

Patterns of Treatment Utilization and Sequencing Across Lines of Therapy in Waldenström Macroglobulinemia: Real-World Evidence from the United States

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CONCLUSIONS

- In this real-world analysis of patients with WM, BTKi-based therapies were the predominant treatment class across all LOTs, with treatment sequencing frequently alternating between BTKi- and B/BR-based regimens
- These findings highlight current treatment patterns in clinical practice for WM, and underscore the need for further studies to inform optimal treatment selection and sequencing

INTRODUCTION

- Waldenström macroglobulinemia (WM) is a rare, indolent, and incurable B-cell non-Hodgkin lymphoma characterized by a chronic, relapsing course that often requires multiple lines of therapy (LOTs) over a patient’s lifetime^{1,2}
- This study aimed to characterize real-world patterns of treatment utilization, sequencing, and healthcare resource utilization (HCRU) in patients with WM in the United States (US)

METHODS

Data Source and Study Population

- A retrospective observational study was conducted using the US Symphony Integrated Dataverse® database (ICON plc), a longitudinal claims database containing medical and pharmacy data from commercially insured and Medicare Advantage populations
- Adults with ≥1 WM diagnostic code who initiated treatment from January 1, 2020, through August 31, 2025 were included

Study Design and Statistical Analysis

- Patients were categorized into eight mutually exclusive treatment groups according to the first observed regimen within each LOT:
 - Bendamustine with/without rituximab (B/BR)
 - Rituximab-monotherapy (R-mono)
 - Rituximab-combinations (R-combo, including R-cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP] and other combinations)
 - Zanubrutinib (B Bruton tyrosine kinase inhibitor [BTKi])
 - Ibrutinib (BTKi)
 - Bortezomib-based regimens
 - Venetoclax-based regimens
 - Other regimens (acalabrutinib- or pirtobrutinib-based regimens, or lenalidomide ± others)

Outcomes

- Patient demographics and clinical characteristics were assessed at the start of each LOT and summarized descriptively
- Treatment utilization was evaluated overall, by calendar year, and by LOT
- Treatment sequencing across LOTs was visualized using Sankey diagrams
- All-cause HCRU during treatment (inpatient, outpatient, and other medical/hospital services) was reported as per-patient-per-year (PPPY) rates to account for differences in treatment duration

RESULTS

Patient Characteristics

- During the study period, 7583, 2251, and 976 patients with WM initiated first-line (1L), second-line (2L), and third or later line (3L+) therapy, respectively
- Patient demographics and characteristics by LOT at baseline are reported in **Table 1**

Treatment Utilization

- Across all LOTs, BTKi (eg, zanubrutinib or ibrutinib) was the most used drug class (1L: 34.2%; 2L: 33.4%; 3L+: 30.1%) (**Figure 1**)
- Treatment patterns over time (2020-2025) showed increasing use of BTKi-based regimens (primarily zanubrutinib) and a corresponding decline in B/BR-based therapy

Table 1. Patient Demographics and Characteristics at Baseline

Characteristic	1L (N=7583)	2L (N=2251)	3L+ (N=976)
Sex, n (%)			
Female	3123 (41.18)	932 (41.4)	413 (42.32)
Male	4460 (58.82)	1319 (58.6)	563 (57.68)
Mean age at index (SD), years			
Age, years			
18-55	361 (4.76)	93 (4.13)	28 (2.87)
56-64	1041 (13.73)	301 (13.37)	116 (11.89)
≥65	6181 (81.51)	1857 (82.5)	832 (85.25)
Race, n (%)			
American Indian/ Alaska Native	12 (0.16)	1 (0.04)	2 (0.02)
Asian	139 (1.83)	34 (1.51)	11 (1.13)
Black	333 (4.39)	110 (4.89)	60 (6.15)
Hispanic	296 (3.9)	93 (4.13)	45 (4.61)
Other	4 (0.05)	2 (0.09)	0
White	5113 (67.43)	1571 (69.79)	680 (69.67)
Unknown/missing	1686 (22.23)	440 (19.55)	178 (18.24)
Payer type, n (%)			
Medicare	4240 (55.91)	1321 (58.69)	600 (61.48)
Commercial	2969 (39.15)	825 (36.65)	322 (32.99)
Medicaid	149 (1.96)	45 (2.0)	17 (1.74)
Unknown/other	225 (2.97)	60 (2.67)	37 (3.79)
Mean Charlson Comorbidity Index (SD)			
	2.42 (1.97)	2.36 (1.97)	2.37 (1.96)

Index dates were between January 1, 2020, through August 31, 2025.
1L, first-line; 2L, second-line; 3L+, third or later line; SD, standard deviation.

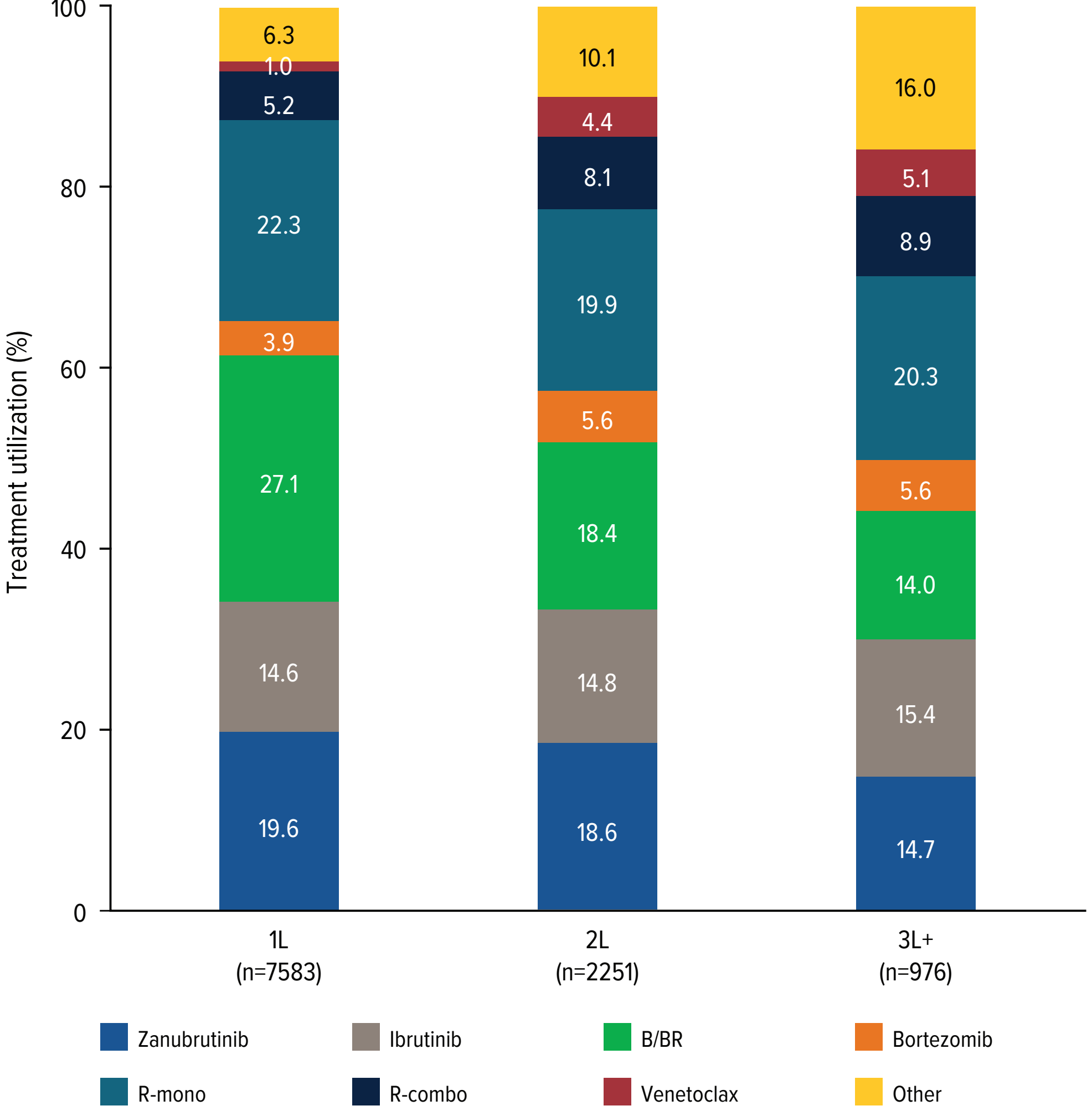
Treatment Sequencing Patterns

- Treatment sequencing patterns demonstrated that B/BR was the most common subsequent treatment in patients who received 1L BTKi and progressed to 2L (42.7% after 1L zanubrutinib, 22.2% after 1L ibrutinib; **Figure 2**)
- Conversely, patients treated with 1L B/BR and progressed to 2L most frequently transitioned to BTKi-based regimens in 2L (zanubrutinib: 35.6%; ibrutinib: 16.4%)
- In patients who received 3L therapy after 2L zanubrutinib, 33.3% received B/BR and 30.0% received venetoclax
- In patients who received 3L therapy after 2L ibrutinib, 50.0% were either treated with zanubrutinib (34.6%) or retreated with ibrutinib (15.4%), and 13.5% received B/BR

HCRU

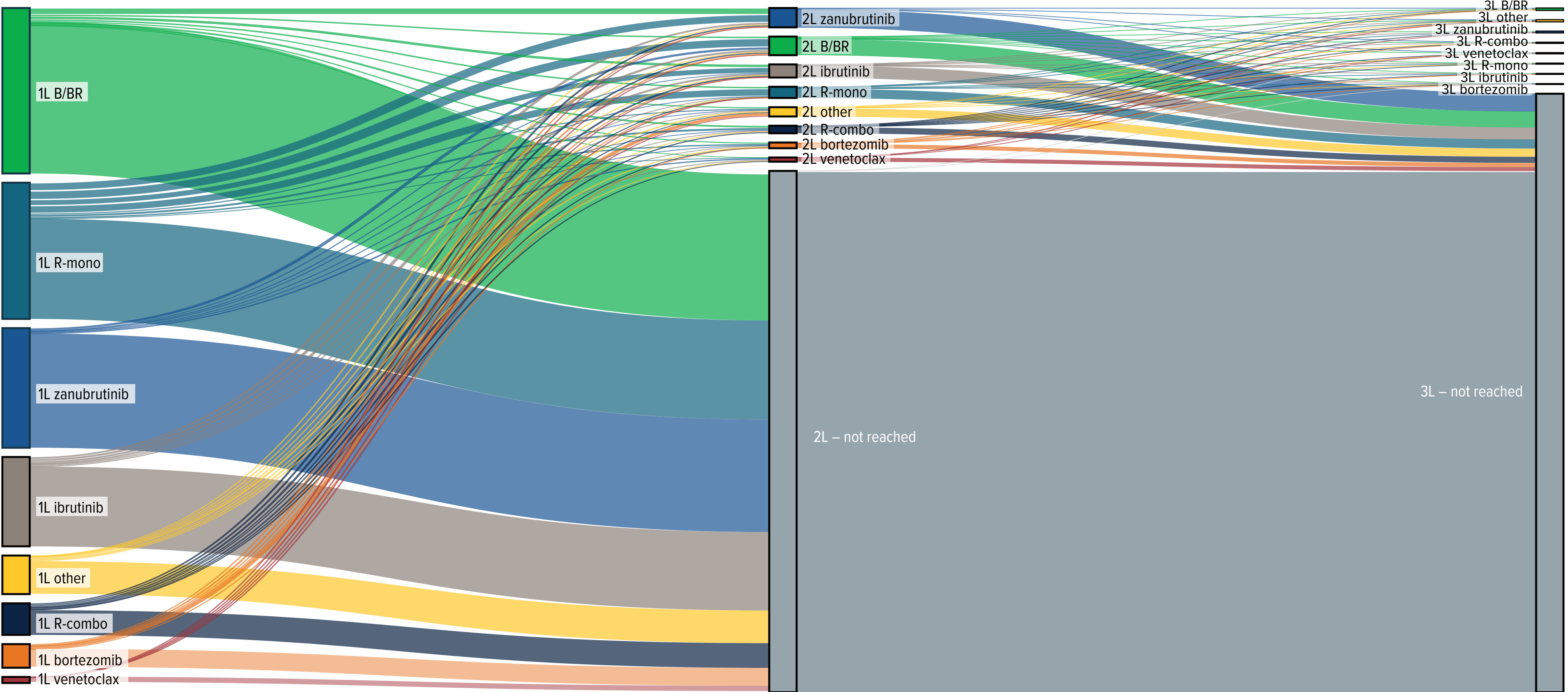
- Substantial HCRU was observed across treatment regimens and LOTs (**Table 2**)
 - Outpatient visits were consistently lower for BTKi-based regimens than for chemoimmunotherapy regimens
 - In patients receiving 1L therapy, inpatient visits were lowest among patients receiving BTKi-based regimens and highest among those treated with venetoclax- or bortezomib-based regimens

Figure 1. Overall Treatment Utilization by LOT



“Other” denotes acalabrutinib- or pirtobrutinib-based regimens, or lenalidomide ± others.
1L, first-line; 2L, second-line; 3L+, third or later line; B/BR, bendamustine with/without rituximab; LOT, line of therapy; R-combo, rituximab-combinations, including R-cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) and other combinations; R-mono, rituximab-monotherapy.

Figure 2. Treatment Sequencing Patterns



“Other” denotes acalabrutinib- or pirtobrutinib-based regimens, or lenalidomide ± others.
1L, first-line; 2L, second-line; 3L, third-line; B/BR, bendamustine with/without rituximab; R-combo, other rituximab-combinations, including R-cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) and other combinations; R-mono, rituximab-monotherapy.

Table 2. HCRU Outcomes Among LOTs and Regimen Types

1L	B/BR (N=2056)	Zanubrutinib (N=1486)	Ibrutinib (N=1110)	R-mono (N=1692)	R-combo (N=392)	Venetoclax (N=75)	Bortezomib (N=293)	Other (N=479)
Outpatient visits, PPPY								
Median (IQR)	2.86 (0.85-4.50)	0.61 (0.16-1.35)	0.72 (0.24-1.54)	2.14 (0.69-4.06)	3.30 (1.02-5.07)	0.48 (0.07-2.03)	3.04 (1.01-4.97)	0.81 (0.08-2.52)
Inpatient visits, PPPY								
Median (IQR)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.04)	0.00 (0.00-0.00)	0.00 (0.00-0.07)	0.00 (0.00-0.24)	0.00 (0.00-0.15)	0.00 (0.00-0.00)
Other medical/hospital services visits, PPPY								
Median (IQR)	1.01 (0.00-3.62)	0.31 (0.00-0.98)	0.37 (0.00-1.21)	1.01 (0.00-3.94)	1.01 (0.00-4.06)	0.25 (0.00-1.00)	2.03 (0.35-4.21)	0.26 (0.00-1.32)
2L	B/BR (N=414)	Zanubrutinib (N=419)	Ibrutinib (N=334)	R-mono (N=447)	R-combo (N=182)	Venetoclax (N=100)	Bortezomib (N=127)	Other (N=228)
Outpatient visits, PPPY								
Median (IQR)	2.62 (0.64-4.54)	0.78 (0.19-1.57)	0.75 (0.26-1.66)	2.03 (0.62-4.06)	2.83 (0.98-4.60)	0.41 (0.00-1.67)	2.16 (0.46-4.83)	0.97 (0.21-2.79)
Inpatient visits, PPPY								
Median (IQR)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.18)	0.00 (0.00-0.00)	0.00 (0.00-0.07)	0.00 (0.00-0.05)
Other medical/hospital services visits, PPPY								
Median (IQR)	1.90 (0.00-3.92)	0.24 (0.00-0.96)	0.41 (0.00-1.26)	1.01 (0.00-3.95)	1.82 (0.08-4.09)	0.11 (0.00-1.00)	2.03 (0.14-3.71)	0.36 (0.00-1.43)
3L+	B/BR (N=137)	Zanubrutinib (N=143)	Ibrutinib (N=150)	R-mono (N=198)	R-combo (N=87)	Venetoclax (N=50)	Bortezomib (N=55)	Other (N=156)
Outpatient visits, PPPY								
Median (IQR)	2.61 (0.77-4.46)	0.82 (0.18-1.47)	0.97 (0.37-1.66)	2.03 (0.61-4.06)	3.28 (0.50-5.10)	0.69 (0.00-1.57)	3.04 (0.85-6.09)	0.67 (0.00-1.93)
Inpatient visits, PPPY								
Median (IQR)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.03)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.10)	0.00 (0.00-0.09)	0.00 (0.00-0.00)
Other medical/hospital services visits, PPPY								
Median (IQR)	2.04 (0.00-4.07)	0.31 (0.00-1.13)	0.47 (0.02-1.47)	1.01 (0.00-4.06)	2.84 (0.46-4.54)	0.16 (0.00-1.71)	2.34 (0.30-4.68)	0.20 (0.00-1.49)

“Other” denotes acalabrutinib- or pirtobrutinib-based regimens, or lenalidomide ± others.
1L, first-line; 2L, second-line; 3L+, third or later line; B/BR, bendamustine with/without rituximab; IQR, interquartile range; PPPY, per-patient-per-year; R-combo, other rituximab-combinations, including R-cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) and other combinations; R-mono, rituximab-monotherapy.

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DISCLOSURES

JJC: Grants or contracts: AbbVie, BeOne Medicines Ltd, Cellectar, Loxo, Pharmacyclics; Consulting: AbbVie, BeOne Medicines Ltd, Cellectar, J&J, Loxo, Mustang Bio, Pharmacyclics. **SKT:** Grants or contracts: AbbVie, AstraZeneca, Bristol Myers Squibb, Genentech, Sanofi, X4 Pharmaceuticals. **MLP:** Advisory boards: BeOne Medicines Ltd, Bristol Myers Squibb, Cellectar, Novartis, Nurix. **KY, MX, QF:** Employment: BeOne Medicines Ltd. **PK:** Grants or contracts: AbbVie, BeOne Medicines Ltd, Bristol Myers Squibb, Genentech, Karyopharm, Regeneron, Sanofi; Honoraria: AbbVie, Angitia Bio, Ascentage, BeOne Medicines Ltd, GlaxoSmithKline, Janssen, Kite, Mustang Bio, Oncopeptides, Pharmacyclics, Sanofi, X4 Pharmaceuticals; Consulting: Keosys. **AC-K:** No disclosures.

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