RESULTS FROM THE PROSPECTIVE RUBIN REGISTRY

CHRONIC LYMPHOCYTIC LEUKEMIA IN ROUTINE CARE IN GERMANY: CHANGES IN STANDARD OF CARE

RUBIN
Registry platform
Hematologic Malignancies

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INTRODUCTION

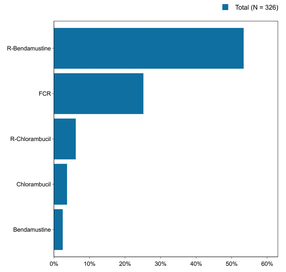
Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in the Western world. Two classes of targeted drugs were introduced in the last decade: Bruton's tyrosine kinase inhibitors (BTKis), with the first one, ibrutinib, approved in 2014 for relapsed/refractory CLL, and the BCL2 inhibitor venetoclax, first approved in 2016 for relapsed/refractory CLL and high-risk patients with no other treatment options. Indications were extended to also include first-line (1L) treatment in 2016 and 2020, respectively. The second- and third-generation BTKis acalabrutinib, zanubrutinib and pirtobrutinib have been approved by the EMA in 2020, 2022 and 2025, respectively.

RUBIN, a continuation of the Tumor Registry Lymphatic Neoplasms (TLN), provides a prospective long-term observation of real-world treatment of patients with CLL in Germany, allowing to analyze the extent to which novel agents are introduced into routine practice.

CONCLUSION AND OUTLOOK

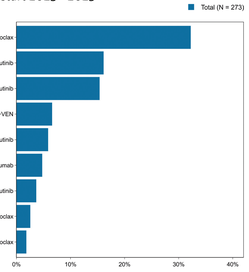
In German real-world practice, targeted agents rapidly replaced chemoimmunotherapy as 1L or 2L treatment of patients with CLL. Since 2023, obinutuzumab + venetoclax is the most common 1L regimen, while 2L shifted from predominant use of ibrutinib to second-generation BTKis. In the future, with longer follow-up of the most recent cohort, RUBIN will enable evaluation of how these changes in treatment pattern affect outcomes in real-world.

Figure 1: 1L treatment – most frequent regimens with start 2009 – 2015



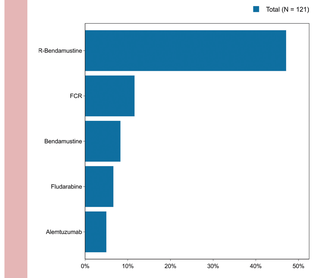
R: rituximab, FCR: fludarabine + cyclophosphamide + rituximab, BEN: bendamustine, RIT: rituximab, VIC: vincristine

Figure 2: 1L treatment – most frequent regimens with start 2023 – 2025



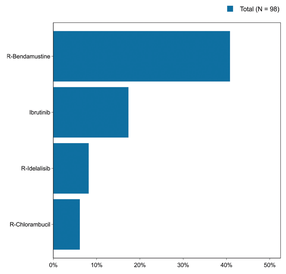
O: obinutuzumab , IBR: ibrutinib, VEN: venetoclax R: rituximab

Figure 3: 2L treatment – most frequent regimens with start 2009 – 2013



R: rituximab , FCR: fludarabine + cyclophosphamide + rituximab

Figure 4: 2L treatment – most frequent regimens with start 2014 – 2018



R: rituximab

Figure 5A: 2L treatment – most frequent regimens with start 2019 – 2025

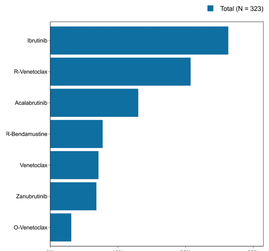
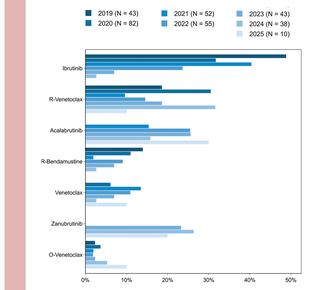


Figure 5B: 2L treatment – most frequent regimens with start 2019 – 2025 by year



PATIENTS AND METHODS

The TLN and RUBIN prospectively have been following patients with non-Hodgkin's lymphoma and CLL in approximately 200 hospitals and office-based sites in Germany since 2009. Details on the methodology have been published previously (Knauf et al., 2015, 2021). RUBIN was approved by ethics committees and is registered at clinicaltrials.gov (NCT06043011). We describe 1L and second-line (2L) CLL treatments across predefined time periods. Data cut: June 30, 2025.

RESULTS

At data cut, data of 1039 patients with CLL from 76 sites were evaluable for analysis. Results are shown for prospectively documented treatments. Of 599 prospective 1L treatments, 326 (54.4 %) started between 2009 and 2015 (before approval of targeted therapies for 1L) and 273 (45.6 %) from 2023 onward. No 1L treatments starting between 2016 and 2022 were documented as recruitment was paused.

Of 542 prospective 2L treatments, 121 (22.3 %) started between 2009 and 2013 (before approval of targeted therapies), 98 (18.1 %) between 2014 and 2018, and 323 (59.6 %) between 2019 and 06/2025.

Patient characteristics at start of 1L and 2L treatment

Median age at start of 1L was 71.2 years for patients starting treatment between 2009 and 2014, and 71.6 for patients starting 1L since 2023. At start of 2L it was 72.4 (2L start between 2009 and 2013), 73.7 (2L start 2014-2018) and 75.9 (2L start 2019-06/2025). Further patient characteristics for the different patient groups are shown in **Table 1.**

Systemic 1L treatment

In 1L, until 2015 rituximab + bendamustine was by far the most frequent regimen, received by 53.4 % of patients **(Figure 1)**. 25.2 % received FCR, other chemotherapy regimens with or without rituximab were less frequently used. Patients receiving rituximab + bendamustine were older than those receiving FCR (in median 72.5 vs 65.4 years), and less frequently had an ECOG of 0 (30.5 % vs 42.7 %) or CCI 0 (55.2 % vs 74.4 %, **Table 2**).

For 1L treatments starting since 2023, obinutuzumab + venetoclax was the most frequently used regimen, received by 32.2 % of patients, followed by acalabrutinib (16.1 %) and zanubrutinib (15.4 %) monotherapies **(Figure 2)**. Patients receiving obinutuzumab+venetoclax were slightly younger than those receiving monotherapy with a BTKi (median age of 70.3 vs 73.4, respectively) and more often had an ECOG of 0 (64.8 % vs 50 %) or a CCI of 0 (64.8 % vs 57.8 %, **Table 3**). Patients receiving a BTKi more frequently had genetic risk factors like a TP53 mutation than those receiving obinutuzumab+venetoclax (21.6 % vs 3.4 %, respectively)

Systemic 2L treatment

Like in 1L, rituximab + bendamustine was the predominant regimen in 2L until 2013, comprising 47.1 % of treatments **(Figure 3)**. It was still the most frequently used regimen between 2014 and 2018 (40.8 % of treatments), followed by ibrutinib (17.3 %) and rituximab + idelalisib (8.2 %, **Figure 4**). From 2019 on, ibrutinib was the most frequent 2L regimen (26.3 %), followed by rituximab + venetoclax (20.7 %) and acalabrutinib monotherapy (13.0 %, **Figure 5A**). However, since 2021 the use of ibrutinib has been continuously decreasing, while use of acalabrutinib and zanubrutinib increased **(Figure 5B)**.

Table 1: Patient characteristics

	Start of 1L 2009 – 2015	Start of 1L 2023 – 2025	Start of 2L 2009 – 2013	Start of 2L 2014 – 2018	Start of 2L 2019 – 2025
Patients (N)	**326**	**273**	**121**	**98**	**323**
Sex					
Female	116 (35.6 %)	88 (32.2 %)	55 (45.5 %)	33 (33.7 %)	118 (36.5 %)
Male	210 (64.4 %)	185 (67.8 %)	66 (54.5 %)	65 (66.3 %)	205 (63.5 %)
Age at start of respective line of treatment [years]					
Median	71.2	71.6	72.4	73.7	75.9
25 %/75 % quantiles	64.9 – 77.1	64.4 – 78.6	68.6 – 78.1	68.3 – 77.2	67.3 – 81.9
< 65 years	82 (25.2 %)	74 (27.1 %)	19 (15.7 %)	24 (24.5 %)	62 (19.2 %)
≥ 65 years	244 (74.8 %)	199 (72.9 %)	102 (84.3 %)	74 (75.5 %)	261 (80.8 %)
ECOG at start of respective line of treatment					
0	116 (35.6 %)	149 (54.6 %)	27 (22.3 %)	25 (25.5 %)	108 (33.4 %)
1	162 (49.7 %)	111 (40.7 %)	53 (43.8 %)	26 (26.5 %)	142 (44.0 %)
≥ 2	24 (7.4 %)	9 (3.3 %)	14 (11.6 %)	8 (8.2 %)	28 (8.7 %)
Unknown to site	24 (7.4 %)	4 (1.5 %)	23 (19.0 %)	23 (23.5 %)	40 (12.4 %)
Missing	0 (0.0 %)	0 (0.0 %)	4 (3.3 %)	16 (16.3 %)	5 (1.5 %)
Any comorbidity at start of respective line of treatment					
Yes	276 (84.7 %)	217 (79.5 %)	106 (87.6 %)	73 (74.5 %)	277 (85.8 %)
No	38 (11.7 %)	55 (20.1 %)	11 (9.1 %)	12 (12.2 %)	41 (12.7 %)
Missing	12 (3.7 %)	1 (0.4 %)	4 (3.3 %)	13 (13.3 %)	5 (1.5 %)
Charlson comorbidity index at start of respective line of treatment					
0	188 (57.7 %)	171 (62.6 %)	64 (52.9 %)	51 (52.0 %)	166 (51.4 %)
1	40 (12.3 %)	25 (9.2 %)	19 (15.7 %)	8 (8.2 %)	33 (10.2 %)
≥2	86 (26.4 %)	76 (27.8 %)	34 (28.1 %)	26 (26.5 %)	119 (36.8 %)
Missing	12 (3.7 %)	1 (0.4 %)	4 (3.3 %)	13 (13.3 %)	5 (1.5 %)

Charlson comorbidity index according to Charlson et al. 1987, current weighting according to Quan et al. 2011. Range 0 – 24. ECOG: Eastern Cooperative Oncology Group (Oken et al. 1982).

Table 2: Patient characteristics of most frequent 1L treatments 2009 – 2013

	R-Bendamustine	FCR
Patients (N)	**174**	**82**
Sex		
Female	57 (32.8 %)	23 (28.0 %)
Male	117 (67.2 %)	59 (72.0 %)
Age at start of respective line of treatment [years]		
Median	72.5	65.4
25 %/75 % quantiles	66.3 – 77.7	57.7 – 69.9
< 65 years	39 (22.4 %)	39 (47.6 %)
≥ 65 years	135 (77.6 %)	43 (52.4 %)
ECOG at start of respective line of treatment		
0	54 (31.0 %)	37 (45.1 %)
1	94 (54.0 %)	36 (43.9 %)
≥ 2	11 (6.3 %)	6 (7.3 %)
Unknown to site	15 (8.6 %)	3 (3.7 %)
Any comorbidity at start of respective line of treatment		
Yes	152 (87.4 %)	60 (73.2 %)
No	15 (8.6 %)	18 (22.0 %)
Missing	7 (4.0 %)	4 (4.9 %)
Charlson comorbidity index at start of respective line of treatment		
0	96 (55.2 %)	61 (74.4 %)
1	26 (14.9 %)	5 (6.1 %)
≥ 2	45 (25.9 %)	12 (14.6 %)
Missing	7 (4.0 %)	4 (4.9 %)

Charlson comorbidity index according to Charlson et al. 1987, current weighting according to Quan et al. 2011. Range 0 – 24. ECOG: Eastern Cooperative Oncology Group (Oken et al. 1982).

Table 3: Patient characteristics of most frequent 1L treatments 2023 – 2025

	O-Venetoclax	BTKi Monotherapy
Patients (N)	**88**	**102**
Sex		
Female	25 (28.4 %)	30 (29.4 %)
Male	63 (71.6 %)	72 (70.6 %)
Age at start of respective line of treatment [years]		
Median	70.3	73.4
25 %/75 % quantiles	63.0 – 75.4	66.8 – 81.2
< 65 years	30 (34.1 %)	20 (19.6 %)
≥ 65 years	58 (65.9 %)	82 (80.4 %)
ECOG at start of respective line of treatment		
0	57 (64.8 %)	51 (50.0 %)
1	29 (33.0 %)	45 (44.1 %)
≥ 2	1 (1.1 %)	5 (4.9 %)
Unknown to site	1 (1.1 %)	1 (1.0 %)
Any comorbidity at start of respective line of treatment		
Yes	69 (78.4 %)	86 (84.3 %)
No	18 (20.5 %)	16 (15.7 %)
Missing	1 (1.1 %)	0 (0.0 %)
Charlson comorbidity index at start of respective line of treatment		
0	57 (64.8 %)	59 (57.8 %)
1	10 (11.4 %)	9 (8.8 %)
≥ 2	20 (22.7 %)	34 (33.3 %)
Missing	1 (1.1 %)	0 (0.0 %)
TP53 mutation at start of respective line of treatment		
Mutation	3 (3.4 %)	22 (21.6 %)
Wild-type	72 (81.8 %)	59 (57.8 %)
Other aberration	0 (0.0 %)	1 (1.0 %)
Not tested	8 (9.1 %)	14 (13.7 %)
Unknown	3 (3.4 %)	1 (1.0 %)
Missing	2 (2.3 %)	5 (4.9 %)

BTKis: Ibrutinib, acalabrutinib or zanubrutinib Charlson comorbidity index according to Charlson et al. 1987, current weighting according to Quan et al. 2011. Range 0 – 24. ECOG: Eastern Cooperative Oncology Group (Oken et al. 1982).

Abbreviations:

BTK(i): Bruton tyrosine kinase (inhibitor) | CCI: Charlson comorbidity index | CLL: Chronic lymphocytic leukemia | ECOG: Eastern Cooperative Oncology Group | FCR: fludarabine + cyclophosphamide + rituximab | TLN: Tumor Registry Lymphatic Neoplasms

Literature:

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Conflicts of interest, general:

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