−O: ¥541,179 R-CHOP: ¥485,136 Incremental: ¥56,043
												QALYs	O+B−O: 5.100 R-CHOP: 4.071 Incremental: 1.029
												ICER	O+B−O versus R-CHOP: ¥54,463
Matasar et al.l[40]	Poster	USA	Payer	Partitioned Survival	R/R FL after ≥ 2 treatment lines	Indirect treatment comparison	Literature and published data	USD (2022)	Values: N/R Source: EQ-5D-5L from NCT02500407 trial	US$150,000/QALY	Mosunetuzumab versus axi-cel	Total costs	Mosunetuzumab: $293,659 Axi-cel: $579,112 Incremental: − $285,453
												QALYs	Mosunetuzumab: 8.63 Axi-cel: 6.46 Incremental: 2.18
												ICER	Mosunetuzumab versus axi-cel: dominant

Table 2 (continued)

Study|reference	Publication type	Setting	Perspective	Model type	Patient population	Clinical data source	Economic data sources	Costs (year)	Utilities and sources	Cost-effectiveness threshold	Comparators	Outcomes	Results
											Mosunetuzumab versus tisa-cel	Total costs	Mosunetuzumab: $289,213 Tisa-cel: $552,338 Incremental: − $263,125
												QALYs	Mosunetuzumab: 7.18 Tisa-cel: 6.61 Incremental: 0.57
												ICER	Mosunetuzumab versus tisa-cel: dominant
											Mosunetuzumab versus tazemetostat	Total costs	Mosunetuzumab: $290,097 Tazemetostat: $394,683 Incremental: − $104,586
												QALYs	Mosunetuzumab: 11.06 Tazemetostat: 3.35 Incremental: 7.72
												ICER	Mosunetuzumab versus tazemetostat: dominant

Table 2 (continued)

Study|reference	Publication type	Setting	Perspective	Model type	Patient population	Clinical data source	Economic data sources	Costs (year)	Utilities and sources	Cost-effectiveness threshold	Comparators	Outcomes	Results
											Mosunetuzumab versus real-world cohort	Total costs	Mosunetuzumab: $290,794 Real-world cohort: $210,510 Incremental: $80,284
												QALYs	Mosunetuzumab: 8.09 Real-world cohort: 4.35 Incremental: 3.75
												ICER	Mosunetuzumab versus real-world cohort: $21,434
											Mosunetuzumab versus O-Benda	Total costs	Mosunetuzumab: $290,925 O-Benda: $231,769 Incremental: $59,156
												QALYs	Mosunetuzumab: 6.95 O-Benda: 5.57 Incremental: 1.38
												ICER	Mosunetuzumab versus O-Benda: $42,731

Table 2 (continued)

Study|reference	Publication type	Setting	Perspective	Model type	Patient population	Clinical data source	Economic data sources	Costs (year)	Utilities and sources	Cost-effectiveness threshold	Comparators	Outcomes	Results
											Mosunetuzumab versus R-Benda	Total costs	Mosunetuzumab: $289,584 R-Benda: $163,774 Incremental: $125,810
												QALYs	Mosunetuzumab: 8.54 R-Benda: 6.94 Incremental: 1.60
												ICER	Mosunetuzumab versus R-Benda: $78,607
											Mosunetuzumab versus R-Len	Total costs	Mosunetuzumab: $283,028 R-Len: $336,467 Incremental: − $53,439
												QALYs	Mosunetuzumab: 10.33 R-Len: 11.09 Incremental: − 0.76
												ICER	Mosunetuzumab versus R-Len: less cost; less QALYs

Table 2 (continued)

Study|reference	Publication type	Setting	Perspective	Model type	Patient population	Clinical data source	Economic data sources	Costs (year)	Utilities and sources	Cost-effectiveness threshold	Comparators	Outcomes	Results
Oluwole et al. 2022|[42]	Abstract	USA	Payer	Partitioned survival	R/R FL after ≥ 2 treatment lines	ZUMA-5 (axi-cel) and SCHOLAR-5 (SoC)	Published list prices and literature	USD (N/S)	Values: N/R Source: literature	US$150,000/QALY	Axi-cel versus SoC	Total costs	Axi-cel costs were $288,979 higher than SoC
												QALYs	Axi-cel QALYs were 3.22 higher than SoC
												ICER	Axi-cel versus SoC: $89,784/QALY
Oluwole et al. 2023|[43]	Abstract	USA	Payer	Partitioned survival	R/R FL after ≥ 2 treatment lines	ZUMA-5 (axi-cel) and GO29781 (mosunezumab)	Literature	USD (N/S)	Values: N/R Source: literature	US$150,000/QALY	Axi-cel versus mosunetuzumab	Total costs	Axi-cel: $613,973 Mosunetuzumab: $462,547 Incremental: $151,425
												QALYs	Axi-cel: 7.77 Mosunetuzumab: 5.97 Incremental: 1.80
												ICER	Axi-cel versus mosunetuzumab: $84,016

Table 2 (continued)

Study|reference	Publication type	Setting	Perspective	Model type	Patient population	Clinical data source	Economic data sources	Costs (year)	Utilities and sources	Cost-effectiveness threshold	Comparators	Outcomes	Results
Potnis et al. 2023|[44]	Manuscript	USA	Payer	Markov	R/R FL after ≥ 2 treatment lines	ZUMA-5 (axi-cel) and LEO CReWE (SoC)	Literature	USD (2021)	Values: axi-cel, months 1 and 2 = 0.646; HSCT months 1 and 2 = 0.646; 3L w/o progression = 0.846; 4L and 5L targeted therapy = 0.785; progression w/o therapy = 0.450; BSC = 0.450 Source: literature	US$150,000/QALY	Axi-cel versus SoC (copanlisib and tazemetostat)	Total costs	Axi-cel: $731,682 SoC: $458,490 Incremental: $273,131
												QALYs	Axi-cel: 7.04 SoC: 5.54 Incremental: 1.50
												ICER	Axi-cel versus Soc: $182,127/QALY
Thielen et al. 2021|[50]	Manuscript	The Netherlands	Healthcare	Partitioned Survival	R/R FL	AUGMENT	AUGMENT	Euro (2022)	Values: PFS = 0.854; PD = 0.854 Source: AUGMENT	€50,000/QALY	Rituximab + lenalidomide versus R-mono	Total costs	Rituximab + lenalidomide: €165,547 Rituximab monotherapy: €102,223 Incremental: €63,324
												QALYs	Rituximab + lenalidomide: 10.8 Rituximab monotherapy: 9.1 Incremental: 1.7
												ICER	Rituximab + lenalidomide versus R-mono: €37,951

Table 2 (continued)

Study/reference	Publication type	Setting	Perspective	Model type	Patient population	Clinical data source	Economic data sources	Costs (year)	Utilities and sources	Cost-effectiveness threshold	Comparators	Outcomes	Results
Vijenthira et al. 2021[51]	Manuscript	Canada	Public health payer	Markov	Transplant-eligible patients with early progression (POD24) of FL	Literature	Published databases	CAD (N/R)	Values: (ranges per arm): allogeneic transplant = 0.35–0.68; ASCT = 0.43–0.7; chemo-immunotherapy = 0.63–0.71; relapse, secondary malignancy, and palliation = 0.4–0.823 Sources: literature and expert opinion	CA$50,000/QALY	AlloSCT versus ASCT	Total costs (CAD) QALYs ICER	AlloSCT: $362,175 ASCT: $195,173 AlloSCT: 7.2 ASCT: 7.9 ASCT dominant
											AlloSCT versus chemo-immunotherapy	Total costs (CAD) QALYs ICER	AlloSCT: $362,175 Chemoimmunotherapy: $232,925 AlloSCT: 7.2 Chemoimmunotherapy: 7.6 Chemoimmunotherapy dominant
Eklund et al. 2023[27]	Poster	Sweden	Swedish healthcare	Partitioned survival	R/R FL after three or more treatment lines	ZUMA-5 (axi-cel) and SCHOLAR-5 ITT (SoC)	Literature and public databases	SEK (2022)	Values: N/R Source: literature	1 million SEK/QALY	Axi-cel versus SoC	Total costs (SEK) QALYs ICER (SEK)	Axi-cel: 4,263,520 SoC: 952,663 Axi-cel: 7.85 SoC: 2.99 Axi-cel versus SoC: 680,001

Table 2 (continued)

Study/reference	Publication type	Setting	Perspective	Model type	Patient population	Clinical data source	Economic data sources	Costs (year)	Utilities and sources	Cost-effectiveness threshold	Comparators	Outcomes	Results
Chen et al. 2023l[25]	Abstract	China	Healthcare	Partitioned Survival	R/R FL with ≥ 2 prior lines	Phase II trial of chinese population	EMR and published literature	USD and RMB (N/S)	Values: N/R sources: EMR and literature	3 × GDP per capita	Duvelisib versus BR	Total costs	Duvelisib: $89,201.15 BR: $65,997.32
												QALYs	Duvelisib: 4.23 BR: 2.73
												ICER	Duvelisib versus BR: $15,521.01

G, Obinutuzumab; B, Bendamustine; QALY, quality-adjusted life-years; LY, life-year; ICER, incremental cost-effectiveness ratio; N/R, not reported; N/S, not specified; PFS, progression-free survival; PD, progressed disease; GDP, gross domestic product; O, obinutuzumab; R/R, relapsed/refractory; FL, follicular lymphoma; BSC, best supportive care; R, rituximab

There were six studies using data from the USA to estimate the costs and/or HCRU associated with different lines of therapy for R/R FL patients [23, 24, 30, 36, 46, 49].

All-cause healthcare costs (USD) per-patient-per-month (PPPM) for patients receiving second-line regimens were reported in three studies and ranged from US$10,466 (adjusted from an annual cost of US$125,586) to US$17,767 [23, 30, 46]. The high estimate of US$17,767 was among a cohort of patients with FL aged 66 years or older at diagnosis and went on to initiate a 3L therapy [23]. Among the four studies evaluating total all-cause healthcare costs in 3L, the range was US$12,872 to US$19,935 PPPM (adjusted from an annual cost of US$239,216) [24, 30, 46]. There were two studies evaluating costs in fourth-line (4L) [30] and later [24, 36]. Fourth-line all-cause costs PPPM were US$30,883 (adjusted from an annual cost (2019 USD) of US$370,597) and US$28,420 for 4L and later. The 4L and later costs were captured for patients with early treatment failure of first-line chemoimmunotherapy [36]. Total costs (2019 USD) for the fifth line (5L) were reported in one study and were US$35,397 PPPM (adjusted from an annual cost of US$424,758) [30].

Among the three studies evaluating more than one line of therapy, the increase from line to line was modest in two studies and impactful in one study [23, 30, 46]. Bains Chawla et al. and Saunders et al. both reported total all-cause healthcare costs PPPM for 2L and 3L patients with FL using claims-based databases. In the Bains Chawla et al. study, the increase in all-cause healthcare costs PPPM from 2L to 3L was 2.8% (US$499) compared with 7.5% (US$900 [2022 USD]) in the Saunders et al. study. The Bains Chawla et al. study evaluated patients aged 66 years and older who initiated a 3L treatment regimen while the Saunders et al. study included patients with progression of disease ≤ 24 months (POD24). The Fowler et al. study reported much larger relative differences in all-cause healthcare costs (2018) between lines with increases of 90.5% (US$9469) from 2L to 3L, 54.9% (US$10,948) from 3L to 4L, and 14.6% (US$4513) from 4L to 5L [30].

Patients with R/R FL incurred frequent hospitalizations and emergency department visits across all treatment lines in the included studies [23, 30, 36, 41, 49]. In the study by Bains Chawla et al. of patients with R/R FL 66 years and older at diagnosis, 19% and 31% of patients had a hospitalization in the 2L and 3L settings, respectively [23]. Emergency department visits were 28% in 2L and 41% in 3L. Similar rates were reported by Fowler et al. as the percentage of patients with a hospitalization annually was 31.1% in the 2L, 37.3% in the 3L, 52.4% in the 4L, and 50.0% in the 5L. The mean length of stay ranged from 2.1 days in the 2L to 3.7 days in the 4L [30]. The mean annual number of hospitalizations was similar in 2L and 3L (0.5 hospitalizations), higher in 4L (0.7 hospitalizations), and lowest in 5L

Table 3 Summary of budget impact and other R/R FL models and analyses

Study|References	Publication type	Setting	Patient population	Data sources	Costs (year)	Treatment regimen(s)	Outcomes	Results
Budget impact								
Appukkutan et al. 2019|[22]	Manuscript	USA	R/R FL after ≥ 2 treatment lines	Clinical trials, literature, prescribing information, and expert opinion	USD (2017)	With versus without copanlisib	1-year budget impact (PMPM) in a 1-million member plan	$242,641 ($0.02)
Proudman et al. 2021|[45]	Abstract	USA	R/R FL ≥ 2 treatment lines	N/R	USD (N/S)	With versus without tazemetostat	Budget impact (PMPM) in a 1-million member plan	Year 1: − $8156 (− $0.0007) Year 2: − $9504 (− $0.0008) Year 3: − $13,285 (− $0.0011)
Lin et al. 2023|[38]	Poster	USA	R/R FL after ≥ 2 treatment lines	Clinical trials, literature, expert opinion, and public databases	USD (2022/3)	With versus without mosunetuzumab	Budget impact (PMPM) in a 1-million member plan	Years 1–3: $69,812 ($0.0019)
							Budget impact in a 1-million member plan	Year 1: $60,596 Year 2: − $3583 Year 3: $12,799
Cost analyses								
Gaballa et al. 2021|[32]	Abstract	Usa	R/r fl after ≥ 2 treatment lines	Maic, costs not reported	USD (N/S)	Tazemetostat versus idelalisib	AE related costs, per episode	Tazemetostat: $5769 Idelalisib: $19,302 Difference in costs: $13,534
							AE related costs, monthly	Tazemetostat: $640 Idelalisib: $3202 Difference in costs: $2,563
						Tazemetostat versus duvelisib	AE related costs, per episode	Tazemetostat: $3427 Duvelisib: $18,197 Difference in costs: $14,770
							AE related costs, monthly	Tazemetostat: $352 Duvelisib: $2916 Difference in costs: $2564
						Tazemetostat versus copanlisib	AE related costs, per episode	Tazemetostat: $3705 Copanlisib: $22,442 Difference in costs: $18,737
							AE related costs, monthly	Tazemetostat: $405 Copanlisib: $4225 Difference in costs: $3820

Table 3 (continued)

Study|References	Publication type	Setting	Patient population	Data sources	Costs (year)	Treatment regimen(s)	Outcomes	Results
Ghanem 2023|[33]	Manuscript	USA	R/R FL after ≥ 2 treatment lines	Clinical trials, literature, public databases	USD (2022)	Axi-cel	Total cost per patient	$512,021
						Tisa-cel	Total cost per patient	$450,885
						Axi-cel versus tisa-cel	Total cost per patient	$61,136 savings for tisa-cel
Jeyakumar et al. 2021|[34]	Abstract	USA	R/R FL	MAIC + public databases	USD (N/S)	Umbralisib	Annual per patient cost of adverse events	$2123
						Copanlisib	Annual per patient cost of adverse events	$5139
						Duvelisib	Annual per patient cost of adverse events	$5818
						Idelalisib	Annual per patient cost of adverse events	$4880
Saunders et al. 2023|[47]	Abstract	USA	R/R FL after ≥ 2 treatment lines	TRANSCEND-FL, ZUMA-5, and ELARA	USD (2023)	Liso-cel	Per patient cost of CRS and NEs	$20,626
						Tisa-cel	Per patient cost of CRS and NEs	$26,460
						Axi-cel	Per patient cost of CRS and NEs	$44,096

AlloSCT, allogeneic stem cell transplantation; CAD, Canadian dollars; CAR-T, chimeric antigen receptor T-cell therapy; CSR, cytokine release syndrome; ER, emergency room; FL, follicular lymphoma; ICER, incremental cost-effectiveness ratio; LoS, length of stay; NE, neurological events; N/S, not specified; PMPM, per-member-per-month, POD24, progression of disease within 24 months; QALY, quality-adjusted life year; R/R, relapsed or refractory

(0.2 hospitalizations). In the study of 3L patients with R/R FL by Matasar et al. the mean annual number of hospitalizations was 0.8 with a mean annual number of days in the hospital of 5.2 [41]. Lastly, the claims analysis by Shah et al. reported an increase in mean all-cause and FL-related hospitalizations PPPM from 2L to 3L, and a relative leveling off between 3L and 4L [49].

3.2 Cost and Healthcare Resource Utilization Associated with R/R FL Treatments

There were four studies evaluating the economic and/or HCRU outcomes of specific treatment regimens in real-world databases or clinical trials [24, 26, 31, 41]. Matasar et al. reported costs (2020 USD) associated with oral phosphoinositide 3-kinase inhibitors (PI3Kis), anti-CD20 monoclonal antibodies (MoAbs) monotherapy, and chemoimmunotherapy in a US claims database among patients with R/R FL with two or more prior treatment lines [41]. In the 3L and later setting, mean total all-cause/FL-related costs per year were highest for chemoimmunotherapy (US$252,654/US$214,631) and lowest for anti-CD20 MoAb monotherapy (US$121,561/US$105,061).

The remaining three studies evaluating economic and/or HCRU included CAR-T [24, 26, 31]. Chan et al. and Di et al. both conducted retrospective analyses of non-product-specific CAR-T in claims databases in the USA [24, 26]. The Chan et al. study included 305 R/R FL patients in Medicare and commercial claims receiving a CAR-T and 4367 patients receiving the standard of care in the 3L setting [24]. Medicare and commercial costs (USD) PPPM after (not including) CAR-T in the 3L and later setting were US$7513 and US$5169, respectively. In the 3L setting, Medicare and commercial costs (USD) PPPM for patients receiving standard of care were US$8860 and US$6297. Di et al. reported total costs (2018 USD) of US$743,100 during the period of time 41 days before and 154 days after CAR-T administration, among six patients receiving CAR-T for R/R FL in the BCBS axis database [26].

Lastly, the ELARA trial of tisa-cel in patients with R/R FL after two or more lines of treatment was analyzed to determine differences in per-patient hospitalization costs (2020 USD) according to the administration site of tisa-cel [31]. There were 17 patients receiving tisa-cel in the outpatient setting with a hospitalization rate of 59% and a per-patient hospitalization cost of US$7477. The overall hospitalization cost among the 80 patients receiving inpatient administration of tisa-cel was US$40,054.

A cost-minimization model was developed to evaluate the total cost (2022 USD) per patient for axi-cel and tisa-cel in R/R FL after two or more lines of treatment in the USA [33]. The total cost per patient was US$61,136 lower for tisa-cel (US$450,885) compared with axi-cel (US$512,021). This difference was primarily driven by a 6% (US$24,890) increase in drug acquisition cost for axi-cel (US$424,000) compared with tisa-cel (US$399,110) and a 55% (US$13,831) higher cost associated with the management of adverse events (AEs) for axi-cel (US$25,109) compared with tisa-cel (US$11,278).

3.2.1 Burden of Adverse Events

Three studies modeled the costs related to AEs events in the USA using clinical trial data [32, 34, 47]. In two studies, a matching-adjusted indirect comparison (MAIC) was performed using clinical trial data to estimate AE rates between comparators [32, 34]. The MAIC conducted by Gaballa et al. evaluated AE-related costs per episode and per month for tazemetostat, and were compared to idelalisib, duvelisib, and copanlisib [32]. In all cases, AE-related costs (USD) per episode and month were lower for tazemetostat, with differences greatest in comparison with copanlisib (US$18,737 difference per episode and US$3820 per month). In the MAIC conducted by Jeyakumar et al., the annual per-patient cost of AEs among PI3Kis was lowest for umbralisib (US$2123) followed by idelalisib (US$4880), copanlisib (US$5139), and duvelisib (US$5818).

A decision-analytic model was developed to estimate the cost (2023 USD) of cytokine release syndrome (CRS), neurological events (NE), and AEs using data from the TRANSCEND-FL (liso-cel) study in R/R FL [47]. The cost results for this model were then applied to CRS and NE rates observed in the TRANSCEND-FL, ZUMA, and ELARA studies to estimate per-patient costs for liso-cel, axi-cel, and tisa-cel, respectively. Per patient costs for CRS and NE AEs were reported to range from US$20,626 (CRS events: US$14,631; NE events: US$5994) for liso-cel to US$44,096 (CRS events: US$21,299; NE events: US$22,797) for axi-cel.

A study evaluating the cost (2023 USD) and healthcare resource utilization for AEs specifically for liso-cel using the TRANSCEND-FL study reported median CRS costs ranging from US$20,306 (grade 1) to US$32,706 (grade 3) with a median length of stay of 3 days (grades 1 and 3) and 5 days (grade 2) [48]. Median NE costs and length of stay were higher than CRS with US$25,605 (length of stay [LoS]: 5 days) in grade 1 and US$48,739 (LoS: 8 days) in grade 3. Median costs associated with the management of concurrent CRS and NEs were considerable at US$42,000 (grade $\geq$ 2) and US$50,400 (grade 3).

3.3 Cost-Effectiveness of Treatments

There were 11 unique cost-effectiveness models published with a total of 24 comparisons of treatment regimens (Table 2) [25, 27, 28, 37, 39, 40, 42–44, 50, 51]. Five studies

were in the USA, two in China, and one each in Turkey, the Netherlands, Canada, and Sweden.

Six recently published studies evaluated one or more of mosunetuzumab, axi-cel, or tisa-cel to each other or other regimens [27, 40, 42–44, 52]. The study by Eklund et al. was the only cost-effectiveness evaluation of mosunetuzumab, axi-cel, or tisa-cel to take place outside of the USA as it took the Swedish healthcare perspective [27]. The analysis reported that axi-cel could be considered cost-effective compared with the standard of care after three or more treatment lines, with an incremental cost-effectiveness ratio (ICER) of 680,001 (2022 SEK) per quality-adjusted life year (QALY) gained.

The remaining five studies including mosunetuzumab, axi-cel, and/or tisa-cel were all conducted with a US payer perspective. Axi-cel was compared with the standard of care in two studies with the analysis by Oluwole et al. using patient data from the SCHOLAR-5 cohort and Potnis et al. using data from the LEO CReWE study for the standard of care arm [42, 44]. Axi-cel was considered cost-effective with an ICER of US$89,784 compared with the standard of care from the SCHOLAR-5 study, but not cost-effective with an ICER of US$182,127 when the standard of care was from the CReWE study [42, 44]. A more recent model by Oluwole et al. compared axi-cel with mosunetuzumab and found axi-cel to be cost-effective, with an ICER of US$84,016 among patients with R/R FL with two or more prior treatment lines [43].

Mosunetuzumab was compared with both axi-cel and tisa-cel in a cost-effectiveness analysis with a 10-year time horizon [52]. The study reported that at 10 years, mosunetuzumab dominated (lower costs; higher QALYs) tisa-cel, and had lower costs and lower QALYs than axi-cel at 10 years, but a higher net monetary benefit.

The cost-effectiveness model developed by Matasar et al. compared mosunetuzumab with axi-cel, tisa-cel, tazemetostat, a real-world cohort, obinutuzumab + bendamustine, rituximab + bendamustine, and R2 among patients with R/R FL after two or more prior treatment lines [40]. Mosunetuzumab was found to be cost-effective across all of the comparisons except for R2, where it had lower costs but also lower QALYs, which resulted in R2 being cost-effective against mosunetuzumab.

3.4 Budget Impact of Treatments

There were three budget impact analyses published covering the introduction of copanlisib, tazemetostat, and mosunetuzumab for R/R FL (Table 3) [22, 38, 45]. All models evaluated the budget impact in a hypothetical 1,000,000-member plan in the USA and were focused on R/R FL after two or more prior treatment lines. The 1-year budget impact for introducing copanlisib was estimated to be US$0.02 per-member-per-month (PMPM) [22]. The financial impact of introducing tazemetostat to the formulary (70% commercial and 30% Medicare) ranged from a saving of US$0.0007 PMPM in year 1 to a saving of US$0.0011 PMPM in year 3. In this model, the savings associated with tazemetostat were driven by reductions in costs related to drug wastage and adverse events.

The budget impact analysis of mosunetuzumab examined a payer mix of 54.1% for Medicare and 55.9% for commercial. Comparison treatments included axi-cel, tisa-cel, R2, tazemetostat, and copanlisib. Of the included therapies, 3-year per-patient costs were estimated to be lowest for copanlisib (US$127,293) followed by mosunetuzumab (US$202,039), tazemetostat (US$250,665), R2 (US$263,520), tisa-cel (US$476,293), and axi-cel (US$505,845). At an uptake of 25%, 30%, and 35% over 3 years, the estimated budget impact for mosunetuzumab was US$0.0019 PMPM [38].

4 Discussion

This is the first literature review to focus on the economic and HCRU burden of R/R FL overall and associated with treatments, and health economic models of novel R/R FL treatments. Our review found a high level of real-world cost and HCRU burden for patients with R/R FL overall [23, 29, 30, 35, 36, 41, 46, 49] and an increasing burden as patients advance through treatment lines with annual all-cause healthcare costs reaching over US$400,000 [23, 30, 46, 49]. However, few retrospective/prospective studies evaluated specific treatments or treatment classes, and no recent studies have reported economic evaluations of specific treatment sequences that could provide stakeholders with a more holistic view of the costs and benefits of potential treatment strategies across lines of therapy.

Previous literature reviews have examined the disease burden and treatment patterns of patients with R/R FL but have not reported the burden associated with specific treatments or all types of health economic models [53, 54]. This study utilized a shorter and more recent search window to provide an update to the previously published literature and focus on capturing studies of novel therapies [54].

The treatment landscape for FL has rapidly changed since 2020 with the FDA approval of novel therapies, including tazemetostat, mosunetuzumab, axi-cel, and tisa-cel [55, 56], as well as the recent accelerated approval of zanubrutinib + obinutuzumab [57]. While these therapies have shown significant clinical benefit for patients in the clinical trial setting [16–19], their real-world impact on clinical outcomes, costs, and HCRU has yet to be fully understood given the limited follow-up time and lack of real-world studies.

An additional challenge that the rapidly changing treatment landscape in FL presents is the need to evaluate the impact of novel therapies throughout the treatment paradigm, which requires significant patient history data in the era of novel therapies. Patient history includes key prognostic indicators such as POD24 and prior treatment history [46]. Therapies being evaluated in later lines may not include patients that have received novel agents in earlier lines, which could potentially impact response to later line therapies.

The studies included in this review that examined the real-world cost and HCRU burden of R/R FL by treatment line mostly included study data through 2021 [23, 29, 30, 35, 36, 41, 46] at the latest, except for one study with data through March 2023 [49]. The findings of these studies may not accurately reflect the impact of these novel agents on the cost and HCRU burden given the more recent approvals for these agents. Studies with long-term follow-up using more recent data are needed to fully evaluate the impact of recently approved novel therapies on preventing progression and other downstream costs of R/R FL.

While the retrospective and prospective studies included in the review showed increasing costs as patients progressed down treatment lines, and considerable costs for CAR-T, there was significant variation between these studies regarding setting, study design, data analyzed, patient populations, and outcomes considered. Included retrospective and prospective studies analyzed real-world data as well as clinical trials in a variety of settings including individual countries and multi-national trials. Most studies reported results according to treatment line and not for specific treatments, which can lead to a lack of comparability across studies with different treatment patterns across treatment lines owing to different patient populations and/or settings. Studies also included different patient populations such as patients aged 66 years or older at diagnosis and initiating a third-line therapy, those with relapse after R-chemotherapy, patients with early treatment failure of first-line chemoimmunotherapy, and others [23, 35, 36]. Lastly, sample sizes were often limited in later lines of therapy and for novel treatments. For example, in Fowler et al. the fourth-line and fifth-line analyses included 21 and 11 patients, respectively, and Di et al. included 6 patients on CAR-T [26, 30].

Few retrospective or prospective studies evaluated economic outcomes associated with specific treatment or classes of treatment. CAR-T as a class was evaluated by Chan et al. and Di et al. in the real-world setting [24, 26]. However, these studies had significant differences in their outcomes measured, as Chan et al. reported PPPM Medicare and commercial costs in the third-line and the later setting post-CAR-T, which were in-line with those being reported by the standard of care in the third-line setting [24]. Di et al. only included six patients and reported costs for the 41 days prior to CAR-T through 154 days after CAR-T [26]. The trials of tisa-cel and liso-cel were also analyzed to examine inpatient versus outpatient administration and the management of CRS and neurological events, respectively [31, 48]. There were no retrospective or prospective studies reporting economic outcomes specifically for mosunetuzumab, tazemetostat, or any other non-CAR-T novel therapy. The analysis of treatment classes by Matasar et al. of oral PI3Kis, anti-CD20s, and chemoimmunotherapy in the third-line and later setting was significantly limited by sample size [41].

While pharmacoeconomic models have shown that novel therapies such as CAR-Ts may, in some cases, be cost-effective in R/R FL [27, 42, 43], the overall cost to the healthcare system is substantial, with estimates ranging from US$450,000 to over US$700,000 per patient [26, 33]. Long-term data will be needed to confirm the cost-effectiveness results, which are largely based on the extrapolation of short-term outcomes in these novel treatments. The differences between the clinical trial setting and real-world setting will be an important consideration for assessing the potential value of novel treatments, especially CAR-T. The analysis of the ELARA trial revealed substantial differences in average hospitalization costs per treated patient for those with tisa-cel administered in the inpatient setting (US$40,054) compared with the outpatient setting (US$7477) [31]. Real-world AE event rates for CAR-T will also need to be studied as average per-patient costs for CRS and NEs using rates from clinical trials have been estimated to range between US$20,626 and US$44,096 between liso-cel, tisa-cel, and axi-cel in R/R FL [47]. The cost-effectiveness models were generally heavily reliant on assumptions and extrapolation of short-term clinical trial data to predict long-term outcomes. It remains to be seen how generalizable these results will be to health systems in the real-world setting.

The budget impact models included in this review reported that the anticipated financial impact of introducing novel therapies, such as tazemetostat and mosunetuzumab, would be minimal and in some cases, cost-saving [38, 45]. However, the models noted that key variables such as compliance, mortality, and post-discontinuation treatment were not assessed, and the models relied on assumptions for some variables. One real-world study reported differences in costs between patients receiving CAR-T and the standard of care for follicular lymphoma showed lower PPPM costs for CAR-T patients following therapy but did not consider the cost of CAR-T itself [24].

As with any systematic literature review, there are several limitations associated with this study.

First, systematic literature reviews are subject to human error during the searching, screening, and extracting phases of the project. Second, the databases used may not index all potential literature relevant to this particular review, or there may be a delay between publication and indexing, resulting

in studies published during our review's timeframe being missed. A manual search was conducted to reduce the risk of studies being missed due to a lag in indexing into the searched databases. This review did not include grey literature or health technology assessments, which could contain economic evaluations of R/R FL intervention. Third, this review included abstracts and posters, which only present limited methodologies, inputs, and results. These studies may not fully describe the included patient population given the restrictions on word/character counts; therefore, it is possible that some included studies may have included patients with transformed FL, other patients with NHL, or patients with non-R/R FL in their patient populations. In cases of ambiguity the reviewers generally leaned towards study inclusion. Lastly, this study reported costs in the currency and cost year reported in the original study and did not adjust for inflation or to a single currency. Costs were not adjusted as several included studies did not report the year of costs. In addition, the objective of this manuscript was not to directly compare the results of studies. It was to identify studies reporting economic results, identify unmet needs, and examine the impact of novel therapies within the population of patients with R/R FL.

4.1 Conclusions

The overall economic and HCRU burden of R/R FL remains high and increases as patients progress through treatment lines. While novel therapies have shown promising clinical benefits in clinical trials, their impact on the cost and HCRU burden in the real-world is only just starting to be realized. Further studies are needed to quantify the impact and validate the health economic models of these novel therapies as they transition to real-world use.

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Declarations

Ethics approval Not applicable.

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Authors' contributions Steering Committee member: B.S., E.K.S., J.K., and K.Y. Contribution to conception/ design: M.X., W.F., E.K.S., and M.D. Acquisition of data: W.F., P.C., and M.D. Analysis of data: W.F., P.C., and M.D. Interpretation of data: B.S., M.X., W.F., and K.Y. Writing—original draft: B.S., M.X., W.F., E.K.S., J.K., P.C., M.D., and K.Y. Writing—review and editing: B.S., M.X., W.F., E.K.S., J.K., P.C., M.D., and K.Y.

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