IBCL-425

# Disease Burden and Treatment Patterns of Relapsed/Refractory Follicular Lymphoma: A Systematic Literature Review

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## BACKGROUND

- Follicular lymphoma (FL) is among the most common forms of indolent non-Hodgkin lymphoma, accounting for 22% of all lymphomas.[1]
- Due in part to the heterogeneity of FL, treatment options are dependent on patient and disease characteristics. While therapy advancements have been made, there are limited treatment options, particularly for those with relapsed/refractory (R/R) FL.[2,3]
- Recommended treatment options for patients with R/R FL include[4]:
  - Second-line recommendations
    - Chemotherapy or lenalidomide plus an anti-CD20 monoclonal antibody (obinutuzumab or rituximab)
    - Lenalidomide monotherapy (if the patient is not a candidate for anti-CD20)
    - Anti-CD20 monotherapy (ibritumomab tiuxetan, obinutuzumab, or rituximab)
  - Third-line and subsequent therapy
    - Phosphatidylinositol 3-kinase inhibitor (PI3KI) (copanlisib)
    - Enhancer of zeste homolog 2 inhibitor (EZH2I) (tazemetostat) for *EZH2* mutation–positive patients and for patients with no satisfactory alternatives
    - Anti–CD-19 CAR T-cell therapy (axicabtagene ciloleucel or tisagenlecleucel)

## OBJECTIVES

- This systematic literature review (SLR) aimed to assess the treatment patterns, disease, and economic burden of R/R FL in the US.

## METHODS

- A comprehensive literature review was conducted for US-based observational studies and indirect comparisons available through MEDLINE, Embase, EconLit, and APA PsycInfo databases from January 1, 2015, to September 23, 2021.
  - Studies reporting real-world treatment patterns and humanistic and economic burden for patients with R/R FL were included.
  - Studies outside the US were considered if no relevant US-based studies were available.
- Key variables extracted included:
  - Demographic and clinical variables, e.g., age, gender, race/ethnicity, country, Eastern Cooperative Oncology Group performance status, disease stage, comorbidities, and risk factors/prognosis
  - Treatment patterns, e.g., treatments observed and treatment duration
  - Clinical outcomes, e.g., objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and time to next treatment (TTNT)
  - Humanistic outcomes, e.g., health-related quality of life (HRQoL)
  - Economic outcomes, e.g., healthcare resource utilization (HCRU) and costs

## RESULTS

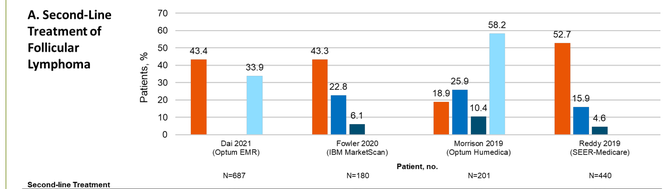
- A total of 2,397 publications were screened for this SLR; 11 real-world observational studies for R/R FL were identified:
  - 6 reported on treatment patterns[5-10]
  - 6 on clinical outcomes[5,7,9-12]
  - 1 on humanistic burden (EU)[13]
  - 3 on economic burden[6,14,15]
- Among these 11 real-world observational studies, the sample size in each study varied, ranging from 100[15] to 1346[7] patients.

### Treatment Patterns

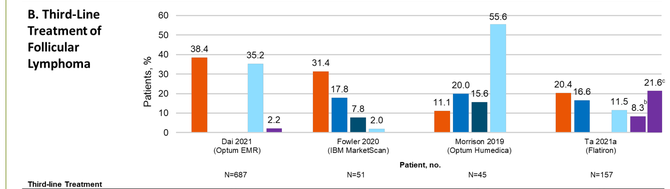
- Among observed systemic treatments in 2008-2021, rituximab (R) monotherapy, rituximab in combination with bendamustine (BR), and rituximab with cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone (R-CHOP) were the most reported second-line and third-line therapies[5-9,14] (Figure 1A and 1B).
- Targeted therapies like anti-CD20 plus lenalidomide and PI3KIs were infrequent across lines of therapy but more common in third-line therapy and greater[5,6,9,11] (Figure 1B).
- Median treatment duration decreased with increased lines of therapy overall, regardless of treatment regimen[6,7] (Table 1).

## RESULTS

**Figure 1. Second- and Third-Line Treatments Observed in R/R Follicular Lymphoma**




| Second-line Treatment | Dai 2021 (Optum EMR) | Fowler 2020 (IBM MarketScan) | Morrison 2019 (Optum Humedica) | Reddy 2019 (SEER-Medicare) |
|---|---|---|---|---|
| Rituximab monotherapy | 298 | 78 | 38 | 232 |
| Bendamustine + rituximab | - | 41 | 52 | 70 |
| R-CHOP | - | 11 | 21 | 20 |
| Rituximab-based combination[a] | 233 | - | 117 | - |




| Third-line Treatment | Dai 2021 (Optum EMR) | Fowler 2020 (IBM MarketScan) | Morrison 2019 (Optum Humedica) | Ta 2021a (Flatiron) |
|---|---|---|---|---|
| Rituximab monotherapy | 264 | 16 | 5 | 32 |
| Bendamustine + rituximab | - | 9 | 9 | 26 |
| R-CHOP | - | 4 | 7 | - |
| Rituximab-based combination[a] | 242 | 1[d] | 25 | 18[d] |
| PI3Ki | 15 | - | - | 13[d]/NR[c] |

Abbreviations: NR, not reported; PI3KI, phosphatidylinositol 3-kinase inhibitor; R-CHOP, rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone; R/R, relapsed/refractory
[a] Rituximab-based combinations included the addition of chemotherapy or non-chemotherapy, e.g., lenalidomide; [b] Number and percent of patients with idelalisib in Ta 2021a[8]; [c] Percent of patients with PI3KI in Ta 2021b[10], patient numbers for third-line treatment not reported in the abstract[10]; [d] Patients treated third-line with rituximab plus lenalidomide

**Table 1. Treatment Duration**

| Author Year (Data Source; Study Time Frame) | Sample Size Treatment Duration | First Line | Second Line | Third Line | Fourth Line | Fifth Line |
|---|---|---|---|---|---|---|
| **Fowler 2020[6] (MarketScan®; 2010-2018)** | N, patients | 598 | 261 | 72 | 24 | 11 |
| | Mean (SD), months | 12.2 (15.3) | 12.9 (14.3) | 5.3 (7.7) | 4.9 (7.5) | 2.9 (5.0) |
| | Median (IQR), months | 4.6 (19.8) | 8.5 (17.8) | 2.8 (4.0) | 1.4 (2.8) | 0.8 (4.4) |
| **Morrison 2019[7] (Humedica; 2008-9/2015)** | N, patients | 1346 | 201 | 45 | NR | NR |
| | Median (IQR)[a], months | 4.3 (8.7) | 3.6 (4.7) | 2.8 (3.3) | NR | NR |

Abbreviations: IQR, interquartile range; NR, not reported; SD, standard deviation

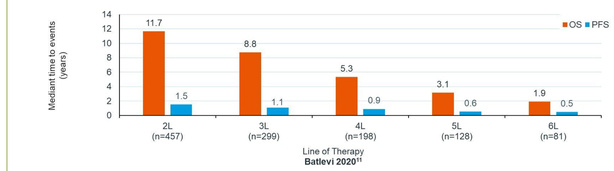
### Clinical Outcomes

- PFS and OS worsened with increasing lines of therapy[11,12] (Figure 2).
- Median TTNT decreased with increasing lines of therapy across all treatments; second-line TTNT was 38.3 months, and third-line and greater was 14.1 months[9,10] (Table 2).

### Humanistic Burden

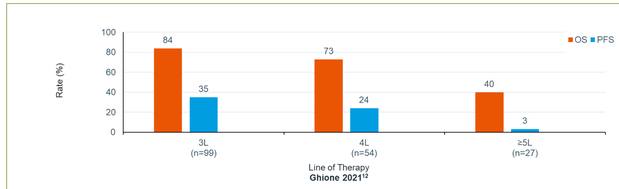
- Of note, there were no US-based studies reporting the real-world HRQoL in patients with R/R FL during the literature screening period (January 1, 2015, to September 23, 2021).
- One ex-US study showed lower HRQoL in later lines of therapy (first line vs. third line, EQ-5D-5L: 0.82 vs. 0.59; Functional Assessment of Cancer Therapy–Lymphoma: 109 vs. 88; $P$<0.0001).[13]

**Figure 2A. Median OS and PFS Observed in R/R Follicular Lymphoma by Line of Therapy**




Abbreviations: 2L, second line; 3L, third line; 4L, fourth line; 5L, fifth line; 6L, sixth line; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory

**Figure 2B. Rate of 18-month OS and PFS Observed in R/R Follicular Lymphoma by Line of Therapy**




Abbreviations: 3L, third line; 4L, fourth line; 5L, fifth line; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory

**Table 2. Clinical Outcomes by Line of Therapy From Six Real-World Studies**

| Author Year (Data Source; Study Time Frame) | Measures of Clinical Outcomes | LOT (Patient Count) | Value |
|---|---|---|---|
| **Batlevi 2020[11] (Memorial Sloan Kettering Cancer Center; 1998-2009)** | EFS, median, years (95% CI) | 2L (457) | 1.04 (0.89-1.31) |
| | | 3L (299) | 0.73 (0.57-0.94) |
| | | 4L (198) | 0.56 (0.48-0.84) |
| | | 5L (128) | 0.35 (0.29-0.62) |
| | | 6L (81) | 0.30 (0.26-0.50) |
| **Dai 2021[5] (Optum Electronic Health Records; 2007-2020)** | Median time to progression, months (95% CI) | 3L (687) | 16.6 (14.4-18.1) |
| | Progression at 5 years, % | | 23.7 |
| | Median TTNT, months (95% CI) | | 18 (15.8-19.9) |
| | TTNT at 5 years, % | | 22.4 |
| | Median PFS, months (95% CI) | | 12.5 (11.3-14.4) |
| | PFS at 5 years, % | | 16.1 |
| **Ghione 2021[12] (Major Lymphoma Centers in the US and EU; 7/2014 and after)** | ORR, % (95% CI) | 3L (99) | 67 (56-76) |
| | | 4L (54) | 55 (40-69) |
| | | ≥5L (27) | 34 (18-56) |
| | CR, % (95% CI) | 3L (99) | 42 (32-53) |
| | | 4L (54) | 31 (19-46) |
| | | ≥5L (27) | 15 (7-30) |
| **Morrison 2019[7,a] (Humedica; 2008-9/2015)** | OS at 1 year, % | ≥2L (1346) | 91.9 |
| | OS at 2 years, % | | 86.9 |
| | PFS at 1 year, % | | 76.4 |
| | PFS at 2 years, % | | 64.6 |
| **Ta 2021a[9] (Flatiron; 2011-9/2020)** | Median TTNT/death, months (95% CI) | ≥3L (157) | 14.1 (10-23.6) |
| **Ta 2021b[10] (Flatiron; 2011-3/2021)** | Median TTNT, months (95% CI) | ≥2L (503) | 38.3 (29.4-54.3) |
| | Median OS, months (95% CI) | | 82.9 (75.6-NR) |

Abbreviations: 2L, second line; 3L, third line; 4L, fourth line; 5L, fifth line; 6L, sixth line; CI, confidence interval; CR, complete response; EFS, event-free survival; LOT, line of therapy; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TTNT, time to next treatment
[a] OS and PFS reported in increments of time after 1L treatment.

### Economic Burden

- After adjustment using the consumer price index, estimated all-cause US healthcare costs increased from $10,466-$16,806 per patient per month in second line to $16,101-$22,879 in third line and $24,198-$30,883 in fourth line[6,14,15] (Table 3).
  - FL systemic treatments and medical services contributed the most to costs.[6,14,15]

**Table 3. Contemporary Healthcare Costs by Line of Therapy From Three Real-World Studies**

| Author Year (Data Source; Study Time Frame) | Sample Size Cost Measure | First Line | Second Line | Third Line | Fourth Line | Fifth Line |
|---|---|---|---|---|---|---|
| **Fowler 2020[6] (MarketScan®; 2010-2018)** | N, patients | 598 | 180 | 51 | 21 | 11 |
| | All-cause, mean (SD) PPPM | $8905 ($12,061) | $10,466 ($23,221) | $19,935 ($45,722) | $30,883 ($59,867) | $35,397 ($59,586) |
| | FL-related, mean (SD) PPPM | $2463 ($6969) | $2455 ($9099) | $8616 ($33,893) | $25,759 ($60,178) | $7146 ($10,957) |
| **Leslie 2021[14] (MarketScan®; 2005-2/2020)** | N, patients | 644 | 644 | 245 | 100 | NR |
| | All-cause, mean PPPM | $17,218 | $16,806 | $22,879 | $28,420 | NR |
| | FL-related, mean PPPM | $12,972 | $12,685 | $14,352 | $20,204 | NR |
| **Matasar 2021[15] (PharMetrics® Plus; 2011-9/2020)** | N, patients | NR | NR | 100 | 44 | NR |
| | All-cause, mean (SD) PPPM | NR | NR | $16,101 ($12,392) | $24,198 ($29,954) | NR |
| | FL-related, mean (SD) PPPM | NR | NR | $13,318 ($11,540) | $18,460 ($21,489) | NR |

Abbreviations: FL, follicular lymphoma; NR, not reported; PPPM, per patient per month; SD, standard deviation

## LIMITATIONS

- Given the fact that this SLR identified 11 real-world studies and the sample size in each study varied, caution is needed when interpreting the results based on retrospective observational studies selecting certain patient populations with a small sample size in 3L or later line settings.
- Treatment paradigms for R/R FL in the US have evolved over the study period and after the end of the literature search as of September 23, 2021. Although this SLR identified studies published between January 1, 2015, and September 23, 2021, most of the findings reflect real-world patient care for R/R FL before the era of targeted, epigenetic, or immunomodulatory therapy.

## CONCLUSIONS

- Based on the real-world studies published between January 2015 and September 23, 2021, chemoimmunotherapy was frequently used for R/R FL in the US real-world setting.
- Only one HRQoL study outside the US was identified in the SLR. It suggests the need for more research to evaluate the impact of R/R FL on patients' quality of life in the US.
- Trends of worsening clinical and humanistic outcomes and increasing healthcare cost in later lines of therapy were consistently observed.
- These data highlight the unmet needs in R/R FL and the importance of continuing clinical research to develop new treatment options that help increase the percentage of patients who have durable treatment benefit.

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