A Comprehensive Global Systematic Literature Review Of Real-World Evidence Of Relapsed/Refractory And Post-Bruton Tyrosine Kinase Inhibitor Mantle Cell Lymphoma

RWD14

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CONCLUSIONS

- This SLR found incomplete reporting of RWE in R/R MCL, with consistent evidence that outcomes worsen with each subsequent line of therapy. Major gaps in HCRU, cost, and PRO reporting (particularly in the post-BTKi setting) highlight the need for more standardized, prospective real-world research to inform treatment decisions and support access to emerging therapies.

BACKGROUND

- Mantle cell lymphoma (MCL) is a rare, aggressive, and incurable subtype of B-cell non-Hodgkin lymphoma (NHL) that accounts for approximately 2%–6% of all NHL cases; incidence is rising globally.[1]
- MCL is marked by a high risk of relapse, with up to 58% of newly diagnosed patients experiencing disease progression following first-line therapy.[2]
- As treatment paradigms have evolved, a growing proportion of patients now relapse after covalent Bruton tyrosine kinase inhibitor (BTKi) therapy; outcomes following BTKi failure remain poor, reflecting the limited availability of effective subsequent treatment options.[3]

OBJECTIVES

- To conduct a systematic literature review (SLR) summarizing real-world evidence (RWE) in relapsed/refractory (R/R) MCL, including the post-BTKi treatment setting.

METHODS

- A global SLR of Embase, PubMed, and CENTRAL was conducted to identify RWE publications and abstracts (January 1, 2020–April 30, 2025).
- Studies were assessed for eligibility (**Table 1**) and selected by two reviewers independently during title, abstract, and full-text screening according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.
- Eligible studies were summarized descriptively by line of therapy, treatments for R/R MCL, and outcomes of interest.

Table 1. Eligibility Criteria

Inclusion Criteria
• Relapsed or refractory MCL • 2 or more lines of therapy • No restrictions on comparators • Reporting outcomes data from at least one of: overall response rate (ORR), complete response (CR), progression-free survival (PFS), overall survival (OS), duration of response (DOR), time to next treatment (TTNT), discontinuation, adherence, healthcare resource utilization (HCRU), costs, or patient-reported outcomes (PROs) • Real-world study design, inclusive of cohort, retrospective, and prospective studies
Exclusion Criteria
• 1L or untreated MCL • Clinical trials, case studies, non-human studies, pre-clinical studies • Non-English studies • Studies published prior to January 1, 2020

RESULTS

Study Identification and Characteristics

- Forty-four R/R MCL studies were identified, including 21 that evaluated patients in post-BTKi settings. Most included studies reported clinical outcomes only (n=42), with OS and PFS being the most frequently evaluated clinical outcome. Six of the identified studies evaluated HCRU (n=6), costs (n=4), or adherence (n=2). No real-world PROs were identified. Study characteristics are summarized in **Table 2**.

Table 2. Characteristics of Included Studies Reporting Real-World Clinical and Economic Outcomes for R/R MCL

Study	Intervention	Line of Therapy	Study design	Data Source	Country	Sample Size	Reported Outcomes
CAR-T Therapy							
Ahmed 2024[4]	Brexu-cel	2L+ (post-BTKi)	Retrospective	Medical records from multiple sites	US	12	CR, OS, PFS
Chong 2024[5]	Brexu-cel	2L+ (post-BTKi)	Retrospective	Medical records from a university hospital	US	17	ORR, CR, OS, PFS, DOR
Herbaux 2024[6]	Brexu-cel	2L+ (post-BTKi)	Retrospective	Medical records from DESCAR-T	France	152	ORR, CR, OS, PFS, HCRU
Iacoboni 2022[7]	Brexu-cel	2L+ (post-BTKi)	Retrospective	Medical records from an Early Access Program	Europe	33	ORR, CR, OS, PFS
Kambhampati 2023[8]	Brexu-cel	2L+	Retrospective	Medical records from CIBMTR	US	446	ORR, CR, DOR
Nie 2024[9]	Brexu-cel	2L+ (post-BTKi)	Retrospective	Medical records from a university hospital	US	10	ORR, CR, OS, PFS, DOR
O'Reilly 2024[10]	Brexu-cel	3L+ (post-BTKi)	Retrospective	EMRs from CAR-T Centers	UK	83	ORR, CR, OS, PFS
Rejeski 2023[11]	Brexu-cel	3L+	Retrospective	Medical records from multiple sites	International	103	ORR, CR, OS, PFS
Stella 2025[12]	Brexu-cel	3L+ (post-BTKi)	Prospective	Medical records from multiple sites	Italy	106	ORR, CR, OS, PFS, DOR
Wang 2023a[13]	Brexu-cel	2L+ (includes post-BTKi)	Retrospective	Medical records from multiple sites	US	Overall: 168 Post-BTKi: 144	ORR, CR, OS, PFS, DOR, HCRU
BTKi Regimens							
Villa 2023[14]	BTKi monotherapy	2L	Retrospective	Medical records from multiple sites	International	160	CR, OS, PFS, discontinuation
Narkhede 2022[15]	BTKis	2L	Retrospective	EMRs from Flatiron Health Research Database	US	647	OS, TTNT
Wang 2023b[16]	BTKis	2L	Retrospective	Medical records from multiple Institutions	US	203	ORR, CR, OS
Hess 2022[17]	Covalent BTKis	2L+ (includes post-BTKi)	Retrospective	EMRs from ConcertAI RWD360	US	Overall: 946 Post-BTKi: 352	OS, TNTT, discontinuation
Cencini 2021[18]	Ibrutinib	2L (includes post-BTKi)	Retrospective	Medical records from onco-Hematological Centers	Italy	Overall: 69 Post-BTKi: 14	OS, CR, OS, PFS, discontinuation
Dartigeas 2022[19]	Ibrutinib	2L	Prospective	Medical records from FIRE Study	Europe	59	OS, CR, OS, PFS, discontinuation
Ghosh 2021[20]	Ibrutinib Chemoimmunotherapy	2L+	Retrospective	Medical records from Optum Research Database	US	Ibrutinib: 144 Chemoimmunotherapy: 156	HCRU, cost
Lee 2023[21]	Ibrutinib	2L	Retrospective	Medical records from Samsung Medical Center	South Korea	42	OS, CR, OS, PFS, discontinuation
Maruyama 2024[22]	Ibrutinib	2L	Prospective	Medical records from multiple centers	Japan	248	OS, CR, OS, PFS
McCulloch 2021[23]	Ibrutinib	2L	Retrospective	Medical records from multiple centers	UK	211	OS, CR, OS, PFS
Obr 2023[24]	Ibrutinib	2L+	Retrospective	Medical records from the Observational Epidemiological and Clinical Study	Czech Republic	77	OS, PFS
Rusconi 2022[25]	Ibrutinib Chemotherapy Mixed Regimens	2L+	Retrospective	Medical records from FIL, EMCLN	International	Ibrutinib: 29 Chemotherapy: 29 Mixed regimens: 30	ORR, OS, PFS
Sancho 2022[26]	Ibrutinib	2L+	Retrospective	Medical records from multiple sites	Spain	66	ORR, CR, OS, PFS, TTD, discontinuation
Sharman 2021[27]	Ibrutinib	2L, 3L	Retrospective	EMRs from iKnowMed	US	2L: 86 3L: 61	OS, PFS, TTD, discontinuation
Tivey 2024[28]	Ibrutinib	2L+ (post-BTKi)	Prospective	Medical records from multiple sites	UK	26	ORR, CR, OS
Tucker 2021[29]	Ibrutinib Chemoimmunotherapy Lenalidomide or Venetoclax	2L+ (includes post-BTKi)	Retrospective	Medical records from multiple sites	UK, Ireland	Ibrutinib: 65 Chemoimmunotherapy: 7 Lenalidomide or Venetoclax: 5	OS, PFS
Yi 2021[30]	Ibrutinib	2L+ (includes post-BTKi)	Retrospective	Medical records from multiple sites	South Korea	Overall: 88 Post-BTKi: 16	CR, PFS, TTD, discontinuation
Zhang 2022[31]	Ibrutinib	2L+	Retrospective	Medical records from multiple sites	China	121	ORR, CR, OS, PFS, discontinuation
Aydilek 2024[32]	Pirtobrutinib	2L+ (post-BTKi)	Retrospective	Medical records from a compassionate use program	Europe	10	ORR, CR, OS, PFS, DOR
Mixed Regimens							
Bock 2023[33]	Mixed Regimens	2L	Prospective	Medical records from Molecular Epidemiology Resource	US	183	ORR, CR, OS
Eskelund 2021[34]	Mixed Regimens	2L+	Retrospective	Medical records from local physicians	Europe	149	ORR
Hess 2023[35]	Mixed Regimens	2L+ (post-BTKi)	Retrospective	Medical records from SCHOLAR-2	Europe	149	OS
Jain 2021[36]	Mixed regimens	2L+ (post-BTKi)	Retrospective	Medical records	US	7	ORR, CR
Keating 2023[37]	Mixed Regimens	2L+	Retrospective	Claims from Merative MarketScan	US	243	HCRU, cost
Kilgore 2025[38]	Mixed Regimens	2L+	Retrospective	Medicare FFS claims data; Inovalon MORE[2] Registry	US	2,835	TTNT, HCRU, cost
Mathys 2022[39]	Mixed Regimens	2L+	Retrospective	Medical records from a university hospital	Switzerland	43	OS, PFS
Minson 2024[40]	Mixed Regimens	2L, 3L	Retrospective	Medical records from institutional databases	Australia, UK	2L: 150 3L: 55	OS, PFS
Rai 2022[41]	Mixed Regimens	2L (includes post-BTKi)	Retrospective	Claims from Medical Data Vision	Japan	Overall: 247 Post-BTKi: 137	OS, discontinuation
Squires 2023[42]	Mixed Regimens	2L+	Retrospective	Claims from Chronic Conditions Warehouse 100% Medicare Parts A, B, and D	US	2L+: 1,476 3L+ 649 4L+: 284	OS, HCRU, costs
Squires 2024[43]	Mixed Regimens	3L (post-BTKi)	Retrospective	Claims from Chronic Conditions Warehouse 100% Medicare Parts A, B, and D	US	230	OS, DOR, TTNT, discontinuation
Chemotherapy Regimens							
Hohloch 2020[44]	Radioimmunotherapy	2L+	Retrospective	Registry data from RIT Network	International	45	CR, OS, PFS
Karadurmus 2021[45]	Bendamustine	3L+	Retrospective	Medical records from multiple sites	Turkey	18	ORR, CR, OS, PFS, discontinuation, TTNT
McCulloch 2020[46]	R-BAC	2L+ (post-BTKi)	Retrospective	Medical records from multiple sites	UK, Italy	36	ORR, OS, PFS, discontinuation, HCRU
BCL2i Regimens							
Sawalha 2023[47]	Venetoclax	2L+ (post-BTKi)	Retrospective	Medical records from multiple sites	US	80	ORR, CR, OS, PFS, discontinuation
Zhao 2020[48]	Venetoclax	2L+ (post-BTKi)	Retrospective	Medical records from university hospital	US	24	ORR, CR, OS, PFS, DOR, discontinuation

Abbreviations: 2L: Second-line treatment, 2L+: Second-line treatment and greater, 3L: Third-line treatment, 3L+: Third-line treatment and greater, 4L: Fourth-line treatment, 4L+: Fourth-line treatment and greater, BCL2i: B-cell lymphoma 2 inhibitor, BTKi: Bruton Tyrosine Kinase inhibitor, CIBMTR: Center for International Blood and Marrow Transplant Research, CR: Complete response, DOR: Duration of response, EMCLN: European MCL Network, EMRs: Electronic Medical Records, FIL: Fondazione Italiana Linfomi, FFS: Fee for service, HCRU: Healthcare resource use, ORR: Overall response rate, OS: Overall survival, PFS: Progression-free survival, TTNT: Time to next treatment

CLINICAL OUTCOMES

Overall Survival

- Thirty-eight studies reported outcomes data for OS, including 17 that reported OS data for post-BTKi settings (**Table 3**). Median OS (n=25) ranged from 1.4 to 105 months, and 1-year OS (n=15) 39.3% to 90.0%. Three-year OS was reported in one study evaluating CAR-T cell therapy in post-BTKi settings (17.0%).
- Among ibrutinib regimens with median OS data (n=12), median OS ranged from 16.8 to 50.1 months. Mixed regimens with OS data (n=7) had a wider range for median (2.8 to 105 months) than BTKi regimens (1.4 to 50.1 months) and chemotherapy regimens (n=4) (4.4 to 46.2 months).
- OS generally decreased with later lines of therapy. In a 2023 study by Squires et al., median OS declined from 22.0 months at 2L+ to 7.8 months at 4L+ in patients receiving mixed regimens.
- Among studies reporting OS for post-BTKi settings, median OS ranged from 5.0 to 24.0 months. Among mixed regimens (n=3) reporting data for the post-BTKi setting, median OS ranged from 1.4 to 24.0 months.

Progression-Free Survival

- Thirty studies reported outcomes data for PFS, including 13 in the post-BTKi setting (**Table 4**). Median PFS (n=26) ranged from 2.2 to 28.0 months in R/R MCL and 1-year PFS rates (n=14) ranged from 33.0% to 82.0%. Three and 5-year PFS rates were not reported.
- Among ibrutinib regimens, median PFS ranged from 10.3 to 21.7 months for the general R/R MCL population. CAR-T therapy (brexucabtagene autoleucel [Brexu-cel]) showed favorable PFS in later lines, with median PFS ranging from 9.5 months in 2L+ to 25.2 months in 3L+ patients.
- Outcomes worsened with later lines of therapy. In Eskelund (2021), median PFS declined from 8.6 months after 2L to 3.6 months after 4L in patients receiving mixed treatment regimens.
- Among studies reporting PFS data for post-BTKi settings, (n=16), median PFS ranged from 3.7 to 16.2 months (**Table 4**), with venetoclax regimens (n=2) reporting median PFS of 3.7 to 8.0 months, CAR-T regimens (n=8) 9.5 to 21.0 months, and chemotherapy regimen R-BAC 10.1 months.

Table 3. Real-World OS Outcomes in R/R MCL

Study	Line of Therapy[a]	Intervention	Evaluable N	Median OS, months[b]	1-Year OS Rate (%)[b]	3-Year OS Rate (%)
CAR-T Therapy						
Ahmed 2024[4]	2L+ (post-BTKi)	Brexu-cel	12	-	67.0%	17.0%
Chong 2024[5]	2L+ (post-BTKi)	Brexu-cel	17	-	64.0%	-
Herbaux 2024[6]	2L+ (post-BTKi)	Brexu-cel	144	-	69.8%	-
Iacoboni 2022[7]	2L+ (post-BTKi)	Brexu-cel	33	-	61.0%	-
Nie 2024[9]	2L+ (post-BTKi)	Brexu-cel	10	-	90.0%	-
O'Reilly 2024[10]	3L+ (post-BTKi)	Brexu-cel	83	-	74.0%	-
Rejeski 2023[11]	3L+	Brexu-cel	103	-	80.0%	-
Stella 2025[12]	3L+ (post-BTKi)	Brexu-cel	106	-	62.0%	-
Wang 2023a[13]	2L+ (includes post-BTKi)	Brexu-cel	Overall: 168 Post-BTKi: 144	-	Overall: 75.0% Post-BTKi: 72.6%	-
BTKi Regimens						
Villa 2023[14]	2L	BTKi monotherapy	160	34.8	-	
Narkhede 2022[15]	2L	BTKis	647	24.0	-	-
Wang 2023b[16]	2L	BTKis	203	24.8	-	-
Hess 2022[17]	2L+ (includes post-BTKi)	Covalent BTKis	Overall: 2L: 284 Overall: 3L: 88 Overall: 4L: 30 Overall: 5L: 13	Overall: 2L: 5.9 Overall: 3L: 8.0 Overall: 4L: 2.5 Overall: 5L: 11.7	-	-
Cencini 2021[18]	2L+ (includes post-BTKi)	Ibrutinib	Overall: 69 Post-BTKi: 14	Overall: 34.8 Post-BTKi: 5.0	-	-
Dartigeas 2022[19]	2L	Ibrutinib	59	-	65.8%	-
Lee 2023[21]	2L+	Ibrutinib	42	50.1	-	-
Maruyama 2024[22]	2L	Ibrutinib	202	-	69.3%	-
McCulloch 2021[23]	2L	Ibrutinib	211	23.9	-	-
Obr 2023[24]	2L+	Ibrutinib	77	23.1		
Rusconi 2022[25]	2L+	Ibrutinib Chemotherapy Mixed Regimens	29 29 30	16.8 4.4 2.8	-	-
Sancho 2022[26]	2L+	Ibrutinib	66	32.0	-	-
Sharman 2021[27]	2L, 3L	Ibrutinib	2L: 86 3L: 61	2L: 22.3 3L: 25.8	-	-
Tivey 2024[28]	2L+ (post-BTKi)	Ibrutinib	26	1.4	-	-
Tucker 2021[29]	2L+ (includes post-BTKi)	Ibrutinib	Overall: 65	Overall: 18.5	-	-
Zhang 2022[31]	2L+	Ibrutinib	121	37.6	86.9%	-
Aydilek 2024[32]	2L+ (post-BTKi)	Pirtobrutinib	10	-	56.0%	-
Mixed Regimens						
Bock 2023[33]	2L	Mixed Regimens	183	43.2	-	-
Hess 2023[35]	2L+ (post-BTKi)	Mixed Regimens	149	9.7	-	-
Mathys 2022[39]	2L+	Mixed Regimens	43	105.0	-	-
Minson 2024[40]	2L, 3L	Mixed Regimens	2L: 150 3L: 55	2L: 30 3L: 14	-	-
Rai 2022[41]	2L+ (includes post-BTKi)	Mixed Regimens	Overall: 247 Post-BTKi: 137	Overall: 5.6 Post-BTKi: 8.7	-	
Rusconi 2022[25]	2L+	Mixed Regimens	30	2.8		
Squires 2023[42]	2L+	Mixed Regimens	2L+: 1,476 3L+ 649 4L+: 284	2L+: 22.0 3L+: 11.8 4L+: 7.8	2L+: 63.8% 3L+: 49.9% 4L+: 39.3%	-
Squires 2024[43]	3L (post-BTKi)	Mixed Regimens	230	9.4	43.7%	-
BCL2i Regimens						
Sawalha 2023[47]	2L+ (post-BTKi)	Venetoclax	80	12.5	-	-
Tucker 2021[29]	2L+ (includes post-BTKi)	Lenalidomide or Venetoclax	Post-BTKi: 5	Post-BTKi: 16.0	-	-
Zhao 2020[48]	2L+ (post-BTKi)	Venetoclax	24	13.5	-	-
Chemotherapy Regimens						
Hohloch 2020[44]	2L+	Radioimmunotherapy	45	46.2	-	-
Karadurmus 2021[45]	3L+	Bendamustine	18	-	74.9%	-
McCulloch 2020[46]	2L+ (post-BTKi)	R-BAC	36	12.5	-	-
Rusconi 2022[25]	2L+	Chemotherapy	29	4.4	-	-
Tucker 2021[29]	2L+ (includes post-BTKi)	Chemoimmunotherapy	Post-BTKi: 7	Post-BTKi: 24.0	-	-

[a]Includes post-BTKi" indicates a study with a post-BTKi subgroup for which there is outcomes data of interest reported; [b]Unless otherwise stated, results are for overall population
Abbreviations: 2L: Second-line treatment, 2L+: Second-line treatment and greater, 3L: Third-line treatment, 3L+: Third-line treatment and greater, 4L+: Fourth-line treatment and greater, BTKi: Bruton tyrosine kinase inhibitor, R/R: Relapsed or refractory, MCL: Mantle cell lymphoma, OS: Overall survival

ORR

- Twenty-seven studies reported outcomes data for ORR in the R/R MCL population, including 13 in the post-BTKi setting. ORR ranged from 40.3% to 100% in the overall R/R MCL population, and from 23.1% to 90.9% in post-BTKi settings.
- CAR-T therapy in post-BTKi settings (n=5) demonstrated ORR ranging from 82.4% to 90.9% and CR rates of 64.7% to 93.8%. These rates were higher than for venetoclax (ORR 40.3%-50%; CR 16.4%–20.8%), BTKi rechallenge/switch (ORR 57.1%–70.0%; CR 10.0%–14.3%), and mixed regimens (ORR 23.1%–28.6%).

TTNT

- Four studies reported outcomes for TNNT, with none reporting data for regimens in post-BTKi settings (**Figure 1**). Median TTNT ranged from 0.4 to 22.7 months in patients receiving mixed regimens and 1.7 to 4.0 months for covalent BTKis.
- Across mixed regimen studies, TTNT generally decreased with later lines of therapy. Median TTNT among patients receiving mixed regimens were observed to have decreasing TTNT as patients progressed from 2L (22.7 months) to 6L (6.1 months) in Kilgore (2025), and 2L+ (2.6 months) to 4L+ (0.4 months) in Squires (2023).

Figure 1. Median TTNT (Months) for R/R MCL

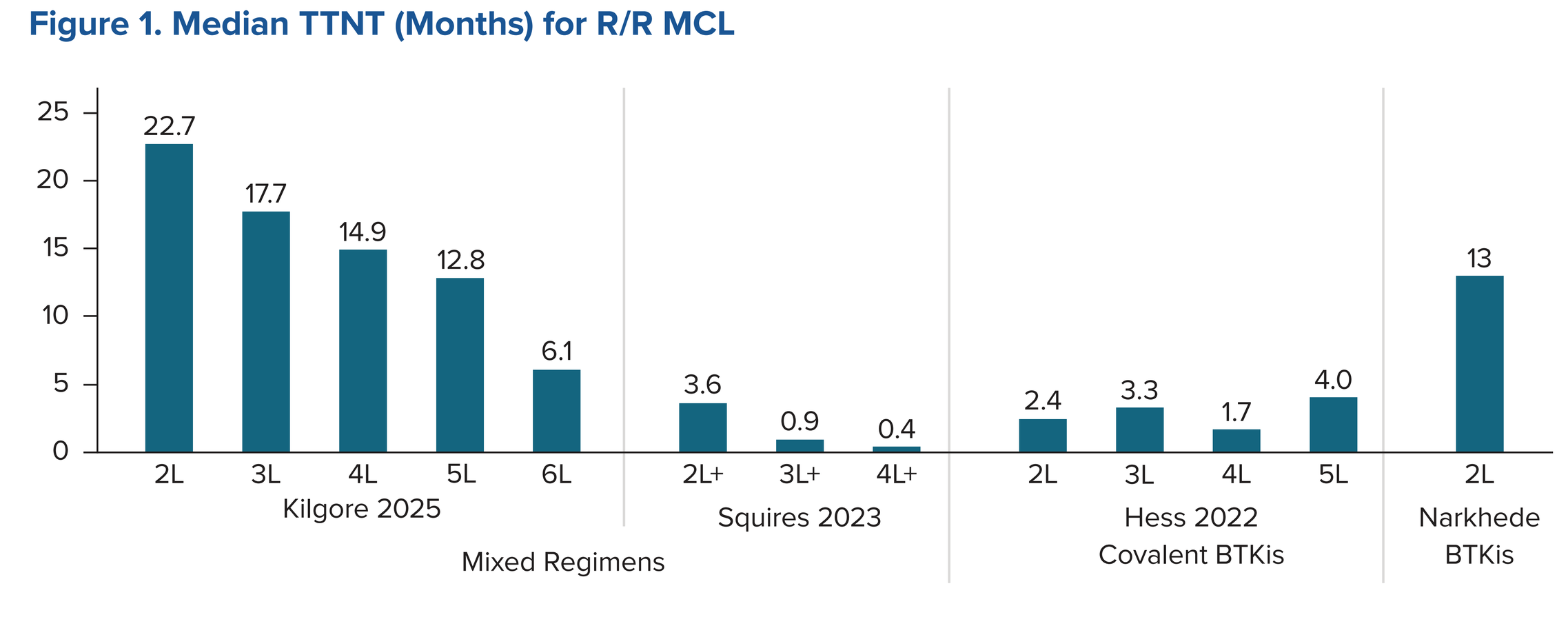

Table 4. Real-World PFS Outcomes in R/R MCL

Study	Study Population[a]	Intervention	Evaluable N	Median PFS, months[b]	1-Year PFS Rate (%)[b]
CAR-T Therapy					
Ahmed 2024[4]	2L+ (post-BTKi)	Brexu-cel	12	-	33.0%
Chong 2024[5]	2L+ (post-BTKi)	Brexu-cel	17	10.0	45.0%
Herbaux 2024[6]	2L+ (post-BTKi)	Brexu-cel	144	9.5	45.6%
Iacoboni 2022[7]	2L+ (post-BTKi)	Brexu-cel	33	-	51.0%
Nie 2024[9]	2L+ (post-BTKi)	Brexu-cel	10	16.2	64.3%
O'Reilly 2024[10]	3L+ (post-BTKi)	Brexu-cel	83	21.0	62.%
Rejeski 2023[11]	3L+	Brexu-cel	103	25.2	67.0%
Stella 2025[12]	3L+ (post-BTKi)	Brexu-cel	106	-	82.0%
Wang 2023a[13]	2L+ (includes post-BTKi)	Brexu-cel	Overall: 168 Post-BTKi: 144	Overall: 16.4 Post-BTKi: NR	Overall: 59.0% Post-BTKi: 57.3%
BTKi Regimens					
Villa 2023[14]	2L	BTKi monotherapy	160	14.4	-
Cencini 2021[18]	2L+ (includes-post-BTKi)	Ibrutinib	Overall: 69 Post-BTKi: 14	Overall: 17.0	-
Dartigeas 2022[19]	2L+	Ibrutinib	59	12.4	53.5%
Lee 2023[21]	2L+	Ibrutinib	42	16.4	-
Maruyama 2024[22]	2L+	Ibrutinib	248	10.5	47.5%
McCulloch 2021[23]	2L	Ibrutinib	211	17.8	-
Obr 2023[24]	2L+	Ibrutinib	77	10.3	-
Rusconi C 2022[25]	2L+	Ibrutinib	29	13.1	-
Sancho 2022[26]	2L+	Ibrutinib	66	20.0	-
Sharman 2021[27]	2L, 3L	Ibrutinib	2L: 86 3L: 61	2L: 19.1 3L: 19.9	-
Tucker 2021[29]	2L+ (includes post-BTKi)	Ibrutinib	Overall: 65	Overall: 12.0	-
Yi 2021[30]	2L+ (includes post-BTKi)	Ibrutinib	Overall: 88 Post-BTKi: 16	Overall: 20.8 Post-BTKi: 4.9	-
Zhang 2022[31]	2L+	Ibrutinib	121	21.7	70.7%
Aydilek 2024[32]	2L+ (post-BTKi)	Pirtobrutinib	10	-	56.0%
Mixed Regimens					
Mathys 2022[39]	2L+	Mixed Regimens	43	28.0	-
Minson 2024[40]	2L, 3L	Mixed Regimens	2L: 150 3L: 55	2L: 14.4 3L: 8.4	-
Rusconi C 2022[25]	2L+	Mixed Regimens	30	2.2	-
BCL2i Regimens					
Sawalha 2023[47]	2L+ (post-BTKi)	Venetoclax	80	3.7	-
Zhao 2020[48]	2L+ (post BTKi)	Venetoclax	24	8.0	-
Chemotherapy Regimens					
Karadurmus 2021[45]	3L+	Bendamustine	18	25.9	63.9%
Hohloch 2020[44]	2L+	Radioimmunotherapy	45	10.56	-
McCulloch 2020[46]	2L+ (post-BTKi)	R-BAC	36	10.1	-
Rusconi C 2022[25]	2L+	Chemotherapy	29	3.0	-

[a]Includes post-BTKi indicates a study with a post-BTKi subgroup for which there is outcomes data of interest reported; [b]Unless otherwise stated, results are for overall population
Abbreviations: 2L: Second-line treatment, 2L+: Second-line treatment and greater, 3L: Third-line treatment, 3L+: Third-line treatment and greater, 4L: Fourth-line treatment, BTKi: Bruton tyrosine kinase inhibitor, R/R: Relapsed or refractory, MCL: Mantle cell lymphoma, NR: Not reported, PFS: Progression-free survival.

HCRU

- HCRU was reported in eight studies, including three in post-BTKi settings. Among these studies, all reported outcomes data for hospitalizations. Wang (2023) and Herbaux (2024) reported intensive care unit (ICU) admissions, and McCulloch (2020) reported unplanned admissions.
- In US studies, annual total costs ranged from $141,958 to $365,892 in R/R MCL. One study (Squires 2024) reported post-BTKi costs, with a mean monthly total healthcare cost of $16,744 per patient.

Discussion

- Clinical outcomes in R/R MCL deteriorated with each subsequent line of therapy, regardless of regimen, as reflected by declining median OS and PFS across multiple studies. Where reported, TTNT findings were directionally consistent with OS and PFS, with shorter TTNT observed in later lines of therapy.
- BTKis were associated with meaningful but variable real-world outcomes in R/R MCL. Between-study variability in outcomes likely reflects differences in patient selection, line of therapy, and follow-up, underscoring the need for more standardized RWE reporting.
- Economic and HCRU evidence was limited, with a consistent focus on hospitalizations, suggesting inpatient care may be a meaningful but under-quantified driver of overall burden.

REFERENCES

1. Silkenstedt E, Dreyling M. Mantle cell lymphoma-Update on molecular biology, prognostication and treatment approaches. *Hematol Oncol*. Jun 2023;41 Suppl 1:36-42. doi:10.1002/hon.3149
2. Kumar A, Sha F, Toure A, et al. Patterns of survival in patients with recurrent mantle cell lymphoma in the modern era: progressive shortening in response duration and survival after each relapse. *Blood Cancer J*. May 20 2019;9(6):50. doi:10.1038/s41408-019-0209-5
3. Sancho JM, Sorigué M, Rubio-Azpeitia E. Real-World Evidence of Relapsed/Refractory Mantle Cell Lymphoma Patients and Treatments: A Systematic Review. *J Blood Med*. 2024;15:239-254. doi:10.2147/jbm.S463946
4. Ahmed G, Alsouqi A, Szabo A, et al. CAR T-cell therapy in mantle cell lymphoma with secondary CNS involvement: a multicenter experience. *Blood Adv*. Jul 9 2024;8(13):3528-3531. doi:10.1182/bloodadvances.2023012255
5. Chong EA, Chong ER, Therwhanger D, et al. Bendamustine as Lymphodepletion for Brexucabtagene Autoleucel Therapy of Mantle Cell Lymphoma. *Transplant Cell Ther*. Jul 2024;30(7):726.e1-726.e8. doi:10.1016/j.jtct.2024.03.015
6. Herbaux C, Bret C, Bachy E, et al. Brexucabtagene autoleucel in relapsed or refractory mantle cell lymphoma, intention-to-treat use in the DESCAR-T registry. *Haematologica*. Nov 1 2024;109(11):3745-3750. doi:10.3324/haematol.2023.284786
7. Iacoboni G, Rejeski K, Villacampa G, et al. Real-world evidence of brexucabtagene autoleucel for the treatment of relapsed or refractory mantle cell lymphoma. *Blood Adv*. Jun 28 2022;6(12):3606-3610. doi:10.1182/bloodadvances.2021006922
8. Kambhampati S, Ahmed N, Hamadani M, et al. Real-World Outcomes of Brexucabtagene Autoleucel (Brexu-cel) for Relapsed or Refractory (R/R) Mantle Cell Lymphoma (MCL): A CIBMTR Subgroup Analysis of High-Risk Characteristics. *Blood*. 2023;142(Supplement 1):107-107. doi:10.1182/blood-2023-179269
9. Nie EH, Su YJ, Baird JH, et al. Clinical features of neurotoxicity after CD19 CAR T-cell therapy in mantle cell lymphoma. *Blood Adv*. Mar 26 2024;8(6):1474-1486. doi:10.1182/bloodadvances.2023011896
10. O'Reilly MA, Wilson W, Burns D, et al. Brexucabtagene autoleucel for relapsed or refractory mantle cell lymphoma in the United Kingdom: A real-world intention-to-treat analysis. *Hemasphere*. Jun 2024;8(6):e87. doi:10.1002/hem3.87
11. Rejeski K, Wang Y, Albanyan O, et al. The CAR-HEMATOTOX score identifies patients at high risk for hematological toxicity, infectious complications, and poor treatment outcomes following brexucabtagene autoleucel for relapsed or refractory MCL. *Am J Hematol*. Nov 2023;98(11):1699-1710. doi:10.1002/ajh.27056
12. Stella F, Chiappella A, Magni M, et al. Brexucabtagene autoleucel in-vivo expansion and BTKi refractoriness have a negative influence on progression-free survival in mantle cell lymphoma: Results from CART-SIE study. *Br J Haematol*. Feb 2025;206(2):644-651. doi:10.1111/bjh.19961
13. Wang Y, Jain P, Locke FL, et al. Brexucabtagene Autoleucel for Relapsed or Refractory Mantle Cell Lymphoma in Standard-of-Care Practice: Results From the US Lymphoma CAR T Consortium. *J Clin Oncol*. May 10 2023;41(14):2594-2606. doi:10.1200/jco.22.01797
14. Villa D, Jiang A, Visco C, et al. Time to progression of disease and outcomes with second-line BTK inhibitors in relapsed/refractory mantle cell lymphoma. *Blood Adv*. Aug 22 2023;7(16):4576-4585. doi:10.1182/bloodadvances.2023009804
15. Narkhede M, Goyal G, Shea L, Mehta A, Giri S. Evaluating real-world treatment patterns and outcomes of mantle cell lymphoma. *Blood Adv*. Jul 26 2022;6(14):4122-4131. doi:10.1182/bloodadvances.2022007247
16. Wang Y, Larson MC, Hwang SR, et al. Multicenter Study of Mantle Cell Lymphoma Outcomes Following First-Line Bendamustine-Rituximab and Second-Line Bruton's Tyrosine Kinase Inhibitor Therapy. *Blood*. 2023;142(Supplement 1):300-300. doi:10.1182/blood-2023-182942
17. Hess LM, Chen Y, Abada PB, Konig H, Walgren RA. Outcomes among Patients with Mantle Cell Lymphoma Post-Covalent BTK Inhibitor Therapy in the United States: A Real-World Electronic Medical Records Study. *Adv Hematol*. 2022;2022:8262787. doi:10.1155/2022/8262787
18. Cencini E, Mecacci B, Morelli F, et al. Ibrutinib in patients with relapsed/refractory mantle cell lymphoma: a real-life, retrospective, multicenter trial on behalf of the "RTL" (regional Tuscan lymphoma network). *Am J Blood Res*. 2021;11(4):373-383.
19. Dartigeas C, Slama B, Doyle M, et al. FIRE Study: Real-World Effectiveness and Safety of Ibrutinib in Clinical Practice in Patients with CLL and MCL. *Clin Hematol Int*. Sep 2022;4(3):65-74. doi:10.1007/s44228-022-00015-5
20. Ghosh N, Emond B, Lafeuille MH, Côté-Sergent A, Lefebvre P, Huang Q. Treatment Patterns Among Patients With Mantle Cell Lymphoma and Comparison of Healthcare Resource Utilization and Costs Among Relapsed/Refractory Patients Treated With Ibrutinib or Chemoimmunotherapy: A Real-world Retrospective Study. *Clin Ther*. Aug 2021;43(8):1285-1299. doi:10.1016/j.clinthera.2021.06.012
21. Lee YP, Jung YJ, Cho J, et al. A retrospective analysis of ibrutinib outcomes in relapsed or refractory mantle cell lymphoma. *Blood Res*. Dec 31 2023;58(4):208-220. doi:10.5045/br.2023.2023208
22. Maruyama D, Omi A, Nomura F, et al. Real-world effectiveness and safety of ibrutinib in relapsed/refractory mantle cell lymphoma in Japan: post-marketing surveillance. *Int J Hematol*. Feb 2024;119(2):146-155. doi:10.1007/s12185-023-03687-8
23. McCulloch R, Lewis D, Crosbie N, et al. Ibrutinib for mantle cell lymphoma at first relapse: a United Kingdom real-world analysis of outcomes in 211 patients. *Br J Haematol*. Apr 2021;193(2):290-298. doi:10.1111/bjh.17363
24. Obr A, Benesova K, Janikova A, et al. Ibrutinib in mantle cell lymphoma: a real-world retrospective multi-center analysis of 77 patients treated in the Czech Republic. *Ann Hematol*. Jan 2023;102(1):107-115. doi:10.1007/s00277-022-05023-2
25. Rusconi C, Cheah CY, Eyre TA, et al. Ibrutinib improves survival compared with chemotherapy in mantle cell lymphoma with central nervous system relapse. *Blood*. Oct 27 2022;140(17):1907-1916. doi:10.1182/blood.2022015560
26. Sancho JM, Marín-Niebla A, Fernández S, et al. IBRORS-MCL study: a Spanish retrospective and observational study of relapsed/refractory mantle-cell lymphoma treated with ibrutinib in routine clinical practice. *Int J Hematol*. Sep 2022;116(3):381-392. doi:10.1007/s12185-022-03367-z
27. Sharman J, Kabadi SM, Clark J, Andorsky D. Treatment patterns and outcomes among mantle cell lymphoma patients treated with ibrutinib in the United States: a retrospective electronic medical record database and chart review study. *Br J Haematol*. Feb 2021;192(4):737-746. doi:10.1111/bjh.16922
28. Tivey A, Shotton R, Eyre TA, et al. Ibrutinib as first-line therapy for mantle cell lymphoma: a multicenter, real-world UK study. *Blood Adv*. Mar 12 2024;8(5):1209-1219. doi:10.1182/bloodadvances.2023011152
29. Tucker D, Morley N, MacLean P, et al. The 5-year follow-up of a real-world observational study of patients in the United Kingdom and Ireland receiving ibrutinib for relapsed/refractory mantle cell lymphoma. *Br J Haematol*. Mar 2021;192(6):1035-1038. doi:10.1111/bjh.16739
30. 3Yi JH, Kim SJ, Yoon DH, et al. Real-world outcomes of ibrutinib therapy in Korean patients with relapsed or refractory mantle cell lymphoma: a multicenter, retrospective analysis. *Cancer Commun (Lond)*. Mar 2021;41(3):275-278. doi:10.1002/cac2.12150
31. Zhang Y, Liu P, Cai J, et al. Ibrutinib as monotherapy versus combination therapy in Chinese patients with relapsed/refractory mantle cell lymphoma: A multicenter study. *Cancer Med*. Nov 2022;11(22):4134-4145. doi:10.1002/cam4.4765
32. 3Aydilek E, Wulf G, Schwarz F, et al. Outcomes of pirtobrutinib for relapsed/refractory mantle cell lymphoma in compassionate use program in Europe. *Cancer Med*. May 2024;13(10):e7289. doi:10.1002/cam4.7289
33. Bock AM, Gile JJ, Larson MC, et al. Evolving treatment patterns and improved outcomes in relapsed/refractory mantle cell lymphoma: a prospective cohort study. *Blood Cancer J*. Nov 13 2023;13(1):169. doi:10.1038/s41408-023-00942-3
34. Eskelund CW, Dimopoulos K, Kolstad A, et al. Detailed Long-Term Follow-Up of Patients Who Relapsed After the Nordic Mantle Cell Lymphoma Trials: MCL2 and MCL3. *Hemasphere*. Jan 2021;5(1):e510. doi:10.1097/hs9.0000000000000510
35. Hess G, Dreyling M, Oberic L, et al. Real-world experience among patients with relapsed/refractory mantle cell lymphoma after Bruton tyrosine kinase inhibitor failure in Europe: The SCHOLAR-2 retrospective chart review study. *Br J Haematol*. Aug 2023;202(4):749-759. doi:10.1111/bjh.18519
36. Jain P, Kanagal-Shamanna R, Zhang S, et al. Outcomes of relapsed mantle cell lymphoma patients after discontinuing acalabrutinib. *Am J Hematol*. May 1 2021;96(5):E137-e140. doi:10.1002/ajh.26109
37. Keating SJ, Inguva S, Qian J, Shah R, Chirikov V. Real-world treatment patterns, healthcare resource utilization and total cost of care in mantle cell lymphoma from US commercial claims. International Journal of Hematologic Oncology. 2023;
38. Kilgore KM, Chan PK, Teigland C, Wade SW, Mohammadi I. Treatment patterns, health care resource utilization, and costs of chimeric antigen receptor T-cell vs standard therapy for relapsed/refractory mantle cell lymphoma in the United States. *J Manag Care Spec Pharm*. Mar 2025;31(3):262-276. doi:10.18553/jmcp.2025.31.3.262
39. Mathys A, Bacher U, Banz Y, et al. Outcome of patients with mantle cell lymphoma after autologous stem cell transplantation in the pre-CAR T-cell era. Hematol Oncol. Apr 2022;40(2):292-296. doi:10.1002/hon.2952
40. Minson A, Hamad N, Cheah CY, et al. CAR T cells and time-limited ibrutinib as treatment for relapsed/refractory mantle cell lymphoma: the phase 2 TARMAC study. *Blood*. Feb 22 2024;143(8):673-684. doi:10.1182/blood.2023021306
41. Rai S, Tanizawa Y, Cai Z, Huang YJ, Taipale K, Tajimi M. Outcomes for Recurrent Mantle Cell Lymphoma Post-Ibrutinib Therapy: A Retrospective Cohort Study from a Japanese Administrative Database. *Adv Ther*. Oct 2022;39(10):4792-4807. doi:10.1007/s12325-022-02258-3
42. Squires P, Puckett J, Ryland KE, et al. Assessing unmet need among elderly Medicare Beneficiaries with Mantle cell lymphoma: an analysis of treatment patterns, survival, healthcare resource utilization, and costs. *Leuk Lymphoma*. Nov-Dec 2023;64(11):1752-1770. doi:10.1080/10428194.2023.2234525
43. Squires P, Puckett J, Ryland KE, et al. Real-World Treatment Patterns, Survival, and Economic Burden Among Elderly MCL Patients Previously Treated With cBTKis. *Clin Lymphoma Myeloma Leuk*. Oct 2024;24(10):e350-e358.e1. doi:10.1016/j.clml.2024.05.023
44. Hohloch K, Windemuth-Kieselbach C, Zinzani PL, et al. Radioimmunotherapy for mantle cell lymphoma: 5-year follow-up of 90 patients from the international RIT registry. *Ann Hematol*. May 2020;99(5):1073-1079. doi:10.1007/s00277-020-03956-0
45. Karadurmus N, Paydas S, Esin E, et al. Effectiveness of bendamustine in relapsed or refractory lymphoma cases: a Turkish Oncology Group study. journal article. *Archives of Medical Science*. 2021;17(4):920-927. doi:10.5114/aoms.2019.83000
46. McCulloch R, Visco C, Eyre TA, et al. Efficacy of R-BAC in relapsed, refractory mantle cell lymphoma post BTK inhibitor therapy. *Br J Haematol*. May 2020;189(4):684-688. doi:10.1111/bjh.16416
47. Sawalha Y, Goyal S, Switchenko JM, et al. A multicenter analysis of the outcomes with venetoclax in patients with relapsed mantle cell lymphoma. *Blood Adv*. Jul 11 2023;7(13):2983-2993. doi:10.1182/bloodadvances.2022008916
48. Zhao S, Kanagal-Shamanna R, Navsaria L, et al. Efficacy of venetoclax in high risk relapsed mantle cell lymphoma (MCL) - outcomes and mutation profile from venetoclax resistant MCL patients. *Am J Hematol*. Jun 2020;95(6):623-629. doi:10.1002/ajh.25796

DISCLOSURES

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