The Clinical Management and Outcome of Marginal Zone Lymphoma (MZL) with a Focus on Relapsed/Refractory Disease: A Report from the Haematological Malignancy Research Network

Synopsis

Title	Clinical Management and Outcome of Marginal Zone Lymphoma (MZL) with a Focus on Relapsed/Refractory Disease
Design	Disease Registry – population-based cohort
Subjects	Patients newly diagnosed with Marginal Zone Lymphoma 2005 to 2020
Sample Size	2,085
Objectives	To describe the disease management of marginal zone lymphoma with a focus on refractory/relapsed disease in patients who have had at least one anti-CD20-based therapy
Secondary Objectives	To examine time to next line of anti-lymphoma treatment, response, progression-free and overall survival
Primary Endpoint	Progression-free and overall survival, time to next line of anti-lymphoma treatment
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Contents

Objectives

1. To describe the disease management and complete treatment pathways including line of therapy for patients with marginal zone lymphoma with a focus on the management of relapsed disease.

2. To examine response, time to next treatment line of anti-lymphoma treatment, progression-free and overall survival.

Setting & Study Design

The Haematological Malignancy Research Network (HMRN) is an ongoing population-based cohort, which was established in 2004 to provide robust, generalizable data to inform clinical practice and research[1]. The HMRN region covers the former two adjacent UK Cancer Networks with a total population of 3.8 million (Yorkshire and the Humber & Yorkshire Coast Cancer Networks) and collects detailed information about all haematological malignancies diagnosed in the region. With an emphasis on primary-source data, prognostic factors, sequential treatment/response history, and socio-demographic details are recorded to clinical trial standards. This is done for all patients newly diagnosed with a haematological malignancy in the HMRN region; there are around 2,500 each year of which approximately 150 are cases of marginal zone lymphoma (MZL). All haematological malignancy diagnoses within the region are made at a single specialist haematopathology laboratory – the Haematological Malignancy Diagnostic Service (HMDS) and it is from here that all HMRN patients are ascertained. A sophisticated custom-designed web database is used to handle clinical diagnoses, specimen tracking and reporting; all diagnoses, including disease transformations and progressions, are automatically coded to International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3). Information on date and cause of death are obtained from the NHS Central Register via monthly downloads.

[1] Alexandra Smith, Debra Howell, Simon Crouch, Dan Painter, John Blase, Han-I Wang, Ann Hewison, Timothy Bagguley, Simon Appleton, Sally Kinsey, Cathy Burton, Russell Patmore, Eve Roman; Cohort Profile: The Haematological Malignancy Research Network (HMRN): a UK population-based patient cohort, International Journal of Epidemiology, Volume 47, Issue 3, 1 June 2018, Pages 700–700g, https://doi.org/10.1093/ije/dyy044

Data Collection and Processing

Data collection is initiated six months after date of diagnosis; research nurses working to agreed operating procedures and data standards visit each of the 14 hospitals in the region and abstract a core clinical dataset from the patients' medical records. The information collected includes demographic details, baseline blood count data and first line treatment. All details are abstracted onto structured forms and entered onto the web-based system, which integrates HMRN and HMDS data. An important feature of data acquisition is the emphasis on primary source information; data from radiology reports, blood tests, clinical examination, and clinician summaries are recorded, enabling embedded algorithms in the database system to automatically generate stage and prognostic scores. Further data abstraction from the medical records has been undertaken to capture information on subsequent treatment lines.

Subjects

The analysis included all adult (18+ years) patients newly diagnosed with *de novo* MZL: extranodal marginal zone lymphoma (also known as MALT lymphoma), nodal marginal zone lymphoma and splenic marginal zone lymphoma (SMZL) (ICD-O-3: 9689/3, 9699/3) by HMDS between 1st January, 2005 and 31st December, 2020 whilst resident in the HMRN region and treated within the Network.

Data Analysis

Subjects have been described in terms of their baseline demographic, diagnostic and prognostic characteristics and each patient's treatment pathway has been characterised from date of diagnosis to end of follow up. Disease management was examined by treatment line and type of treatment. Standard statistical methods have been used to describe the demographics (sex, age at diagnosis and treatment), diagnostics, prognostics and disease management. Data have been presented as proportions, means and medians with corresponding ranges and confidence intervals where appropriate. Time to event analyses, including Kaplan-Meier, have been used to estimate progression-free and overall survival by demographic and clinical factors including line of treatment.

Overall survival (OS)

OS was defined as the time (in years) from either diagnosis or initiation of treatment to death (any cause). Patients who had not died within the study observation period were censored on

the last date they are known to be alive (1st August, 2023), according to national central register.

Progression-free survival (PFS)

PFS was defined as the time (in years) from initiation of treatment to date of disease progression or date of death due to any cause. For patients who had neither disease progression nor died, the last date of follow-up of the medical records was used as the censor date. Additionally, any patients that had moved out of the clinical network and/or ceased attending clinic appointments were censored on the last date they attended.

Time to next line of anti-lymphoma treatment (TTNT)

TTNT was defined as the time (in years) from end of treatment to the initiation date of the next line of treatment. For patients who had died from any cause without commencing another line of treatment their date of death was used as the censor date and for patients who had not started a new line of therapy nor died, the last date of follow-up of the medical records was used as the censor date.

Relapsed/Refractory (R/R) Subgroup Analysis

Further assessment of the outcomes for relapsed/refractory patients were explored; these were defined as having received one or more lines of treatment, including rituximab, had relapsed (recurrence after complete response or presented progression after partial response) or were refractory after the last rituximab-, rituximab biosimilars-, or other anti-CD20 monoclonal antibody (e.g. obinutuzumab)-containing therapy were identified. A previous regimen was defined as one of the following: at least 2 months of single-agent therapy (less than 2 months of therapy was allowed for patients who responded to single-agent rituximab, rituximab biosimilars, or anti-CD20 monoclonal antibody); at least 2 consecutive cycles of polychemotherapy; autologous transplant; radioimmunotherapy. In order to compare outcomes to recent trials examining R/R (MAGNOLIA, NCT03846427) an additional analysis was undertaken in patients treated for R/R disease 2014 onwards, with an ECOG performance status <3 at this time, and who received chemoimmunotherapy (CIT) or chemotherapy after having previously received at least one anti-CD20-based therapy.

Results

There were 2,085 patients newly diagnosed with *de novo* MZL from 1st January 2005 to 31st December 2020 with a male predominance (55.9%), a median age of 72.3 years and the majority were systemic MZL (76.7%) (Table 1). Median follow-up was 8.1 years (95% CI: 7.8-8.5 years) and median overall survival was 9.0 years (95% CI:8.4-9.9); Figure 1 and Figure 2. Medical records for data abstraction were available for 2,039 patients (97.8%) and the remaining analysis focused on these.

The majority of patients had an ECOG performance status of 0 or 1 (n=1711, 84.6%) and only 3.6% (n=73) ECOG 3 or 4. The most frequent constitutional symptom was weight loss (n=400, 21.1%) followed by night sweats (n=219, 11.7%) and fever (n=40, 2.1%). Over fourth-fifths of patients (n=1466, 83.2%) were Ann Arbor stage IV and, of those where paraprotein was tested for, over half had an IgM type present (n=747, 58.1%) (Table 2).

For the initial disease management, just over half of patients (n=1087, 53.3%) were initially managed via watch and wait (W&W), 605 patients (29.7%) received chemotherapy from diagnosis, 153 (7.5%) radiotherapy, only 83 (4.1%) H. pylori eradication and 84 (4.1%) patients were treated palliatively (Table 3). In addition, a small number of patients owing to other serious co-morbidities were not treated for MZL (n=27, 1.3%). Patients treated with radiotherapy or H. pylori eradication were slightly younger (median 68.1 and 66.8 years, respectively) than those on W&W or treated with chemotherapy. The number of patients going on to chemotherapy following W&W or radiotherapy are also shown in Table 3, for example 229 patients initially managed with W&W went on to later receive chemotherapy at a median of 729 days from diagnosis (IQR: 348-1146 days). Patients receiving chlorambucil were older and patients with extranodal MZL were more likely to be treated with radiotherapy. The majority of patients were assessed for response (78.5%) and the overall response rate (defined as either achieving a complete or partial response) was 84.1% (Table 5). In total, 278 patients went onto receive second line therapy either as a consequence of refractory of subsequently relapsing, median time-to-next-treatment (TTNT) was 5.1 years (Figures 3-4).

In total, 864 patients received chemotherapy treatment and overall the most common regimen was chlorambucil (n=254, 29.4%) followed by bendamustine/rituximab (BR) (n=136, 15.7%) (Table 6). This varied over time, however, and for those patients initiating treatment

in 2005-08, 72.3% received chlorambucil, whereas in 2016-23, this was only 3.1%, BR and Dexamethasone/Rituximab/Cyclophosphamide (DRC) becoming the most frequently used regiments since 2014 (Figure 5).

A total of 278 patients went on to receive second line chemotherapy; the median age at start of second line was 73.2 years (Table 7). The most common regimen being single agent rituximab, but once again, however this varied over time. For those initiating second line during 2005-08, fludarabine/cyclophosphamide (FC) was the most frequently given (45.9%), whereas this was no longer used in 2016-22 where ibrutinib was most common (24.7%) (Table 8). The majority were formally assessed for a response (72.7%) and of these the overall response rate was 70.3 percent (n=142) and 25.1 percent (n=52) were refractory (Table 9). Of the 278 patients treated at second line, 103 (37.1%) went on to third line treatment and the median TTNT was 1.2 years (95% CI: 0.8-1.7 years) (Figures 7-8).

Moving on to third line, 103 patients received treatment and the most common regimen was single agent rituximab (24.3%) and the median age at start of treatment was 74.2 years (Table 10). The overall response rate was 76.9% (Table 11) and 36 patients went on to receive further treatment (35.0%); TTNT was 1.7 years (95% CI: 1.3-2.3 years) (Figure 9).

The complete sequential chemotherapy treatment pathways for all patients receiving chemotherapy, including those initially on watch and wait, are shown in Figure 10.

Overall survival from diagnosis was 9.0 years (95% CI: 8.3-9.7 years) (Table 12, Figure 11) with no difference observed by sex (Figure 12), but significant differences by age with median survival not reached for those under 60 at diagnosis and 13.8 years (95% CI: 12.4-15.3 years) for those aged 60-69 compared to 3.5 years (95% CI: 2.9-3.9 years) for those aged 80 years or older (Figure 13). From the start of treatment, including those receiving radiotherapy, median survival was 8.8 years (95% CI: 7.9-9.8), although was generally shorter for those receiving chlorambucil at 4.5 years (95% CI: 3.4-5.3 years) and median survival was not reached in patients receiving bendamustine/rituximab (Table 13, Figure 17).

From the start of second line treatment overall survival was 5.1 years (95% CI: 3.8-7.4 years) (Table 14, Figure 18); variation was seen by regimen and for the most common regimen, single agent rituximab, this was 4.0 years (95% CI: 2.4-7.4 years) (Figure 19). From the start of third line treatment overall survival was 4.6 years (95% CI: 2.4-7.1 years) (Table 15, Figure 20).

Progression-free survival, from the start of first line treatment was 2.9 years (95% CI: 2.6-3.3 years) (Table 16, Figure 22), although it was 1.8 years (95% CI: 1.4-2.0 years) for chlorambucil treated patients compared to 5.7 years (95% CI: 4.1 - not reached) for patients treated with bendamustine/rituximab (Figure 23). At second line, PFS was 1.8 years (95% CI: 1.4-2.2 years) (Table 17,Figure 24). For patients treated at third line, median PFS was 2.1 years (95% CI: 1.4-2.8 years) (Table 18, Figure 26-27).

Relapse/Refractory Treatment in patients previously treated with an anti-CD20 monoclonal antibody

In total, 650 patients (31.9%) of patients had received treatment with an anti-CD20 monoclonal antibody and of these 155 (23.8%) went on to receive further chemotherapy (Figure 28); a Sankey diagram of the further chemotherapy treatments received is shown in Figure 29 and Table 19. Overall survival from the start of relapsed/refractory treatment following anti-CD20 monoclonal antibody treatment was 4.7 years (95% CI: 3.3-5.5 years) (Table 20, Figure 30) and PFS was 2.0 years (95% CI: 1.4-2.4 years) (Table 21, Figure 32).

To explore the findings with a recent phase 2 study those treated with any chemotherapy regimen since 2014 and an ECOG<3 (Table 22, Figure 34-Figure 36). These subgroups are presented alongside the results for the phase 2 MAGNOLIA study where all patients received the Bruton tyrosine kinase (BTK) inhibitor Zanubrutinib. Reflecting the real-world nature of HMRN, R/R patients were on average older than the patients recruited to the trial. Outcomes were poorer than observed in the Zanubritinib with a median OS of 4.2 years (95% CI: 2.4-4.9) and PFS 2.1 years (95% CI: 1.2 – 2.6).

Table 1 Baseline demographic characteristics of *de novo* MZL patients newly diagnosed 1st January 2005 to 31st December 2020

		n (%)
Total		2,085
Sex:	Male	1,165 (55.9)
	Female	920 (44.1)
Age at diagnosis (years):	Mean (sd)	71.0 (11.4)
	Median (min-max)	72.3 (19.5 - 97.7)
Age group:	<60	337 (16.2)
	60-69	554 (26.6)
	70-79	727 (34.9)
	≥80	467 (22.4)
Subtype	Systemic MZL	1599 (76.7)
	Extranodal MZL (MALT)	486 (23.3)
Follow up (years):	Median (95% CI)	8.1 (7.8 - 8.5)
Median overall survival (years):	Median (95% CI)	9.0 (8.4 - 9.9)
Notes abstracted:	Yes	2,039 (97.8)
	No	46 (2.2)

Figure 1 Follow up time for *de novo* MZL patients newly diagnosed 1st January 2005 to 31st December 2020

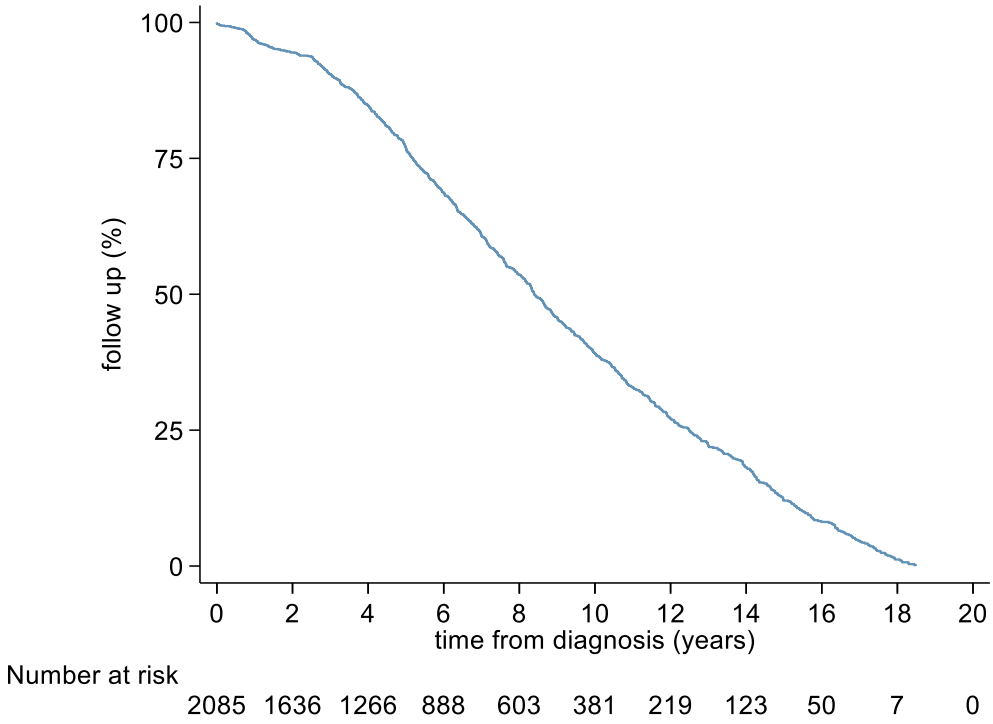


Figure 2 Overall survival from diagnosis for *de novo* MZL patients newly diagnosed 1st January 2005 to 31st December 2020, followed up to August 2023

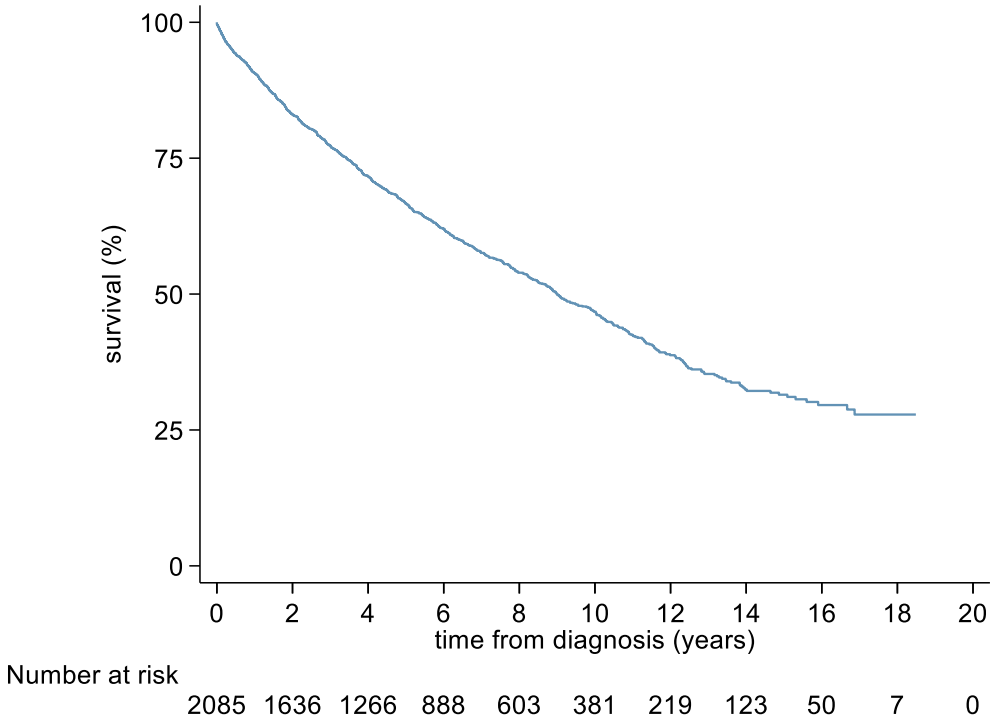


Table 2 Presentation characteristics at time of diagnosis for marginal zone lymphoma patients diagnosed 1st January 2005 to 31st December 2020

		n (%)
Total		**2039**
ECOG performance status	0	910 (45.0)
	1	801 (39.6)
	2	240 (11.9)
	3/4	73 (3.6)
	Not known	15
Night sweats	No	1654 (88.3)
	Yes	219 (11.7)
	Not known	166
Fever	No	1829 (97.9)
	Yes	40 (2.1)
	Not known	170
Weight loss	No	1496 (78.9)
	Yes	400 (21.1)
	Not known	143
Ann Arbor Stage	I	175 (9.9)
	II	77 (4.4)
	III	44 (2.5)
	IV	1466 (83.2)
	Not known	277
Paraprotein Type[1]	IgA	14 (1.1)
	IgA & IgG	1 (0.1)
	IgA & IgM	1 (0.1)
	IgG	91 (7.1)
	IgG & IgM	23 (1.8)
	IgM	747 (58.1)
	light-chain only	2 (0.2)
	non-secretory	1 (0.1)
	none	405 (31.5)
	not done/not known	754
Lactate dehydrogenase level	Low	60 (3.6)
	Normal	1144 (69.6)
	Raised	440 (26.8)
	not done/not known	395
Haemoglobin (g/dL)	mean (SD)	11.9 (2.4)
	median (IQR)	12.3 (10.4 - 13.6)
White blood cell count (10^9/L)	mean (SD)	10.2 (20.8)

		n (%)
Total		**2039**
	median (IQR)	7.2 (5.6 - 9.5)
Lymphocytes count (10^9/L)	mean (SD)	4.3 (15.2)
	median (IQR)	1.9 (1.3 - 2.8)
Albumin (g/L)	mean (SD)	37.7 (6.3)
	median (IQR)	39.0 (35.0 - 42.0)
beta-2 microglobulin (mg/L)	mean (SD)	4.1 (3.4)
	median (IQR)	3.1 (2.3 - 4.7)
Platelet count (10^9/L)	mean (SD)	236.2 (111.3)
	median (IQR)	229.0 (161.0 - 295.0)
Packed cell volume (%)	mean (SD)	35.7 (7.3)
	median (IQR)	37.0 (32.0 - 40.8)
Absolute monocyte count (10^9/L)	mean (SD)	0.7 (1.6)
	median (IQR)	0.6 (0.4 - 0.8)
Paraprotein level (g/L)	mean (SD)	11.0 (12.8)
	median (IQR)	7.0 (0.0 - 16.0)
Absolute neutrophil count (10^9/L)	mean (SD)	4.4 (2.3)
	median (IQR)	4.1 (2.9 - 5.4)

[1] Paraproteins not originally recorded; these have been recorded since 2016

Table 3 Initial disease management by age and sex for marginal zone lymphoma patients diagnosed 1st January 2005 to 31st December 2020

	Total n (%)	Age at diagnosis (years) n (%)						Sex n (%)		Time from diagnosis to chemotherapy (days)
		Mean (SD)	Median (min – max)	<60	60-69	70-79	≥80	Male	Female	Median (IQR)
Total	2039 (100.0) [1]	71.1 (11.3)	72.3 (19.5 - 97.7)	326 (100.0)	541 (100.0)	713 (100.0)	459 (100.0)	1135 (100.0)	904 (100.0)	49 (21 - 296.5)
Watch & Wait	1087 (53.3)	71.7 (10.9)	72.7 (19.5 - 93.9)	152 (46.6)	296 (54.7)	385 (54.0)	254 (55.3)	633 (55.8)	454 (50.2)	-
Continued on watch & wait	858 (42.1)	72.5 (11.0)	73.4 (19.5 - 93.9)	110 (33.7)	217 (40.1)	306 (42.9)	225 (49.0)	503 (44.3)	355 (39.3)	-
Started chemotherapy	229 (11.2)	68.8 (10.0)	69.5 (33.7 - 88.3)	42 (12.9)	79 (14.6)	79 (11.1)	29 (6.3)	130 (11.5)	99 (11.0)	729 (348 - 1146)
Chemotherapy	605 (29.7)	71.5 (10.5)	72.3 (37.0 - 97.7)	88 (27.0)	168 (31.1)	212 (29.7)	137 (29.8)	328 (28.9)	277 (30.6)	29 (16 - 55)
Radiotherapy	153 (7.5)	66.2 (13.0)	68.1 (26.5 - 93.8)	46 (14.1)	39 (7.2)	50 (7.0)	18 (3.9)	68 (6.0)	85 (9.4)	-
Radiotherapy only	140 (6.9)	66.5 (13.2)	68.1 (26.5 - 93.8)	40 (12.3)	37 (6.8)	45 (6.3)	18 (3.9)	62 (5.5)	78 (8.6)	-
Started chemotherapy	13 (0.6)	61.9 (11.1)	60.5 (44.8 - 75.9)	6 (1.8)	2 (0.4)	5 (0.7)	-	6 (0.5)	7 (0.8)	1051 (535 - 1929)
H. pylori eradication	83 (4.1)	65.9 (15.1)	66.8 (24.7 - 95.1)	28 (8.6)	16 (3.0)	25 (3.5)	14 (3.1)	49 (4.3)	34 (3.8)	-
H. pylori eradication only	77 (3.8)	65.9 (15.1)	66.8 (24.7 - 95.1)	25 (7.7)	16 (3.0)	24 (3.4)	12 (2.6)	44 (3.9)	33 (3.7)	-
Started chemotherapy	6 (0.3)	65.2 (15.9)	61.6 (50.3 - 85.0)	3 (0.9)	-	1 (0.1)	2 (0.4)	5 (0.4)	1 (0.1)	775 (504 - 1705)
Supportive/palliative care	84 (4.1)	75.3 (11.1)	75.0 (41.0 - 96.2)	7 (2.1)	17 (3.1)	30 (4.2)	30 (6.5)	44 (3.9)	40 (4.4)	-
Supportive/palliative care only	73 (3.6)	76.0 (11.4)	75.9 (41.0 - 96.2)	6 (1.8)	15 (2.8)	22 (3.1)	30 (6.5)	38 (3.3)	35 (3.9)	-
Started chemotherapy	11 (0.5)	70.4 (7.5)	71.3 (50.9 - 79.2)	1 (0.3)	2 (0.4)	8 (1.1)	-	6 (0.5)	5 (0.6)	434 (246 - 728)
Non-haematological comorbidity[2]	27 (1.3)	70.7 (14.0)	74.2 (28.8 - 91.8)	5 (1.5)	5 (0.9)	11 (1.5)	6 (1.3)	13 (1.1)	14 (1.5)	-

[1] 31 patients (1.5%) underwent a splenectomy. [2] Patient has a more serious competing comorbidity which took precedence over the treatment of their lymphoma diagnosis

Table 4 First line treatment by baseline characteristics

	Total	Sex		Age at treatment start		Subtype	
	n (%)	Male	Female	Mean (sd)	Median (min-max)	Systemic	Extranodal (MALT)
Total	1008 (100.0)	540 (100.0)	468 (100.0)	70.8 (10.9)	72.2 (26.7 - 97.7)	764 (100.0)	244 (100.0)
Chlorambucil	252 (25.0)	125 (23.1)	127 (27.1)	75.5 (9.6)	76.6 (48.2 - 97.7)	213 (27.9)	39 (16.0)
Bendamustine / Rituximab	135 (13.4)	85 (15.7)	50 (10.7)	67.2 (8.8)	67.4 (38.1 - 87.6)	120 (15.7)	15 (6.1)
R-CVP	97 (9.6)	52 (9.6)	45 (9.6)	70.6 (9.4)	72.1 (42.4 - 86.0)	82 (10.7)	15 (6.1)
Dexamethasone/Rituximab/Cyclophosphamide	94 (9.3)	63 (11.7)	31 (6.6)	74.1 (8.6)	75.2 (49.3 - 89.8)	85 (11.1)	9 (3.7)
Single Agent Rituximab	77 (7.6)	36 (6.7)	41 (8.8)	74.0 (10.8)	77.3 (50.1 - 95.1)	66 (8.6)	11 (4.5)
FCR	65 (6.4)	40 (7.4)	25 (5.3)	63.7 (10.0)	65.7 (34.3 - 81.4)	60 (7.9)	5 (2.0)
FC	59 (5.9)	25 (4.6)	34 (7.3)	64.2 (9.4)	65.3 (44.2 - 89.1)	54 (7.1)	5 (2.0)
Chlorambucil / Rituximab	29 (2.9)	12 (2.2)	17 (3.6)	80.0 (6.1)	81.2 (62.5 - 89.1)	26 (3.4)	3 (1.2)
R-CHOP	21 (2.1)	15 (2.8)	6 (1.3)	71.9 (7.0)	74.3 (57.6 - 80.0)	16 (2.1)	5 (2.0)
Other Rituximab[1]	7 (0.7)	5 (0.9)	2 (0.4)	67.9 (9.4)	68.7 (49.8 - 77.1)	7 (0.9)	-
Other non-Rituximab[2]	14 (1.4)	9 (1.7)	5 (1.1)	70.0 (8.4)	69.3 (51.6 - 86.7)	13 (1.7)	1 (0.4)
Radiotherapy	158 (15.7)	73 (13.5)	85 (18.2)	66.3 (13.0)	68.3 (26.7 - 93.9)	22 (2.9)	136 (55.7)

[1] VCR (n=4), Rituximab / Prednisolone (n=2), Rituximab / Dexamethasone (n=1)

[2] Bendamustine (n=2), Lenalidomide / Cyclophosphamide / Dexamethasone (n=2), Methotrexate (IT) (n=2), Acalabrutinib (n=1), Bendamustine / Dexamethasone (n=1), C-Z-Dex (n=1), CHOP (n=1), CTDa (n=1), Cyclophosphamide (n=1), Etoposide (n=1), Methotrexate (HD)

Table 5 First line treatment, response assessment, overall response rate and time to next line

	Total n (%)	Response assessed n (%)		Overall response rate n (%)	Refractory n (%)	Next line n (%)		TTNT Years (95% CI)
		No	Yes			No	Yes	
Total	1008 (100.0)	217 (21.5)	791 (78.5)	665 (84.1)	119 (14.8)	730 (72.4)	278 (27.6)	5.1 (4.5 - 5.7)
Chlorambucil	252 (25.0)	66 (26.2)	186 (73.8)	127 (68.3)	54 (28.1)	134 (53.2)	118 (46.8)	2.8 (2.2 - 3.7)
Bendamustine / Rituximab	135 (13.4)	18 (13.3)	117 (86.7)	114 (97.4)	7 (5.9)	123 (91.1)	12 (8.9)	NR (7.4 - NR)
R-CVP	97 (9.6)	11 (11.3)	86 (88.7)	73 (84.9)	12 (14.0)	69 (71.1)	28 (28.9)	5.6 (2.9 - NR)
Dexamethasone/Rituximab/Cyclophosphamide	94 (9.3)	16 (17.0)	78 (83.0)	65 (83.3)	9 (11.2)	70 (74.5)	24 (25.5)	5.2 (3.2 - NR)
Single Agent Rituximab	77 (7.6)	30 (39.0)	47 (61.0)	36 (76.6)	6 (12.8)	58 (75.3)	19 (24.7)	5.1 (4.0 - NR)
FCR	65 (6.4)	11 (16.9)	54 (83.1)	51 (94.4)	5 (9.1)	53 (81.5)	12 (18.5)	NR (5.6 - NR)
FC	59 (5.9)	9 (15.3)	50 (84.7)	38 (76.0)	12 (23.5)	32 (54.2)	27 (45.8)	6.0 (2.9 - 7.2)
Chlorambucil / Rituximab	29 (2.9)	10 (34.5)	19 (65.5)	15 (78.9)	4 (21.1)	23 (79.3)	6 (20.7)	3.8 (1.5 - NR)
R-CHOP	21 (2.1)	3 (14.3)	18 (85.7)	16 (88.9)	2 (10.5)	16 (76.2)	5 (23.8)	6.6 (1.4 - NR)
Other Rituximab[1]	7 (0.7)	2 (28.6)	5 (71.4)	4 (80.0)	-	5 (71.4)	2 (28.6)	5.7 (2.1 - NR)
Other non-Rituximab[2]	14 (1.4)	7 (50.0)	7 (50.0)	4 (57.1)	6 (66.7)	8 (57.1)	6 (42.9)	0.2 (0.0 - NR)
Radiotherapy	158 (15.7)	34 (21.5)	124 (78.5)	122 (98.4)	2 (1.6)	139 (88.0)	19 (12.0)	5.3 (4.3 - NR)

NR = not reached

[1] VCR (n=4), Rituximab / Prednisolone (n=2), Rituximab / Dexamethasone (n=1)

[2] Bendamustine (n=2), Lenalidomide / Cyclophosphamide / Dexamethasone (n=2), Methotrexate (IT) (n=2), Acalabrutinib (n=1), Bendamustine / Dexamethasone (n=1), C-Z-Dex (n=1), CHOP (n=1), CTDa (n=1), Cyclophosphamide (n=1), Etoposide (n=1), Methotrexate (HD)

Figure 3 Time to next line of treatment from end of first line

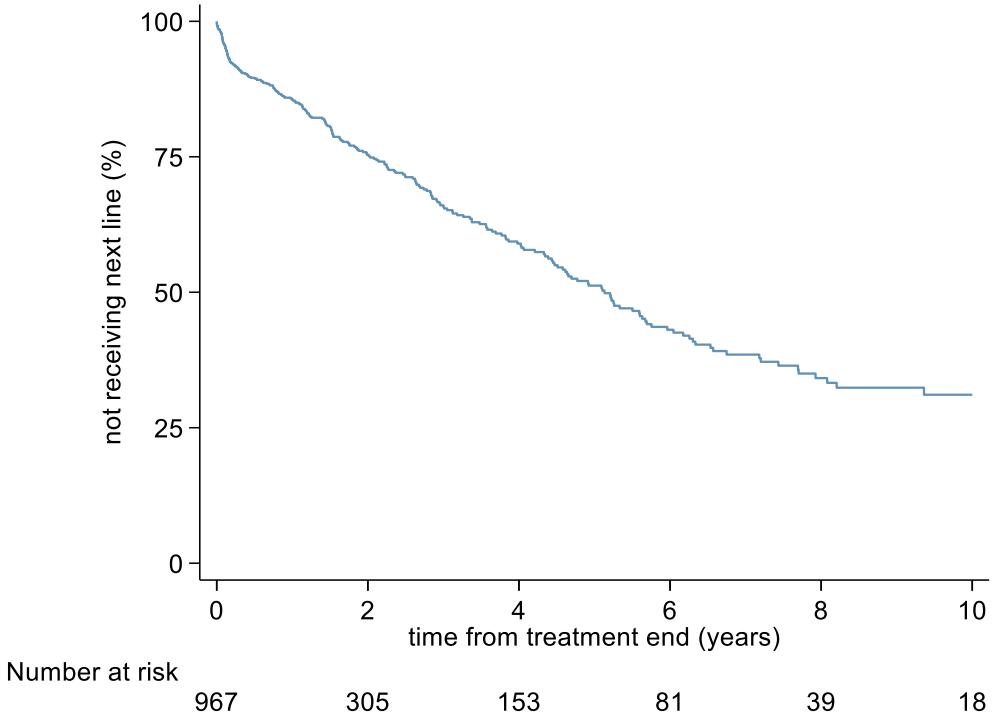


Figure 4 Time to next line of treatment from end of first line by regimen

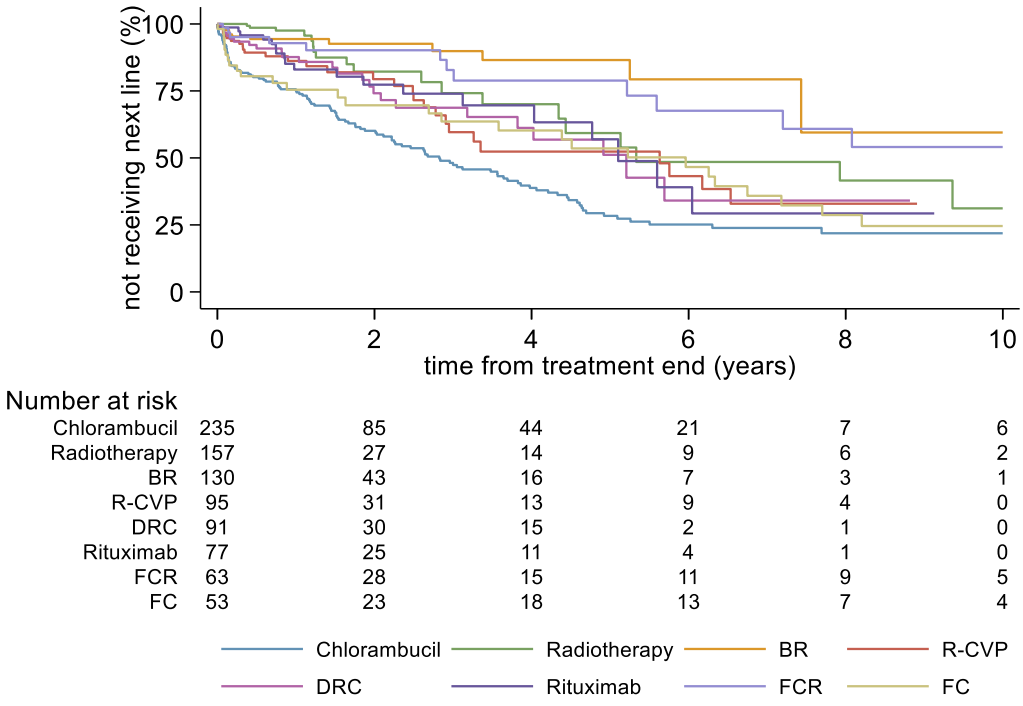


Table 6 First line chemotherapy regimen by year group started treatment

	Total	Year treatment started			
	n (%)	2005-08	2009-12	2013-16	2016-23
Total	864 (100.0)	155 (100.0)	215 (100.0)	234 (100.0)	260 (100.0)
Chlorambucil	254 (29.4)	112 (72.3)	116 (54.0)	18 (7.7)	8 (3.1)
Bendamustine / Rituximab	136 (15.7)	-	2 (0.9)	51 (21.8)	83 (31.9)
R-CVP	100 (11.6)	3 (1.9)	14 (6.5)	57 (24.4)	26 (10.0)
Dexamethasone/Rituximab/Cyclophosphamide	94 (10.9)	-	4 (1.9)	14 (6.0)	76 (29.2)
Single Agent Rituximab	82 (9.5)	2 (1.3)	6 (2.8)	27 (11.5)	47 (18.1)
FCR	66 (7.6)	3 (1.9)	32 (14.9)	30 (12.8)	1 (0.4)
FC	61 (7.1)	28 (18.1)	29 (13.5)	4 (1.7)	-
Chlorambucil / Rituximab	29 (3.4)	1 (0.6)	2 (0.9)	17 (7.3)	9 (3.5)
R-CHOP	21 (2.4)	3 (1.9)	6 (2.8)	7 (3.0)	5 (1.9)
Other Rituximab[1]	7 (0.8)	-	1 (0.5)	5 (2.1)	1 (0.4)
Other non-Rituximab[2]	14 (1.6)	3 (1.9)	3 (1.4)	4 (1.7)	4 (1.5)

[1] VCR (n=4), Rituximab / Prednisolone (n=2), Rituximab / Dexamethasone (n=1)

[2] Bendamustine (n=2), Lenalidomide / Cyclophosphamide / Dexamethasone (n=2), Methotrexate (IT) (n=2), Acalabrutinib (n=1), Bendamustine / Dexamethasone (n=1), C-Z-Dex (n=1), CHOP (n=1), CTDa (n=1), Cyclophosphamide (n=1), Etoposide (n=1), Methotrexate (HD)

Figure 5 First line chemotherapy regimen by year started treatment

Table 7 Second line chemotherapy treatment by sex, age and subtype

	Total	Sex		Age at treatment start		Subtype	
	n (%)	Male	Female	Mean (sd)	Median (min-max)	Systemic	Extranodal (MALT)
Total	278 (100.0)	156 (100.0)	122 (100.0)	72.5 (9.9)	73.2 (40.0 - 90.9)	244 (100.0)	34 (100.0)
Single Agent Rituximab	54 (19.4)	24 (15.4)	30 (24.6)	75.7 (8.5)	76.6 (51.6 - 89.7)	46 (18.9)	8 (23.5)
Chlorambucil	33 (11.9)	13 (8.3)	20 (16.4)	78.6 (7.3)	80.0 (60.4 - 90.0)	31 (12.7)	2 (5.9)
FC	30 (10.8)	17 (10.9)	13 (10.7)	68.3 (10.5)	68.4 (49.3 - 90.9)	28 (11.5)	2 (5.9)
R-CVP	30 (10.8)	19 (12.2)	11 (9.0)	68.1 (10.2)	68.5 (48.6 - 85.8)	25 (10.2)	5 (14.7)
Bendamustine / Rituximab	29 (10.4)	21 (13.5)	8 (6.6)	70.4 (7.4)	69.7 (51.9 - 85.1)	25 (10.2)	4 (11.8)
Ibrutinib	22 (7.9)	13 (8.3)	9 (7.4)	72.4 (10.7)	74.6 (51.6 - 88.0)	22 (9.0)	-
FCR	17 (6.1)	14 (9.0)	3 (2.5)	68.8 (8.1)	67.1 (58.3 - 84.3)	15 (6.1)	2 (5.9)
Dexamethasone/Rituximab/Cyclophosphamide	15 (5.4)	9 (5.8)	6 (4.9)	79.5 (6.2)	79.1 (67.3 - 88.4)	13 (5.3)	2 (5.9)
R-CHOP	8 (2.9)	7 (4.5)	1 (0.8)	64.0 (10.1)	64.5 (46.5 - 77.9)	8 (3.3)	-
Other Rituximab[1]	10 (3.6)	2 (1.3)	8 (6.6)	74.8 (8.2)	75.0 (60.6 - 83.8)	9 (3.7)	1 (2.9)
Other non-Rituximab[2]	20 (7.2)	13 (8.3)	7 (5.7)	70.1 (10.4)	69.6 (40.0 - 84.1)	20 (8.2)	-
Radiotherapy	10 (3.6)	4 (2.6)	6 (4.9)	71.1 (14.8)	76.4 (42.1 - 86.0)	2 (0.9)	8 (23.5)

[1] Chlorambucil / Rituximab (n=4), Fludarabine / Rituximab (n=2), Gemcitabine / Dexamethasone / Cisplatin / Rituximab (n=1), IVE / Rituximab (n=1), Velcade / Dexamethasone / Rituximab (n=1), Venetoclax / Rituximab (n=1)

[2] Acalabrutinib (n=5), Bendamustine (n=3), CVP (n=2), Ublituximab / Umbralisib (n=2), Alemtuzumab (n=1), Bendamustine / Methylprednisolone (n=1), Cyclophosphamide / Dexamethasone (n=1), Cyclophosphamide / Prednisolone (n=1), Methotrexate (IT) (n=1), VCD (n=1), Vincristine / Prednisolone (n=1), Zanubrutinib (n=1)

Table 8 Second line chemotherapy regimen by year group started treatment

	Total	Year treatment started			
	n (%)	2005-08	2009-12	2013-16	2016-22
Total	259 (100.0)	37 (100.0)	65 (100.0)	68 (100.0)	89 (100.0)
Single Agent Rituximab	49 (18.9)	4 (10.8)	21 (32.3)	12 (17.6)	12 (13.5)
Bendamustine / Rituximab	31 (12.0)	-	-	15 (22.1)	16 (18.0)
Chlorambucil	31 (12.0)	7 (18.9)	11 (16.9)	9 (13.2)	4 (4.5)
FC	28 (10.8)	17 (45.9)	10 (15.4)	1 (1.5)	-
R-CVP	28 (10.8)	2 (5.4)	10 (15.4)	7 (10.3)	9 (10.1)
Ibrutinib	22 (8.5)	-	-	-	22 (24.7)
FCR	16 (6.2)	3 (8.1)	9 (13.8)	3 (4.4)	1 (1.1)
Dexamethasone/Rituximab/Cyclophosphamide	15 (5.8)	-	1 (1.5)	4 (5.9)	10 (11.2)
R-CHOP	9 (3.5)	1 (2.7)	2 (3.1)	6 (8.8)	-
Other Rituximab[1]	10 (3.9)	-	-	5 (7.4)	5 (5.6)
Other non-Rituximab[2]	20 (7.7)	3 (8.1)	1 (1.5)	6 (8.8)	10 (11.2)

[1] Chlorambucil / Rituximab (n=4), Fludarabine / Rituximab (n=2), Gemcitabine / Dexamethasone / Cisplatin / Rituximab (n=1), IVE / Rituximab (n=1), Velcade / Dexamethasone / Rituximab (n=1), Venetoclax / Rituximab (n=1)

[2] Acalabrutinib (n=5), Bendamustine (n=3), CVP (n=2), Ublituximab / Umbralisib (n=2), Alemtuzumab (n=1), Bendamustine / Methylprednisolone (n=1), Cyclophosphamide / Dexamethasone (n=1), Cyclophosphamide / Prednisolone (n=1), Methotrexate (IT) (n=1), VCD (n=1), Vincristine / Prednisolone (n=1), Zanubrutinib (n=1)

Figure 6 Second line chemotherapy regimen by year started treatment

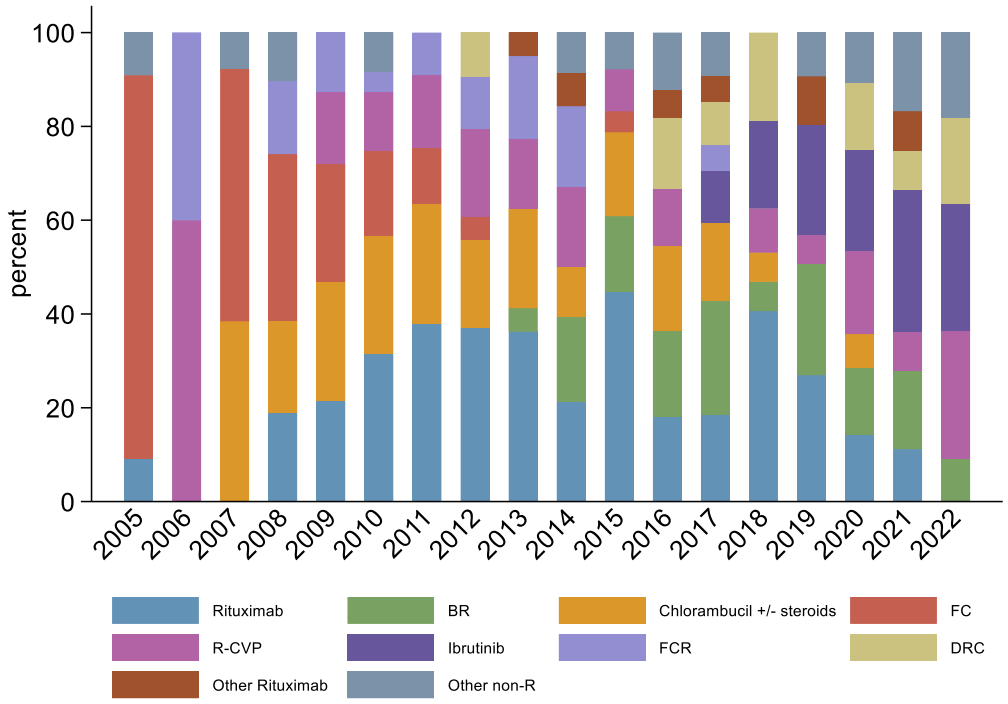


Table 9 Second line chemotherapy treatment, response assessment, overall response rate and time to next line

	Total n (%)	Response assessed n (%)		Overall response rate n (%)	Refractory n (%)	Next line n (%)		TTNT Years (95% CI)
		No	Yes			No	Yes	
Total	278 (100.0)	76 (27.3)	202 (72.7)	142 (70.3)	52 (25.1)	175 (62.9)	103 (37.1)	1.2 (0.8 - 1.7)
Single Agent Rituximab	54 (19.4)	23 (42.6)	31 (57.4)	20 (64.5)	10 (30.3)	31 (57.4)	23 (42.6)	1.0 (0.2 - 1.4)
Chlorambucil	33 (11.9)	10 (30.3)	23 (69.7)	12 (52.2)	6 (25.0)	23 (69.7)	10 (30.3)	1.1 (0.1 - 2.5)
FC	30 (10.8)	7 (23.3)	23 (76.7)	16 (69.6)	8 (32.0)	12 (40.0)	18 (60.0)	1.3 (0.2 - 2.3)
R-CVP	30 (10.8)	3 (10.0)	27 (90.0)	22 (81.5)	3 (11.1)	18 (60.0)	12 (40.0)	2.2 (0.2 - 2.6)
Bendamustine / Rituximab	29 (10.4)	3 (10.3)	26 (89.7)	22 (84.6)	4 (15.4)	22 (75.9)	7 (24.1)	1.7 (0.1 - 3.7)
Ibrutinib	22 (7.9)	11 (50.0)	11 (50.0)	6 (54.5)	6 (54.5)	17 (77.3)	5 (22.7)	0.2 (0.0 - NR)
FCR	17 (6.1)	4 (23.5)	13 (76.5)	12 (92.3)	2 (15.4)	11 (64.7)	6 (35.3)	0.5 (0.1 - NR)
Dexamethasone/Rituximab/Cyclophosphamide	15 (5.4)	3 (20.0)	12 (80.0)	10 (83.3)	2 (16.7)	12 (80.0)	3 (20.0)	2.2 (0.2 - NR)
R-CHOP	8 (2.9)	2 (25.0)	6 (75.0)	2 (33.3)	3 (50.0)	8 (100.0)	-	-
Other Rituximab[1]	10 (3.6)	2 (20.0)	8 (80.0)	6 (75.0)	1 (12.5)	5 (50.0)	5 (50.0)	1.6 (0.5 - NR)
Other non-Rituximab[2]	20 (7.2)	6 (30.0)	14 (70.0)	6 (42.9)	7 (50.0)	9 (45.0)	11 (55.0)	0.2 (0.0 - 2.0)
Radiotherapy	10 (3.6)	2 (20.0)	8 (80.0)	8 (100.0)	-	7 (70.0)	3 (30.0)	2.4 (1.1 - NR)

NR = not reached

[1] Chlorambucil / Rituximab (n=4), Fludarabine / Rituximab (n=2), Gemcitabine / Dexamethasone / Cisplatin / Rituximab (n=1), IVE / Rituximab (n=1), Velcade / Dexamethasone / Rituximab (n=1), Venetoclax / Rituximab (n=1)

[2] Acalabrutinib (n=5), Bendamustine (n=3), CVP (n=2), Ublituximab / Umbralisib (n=2), Alemtuzumab (n=1), Bendamustine / Methylprednisolone (n=1), Cyclophosphamide / Dexamethasone (n=1), Cyclophosphamide / Prednisolone (n=1), Methotrexate (IT) (n=1), VCD (n=1), Vincristine / Prednisolone (n=1), Zanubrutinib (n=1)

Figure 7 Time to next line of treatment from end of second line

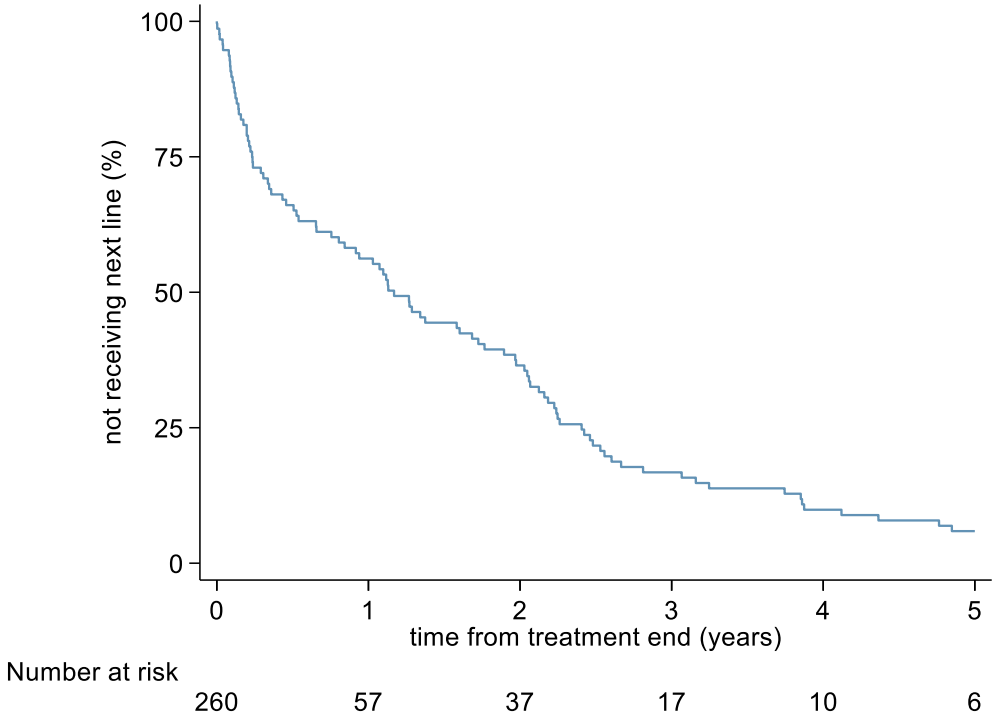


Figure 8 Time to next line of treatment from end of second line by regimen

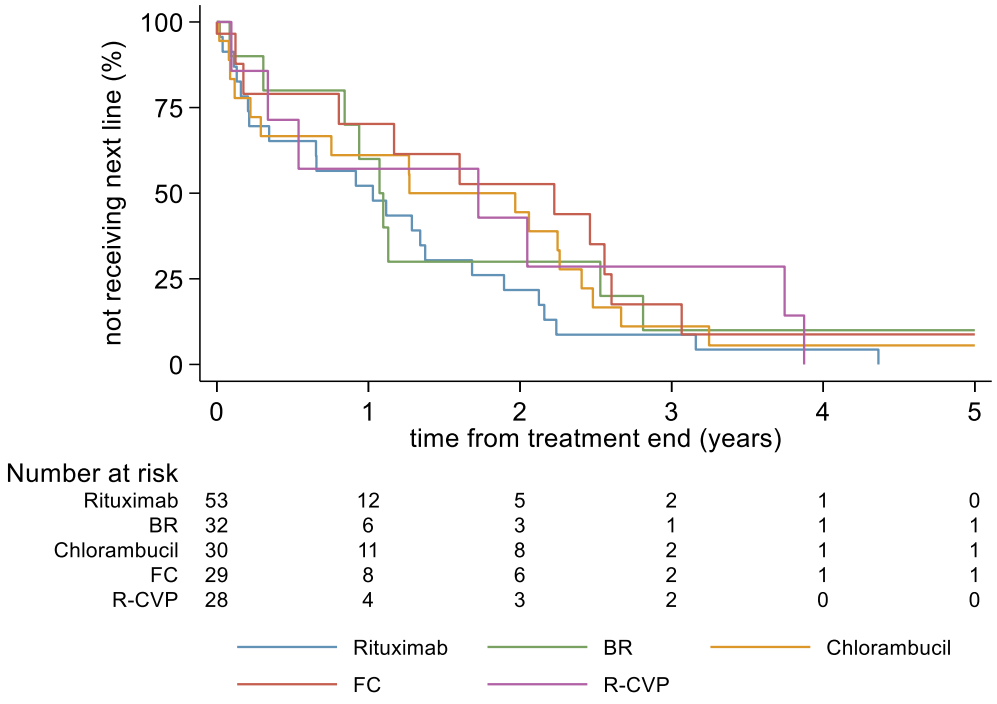


Table 10 Third line chemotherapy treatment by sex, age and subtype

	Total	Sex		Age at treatment start		Subtype	
	n (%)	Male	Female	Mean (sd)	Median (min-max)	Systemic	Extranodal (MALT)
Total	103 (100.0)	53 (100.0)	50 (100.0)	74.0 (10.0)	74.2 (49.6 - 91.0)	94 (100.0)	9 (100.0)
Single Agent Rituximab	25 (24.3)	15 (28.3)	10 (20.0)	74.9 (10.9)	78.1 (49.6 - 90.7)	25 (26.6)	-
Bendamustine / Rituximab	18 (17.5)	9 (17.0)	9 (18.0)	67.1 (6.9)	66.6 (56.4 - 80.2)	15 (16.0)	3 (33.3)
R-CVP	10 (9.7)	4 (7.5)	6 (12.0)	74.7 (9.3)	74.7 (62.4 - 90.2)	10 (10.6)	-
Ibrutinib	8 (7.8)	5 (9.4)	3 (6.0)	76.7 (9.1)	78.1 (64.5 - 89.1)	7 (7.4)	1 (11.1)
Chlorambucil	7 (6.8)	2 (3.8)	5 (10.0)	84.5 (7.1)	87.7 (70.4 - 91.0)	6 (6.4)	1 (11.1)
Other Rituximab[1]	14 (13.6)	8 (15.1)	6 (12.0)	73.2 (10.7)	71.6 (49.9 - 89.2)	12 (12.8)	2 (22.2)
Other non-Rituximab[2]	18 (17.5)	10 (18.9)	8 (16.0)	73.2 (8.8)	72.3 (52.5 - 88.0)	18 (19.1)	-
Radiotherapy	3 (2.9)	-	3 (6.0)	82.5 (4.1)	80.2 (80.0 - 87.3)	1 (1.1)	2 (22.2)

[1] R-CHOP (n=5), Chlorambucil / Rituximab (n=3), Cyclophosphamide / Prednisolone / Rituximab (n=2), FCR (n=2), DRC (n=1), Eltrombopag / Rituximab (n=1)

[2] Fludarabine (n=3), Venetoclax (n=3), Acalabrutinib (n=2), Bendamustine (n=2), CVP (n=2), FC (n=2), Zanubrutinib (n=2), CHOP (n=1), Velcade / Dexamethasone (n=1)

Table 11 Third line chemotherapy treatment, response assessment, overall response rate and time to next line

	Total n (%)	Response Assessed n (%)		Overall response rate n (%)	Refractory n (%)	Next line n (%)		TTNT Years (95% CI)
		No	Yes			No	Yes	
Total	103 (100.0)	25 (24.3)	78 (75.7)	60 (76.9)	16 (20.3)	67 (65.0)	36 (35.0)	1.7 (1.3 - 2.3)
Single Agent Rituximab	25 (24.3)	7 (28.0)	18 (72.0)	15 (83.3)	3 (15.8)	10 (40.0)	15 (60.0)	1.3 (0.5 - 3.1)
Bendamustine / Rituximab	18 (17.5)	3 (16.7)	15 (83.3)	14 (93.3)	1 (6.7)	11 (61.1)	7 (38.9)	4.1 (2.3 - 4.6)
R-CVP	10 (9.7)	1 (10.0)	9 (90.0)	5 (55.6)	3 (33.3)	9 (90.0)	1 (10.0)	0.1 (. - NR)
Ibrutinib	8 (7.8)	4 (50.0)	4 (50.0)	3 (75.0)	1 (25.0)	7 (87.5)	1 (12.5)	1.7 (. - NR)
Chlorambucil	7 (6.8)	1 (14.3)	6 (85.7)	5 (83.3)	1 (16.7)	4 (57.1)	3 (42.9)	1.7 (0.2 - NR)
Other Rituximab[1]	14 (13.6)	3 (21.4)	11 (78.6)	9 (81.8)	2 (18.2)	11 (78.6)	3 (21.4)	1.3 (0.6 - NR)
Other non-Rituximab[2]	18 (17.5)	5 (27.8)	13 (72.2)	7 (53.8)	5 (38.5)	13 (72.2)	5 (27.8)	1.5 (0.0 - NR)
Radiotherapy	3 (2.9)	1 (33.3)	2 (66.7)	2 (100.0)	-	2 (66.7)	1 (33.3)	2.0 (. - NR)

NR = not reached

[1] R-CHOP (n=5), Chlorambucil / Rituximab (n=3), Cyclophosphamide / Prednisolone / Rituximab (n=2), FCR (n=2), DRC (n=1), Eltrombopag / Rituximab (n=1)

[2] Fludarabine (n=3), Venetoclax (n=3), Acalabrutinib (n=2), Bendamustine (n=2), CVP (n=2), FC (n=2), Zanubrutinib (n=2), CHOP (n=1), Velcade / Dexamethasone (n=1)

Figure 9 Time to next line of treatment from end of third line

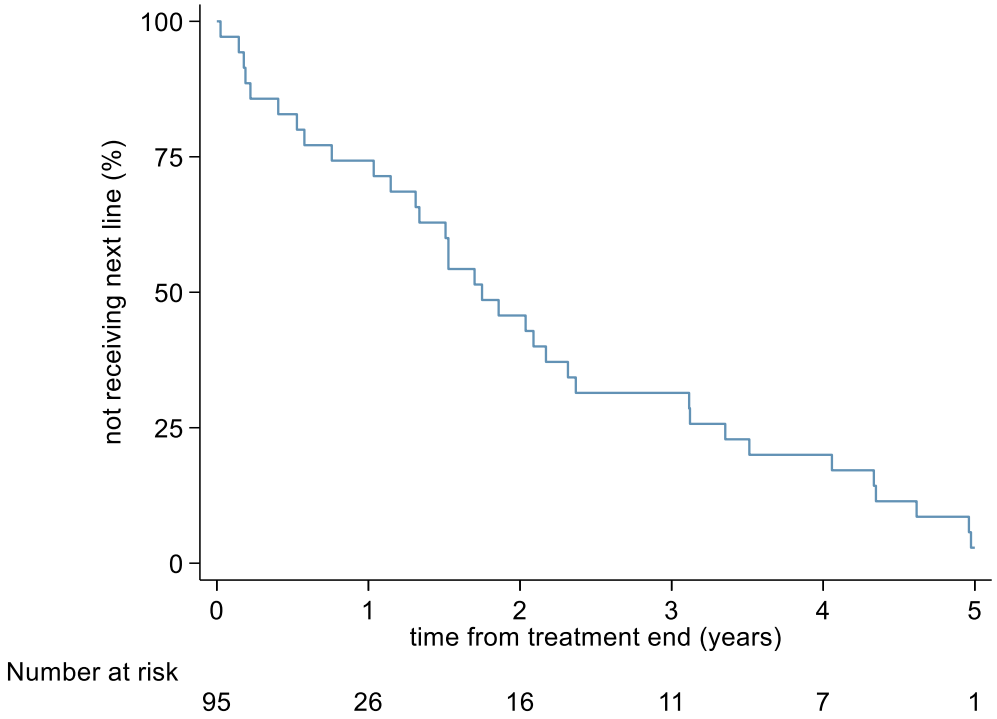
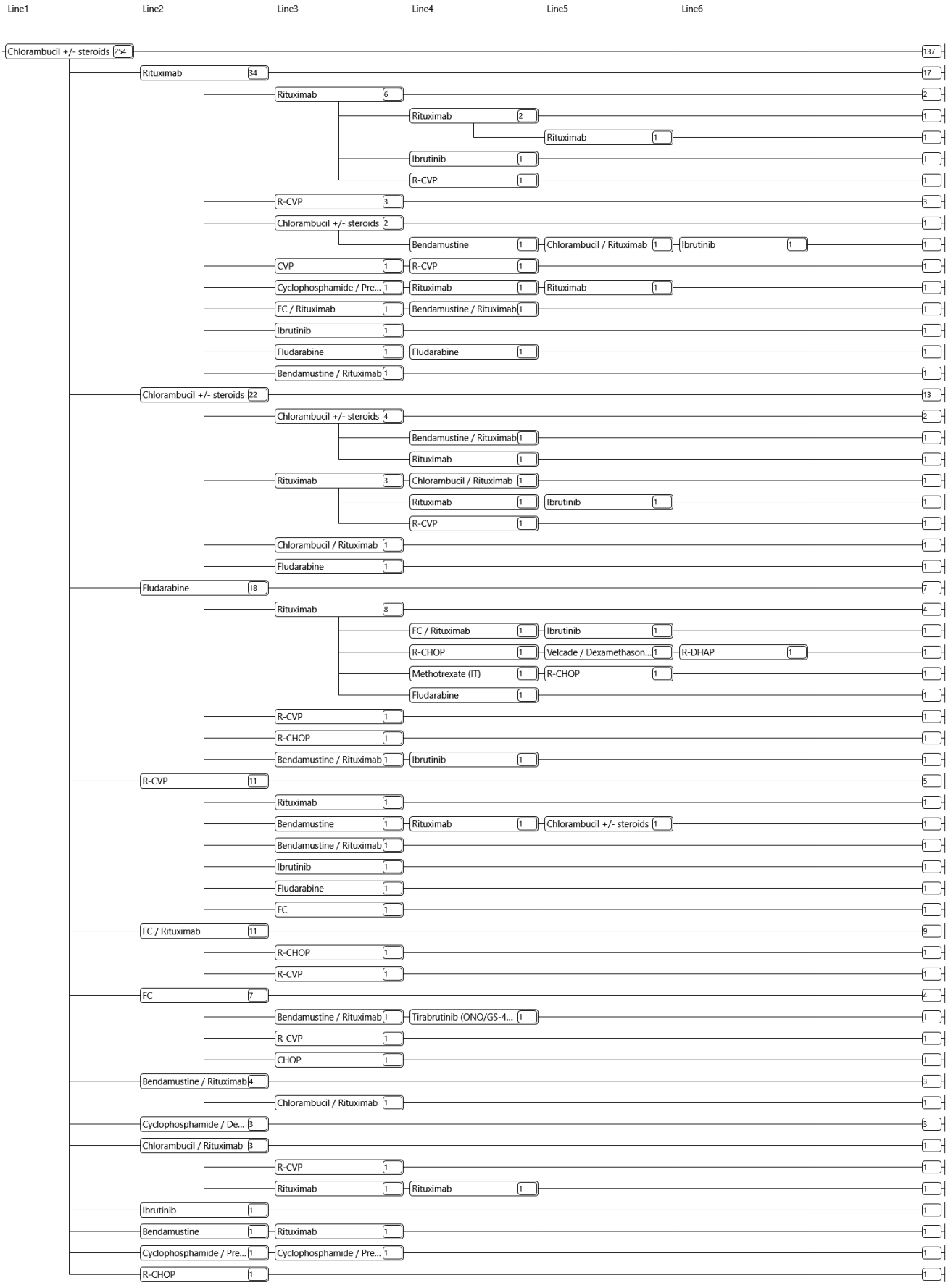
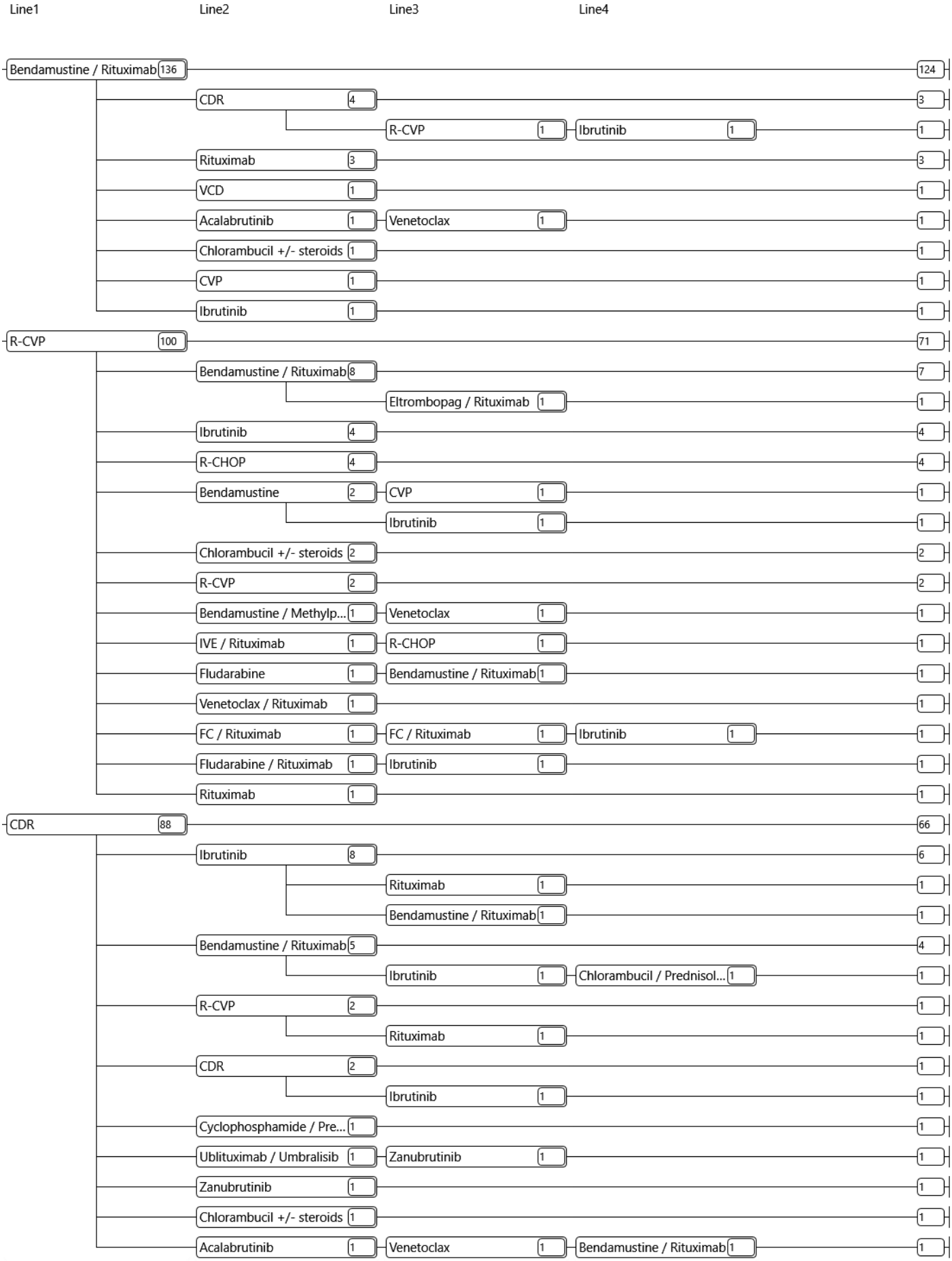
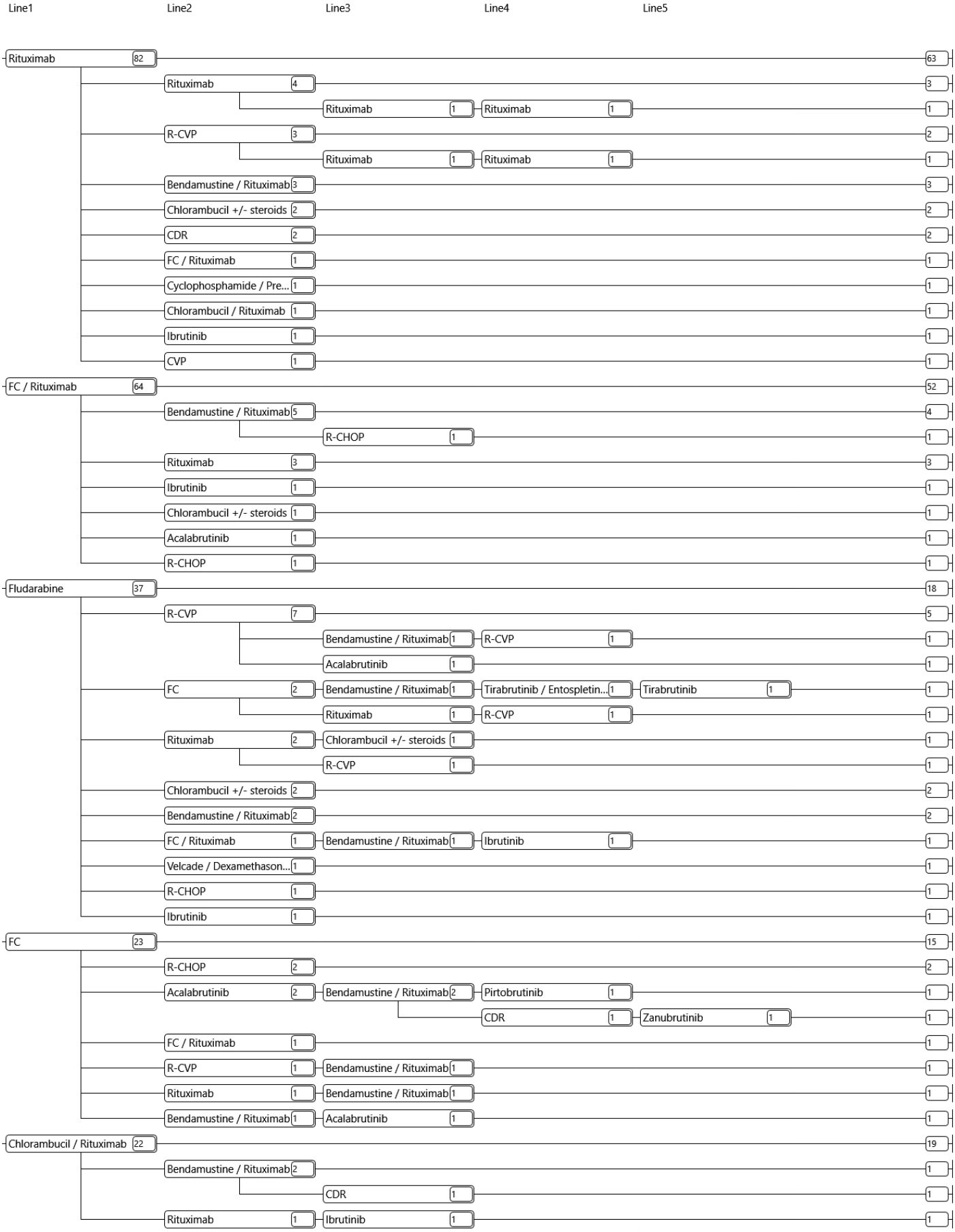


Figure 10 Sequential chemotherapy treatment pathway from first line treatment (including those previous on watch and wait or other initial management)




Line1
Line2
Line3
Line4
Bendamustine / Rituximab 136
124
CDR 4
3
R-CVP 1
Ibrutinib 1
1
Rituximab 3
3
VCD 1
1
Acalabrutinib 1
Venetoclax 1
1
Chlorambucil +/- steroids 1
1
CVP 1
1
Ibrutinib 1
1
R-CVP 100
71
Bendamustine / Rituximab 8
7
Eltrombopag / Rituximab 1
1
Ibrutinib 4
4
R-CHOP 4
4
Bendamustine 2
CVP 1
1
Ibrutinib 1
1
Chlorambucil +/- steroids 2
2
R-CVP 2
2
Bendamustine / Methylp... 1
Venetoclax 1
1
IVE / Rituximab 1
R-CHOP 1
1
Fludarabine 1
Bendamustine / Rituximab 1
1
Venetoclax / Rituximab 1
1
FC / Rituximab 1
FC / Rituximab 1
Ibrutinib 1
1
Fludarabine / Rituximab 1
Ibrutinib 1
1
Rituximab 1
1
CDR 88
66
Ibrutinib 8
6
Rituximab 1
1
Bendamustine / Rituximab 1
1
Bendamustine / Rituximab 5
4
Ibrutinib 1
Chlorambucil / Prednisol... 1
1
R-CVP 2
1
Rituximab 1
1
CDR 2
1
Ibrutinib 1
1
Cyclophosphamide / Pre... 1
1
Ublituximab / Umbralisib 1
Zanubrutinib 1
1
Zanubrutinib 1
1
Chlorambucil +/- steroids 1
1
Acalabrutinib 1
Venetoclax 1
Bendamustine / Rituximab 1
1


Line1
Line2
Line3
Line4
Line5
Rituximab 82
Rituximab 4
Rituximab 1
Rituximab 1
R-CVP 3
Rituximab 1
Rituximab 1
Bendamustine / Rituximab 3
Chlorambucil +/- steroids 2
CDR 2
FC / Rituximab 1
Cyclophosphamide / Pre... 1
Chlorambucil / Rituximab 1
Ibrutinib 1
CVP 1
FC / Rituximab 64
Bendamustine / Rituximab 5
R-CHOP 1
Rituximab 3
Ibrutinib 1
Chlorambucil +/- steroids 1
Acalabrutinib 1
R-CHOP 1
Fludarabine 37
R-CVP 7
Bendamustine / Rituximab 1
R-CVP 1
Acalabrutinib 1
FC 2
Bendamustine / Rituximab 1
Tirabrutinib / Entospletin... 1
Tirabrutinib 1
Rituximab 1
R-CVP 1
Rituximab 2
Chlorambucil +/- steroids 1
R-CVP 1
Chlorambucil +/- steroids 2
Bendamustine / Rituximab 2
FC / Rituximab 1
Bendamustine / Rituximab 1
Ibrutinib 1
Velcade / Dexamethason... 1
R-CHOP 1
Ibrutinib 1
FC 23
R-CHOP 2
Acalabrutinib 2
Bendamustine / Rituximab 2
Pirtobrutinib 1
CDR 1
Zanubrutinib 1
FC / Rituximab 1
R-CVP 1
Bendamustine / Rituximab 1
Rituximab 1
Bendamustine / Rituximab 1
Bendamustine / Rituximab 1
Acalabrutinib 1
Chlorambucil / Rituximab 22
Bendamustine / Rituximab 2
CDR 1
Rituximab 1
Ibrutinib 1
63
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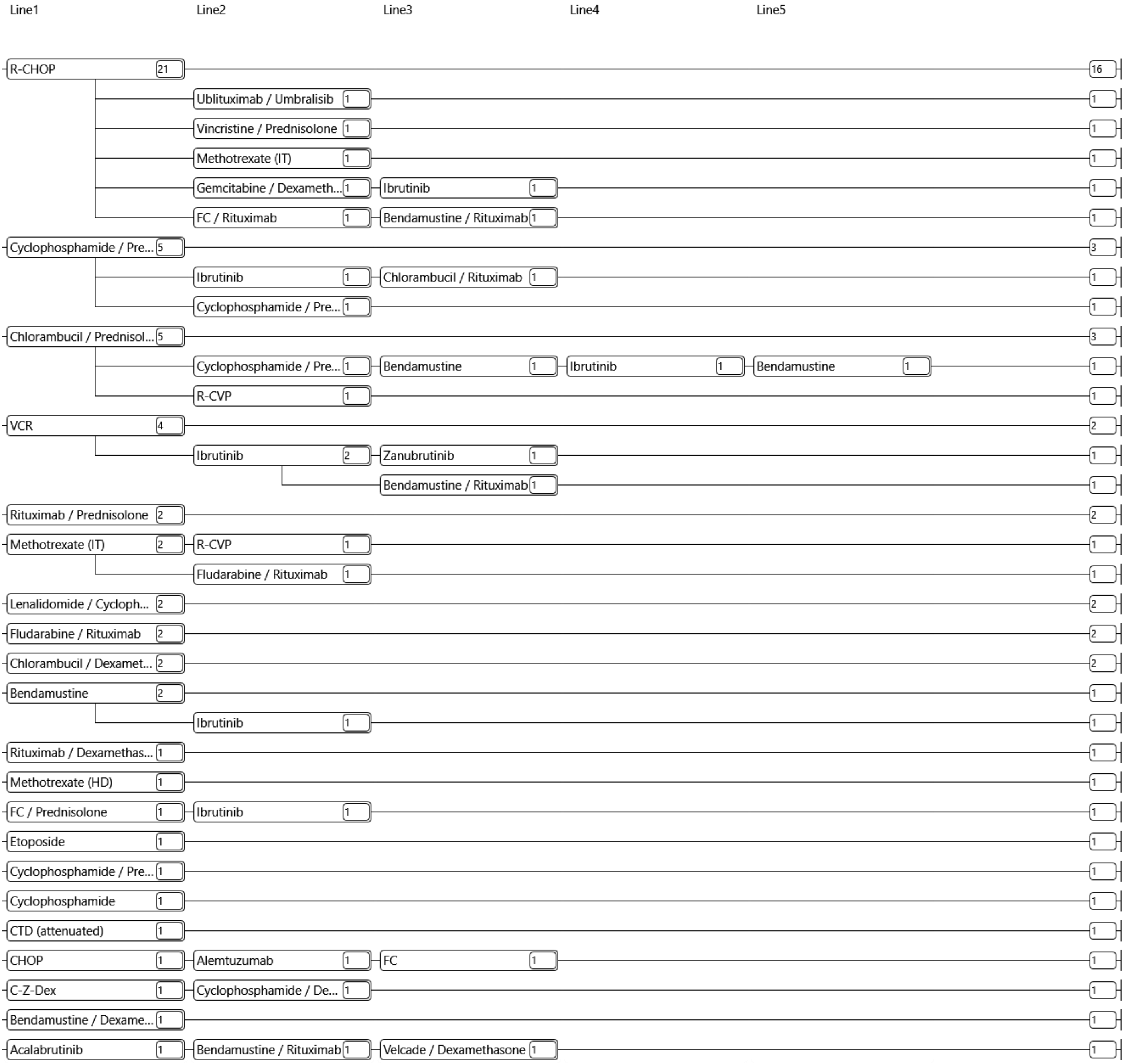

Line1
Line2
Line3
Line4
Line5
R-CHOP 21
16
Ublituximab / Umbralisib 1
1
Vincristine / Prednisolone 1
1
Methotrexate (IT) 1
1
Gemcitabine / Dexameth... 1
Ibrutinib 1
1
FC / Rituximab 1
Bendamustine / Rituximab 1
1
Cyclophosphamide / Pre... 5
3
Ibrutinib 1
Chlorambucil / Rituximab 1
1
Cyclophosphamide / Pre... 1
1
Chlorambucil / Prednisol... 5
3
Cyclophosphamide / Pre... 1
Bendamustine 1
Ibrutinib 1
Bendamustine 1
1
R-CVP 1
1
VCR 4
2
Ibrutinib 2
Zanubrutinib 1
1
Bendamustine / Rituximab 1
1
Rituximab / Prednisolone 2
2
Methotrexate (IT) 2
R-CVP 1
1
Fludarabine / Rituximab 1
1
Lenalidomide / Cycloph... 2
2
Fludarabine / Rituximab 2
2
Chlorambucil / Dexamet... 2
2
Bendamustine 2
1
Ibrutinib 1
1
Rituximab / Dexamethas... 1
1
Methotrexate (HD) 1
1
FC / Prednisolone 1
Ibrutinib 1
1
Etoposide 1
1
Cyclophosphamide / Pre... 1
1
Cyclophosphamide 1
1
CTD (attenuated) 1
1
CHOP 1
Alemtuzumab 1
FC 1
1
C-Z-Dex 1
Cyclophosphamide / De... 1
1
Bendamustine / Dexame... 1
1
Acalabrutinib 1
Bendamustine / Rituximab 1
Velcade / Dexamethasone 1
1

Survival

Overall survival from diagnosis

Table 12 Overall survival from diagnosis by sex, age and initial disease management

	n	Status n (row %)		Median survival (years) (95% CI)
		Alive	Dead	
Total	2039	1071 (52.5)	968 (47.5)	9.0 (8.3 - 9.7)
Sex				
Male	1135	588 (51.8)	547 (48.2)	8.6 (7.7 - 9.5)
Female	904	483 (53.4)	421 (46.6)	9.3 (8.5 - 10.3)
Age group				
<60	326	273 (83.7)	53 (16.3)	Not reached
60-69	541	362 (66.9)	179 (33.1)	13.8 (12.4 - 15.3)
70-79	713	343 (48.1)	370 (51.9)	8.3 (7.5 - 9.0)
≥80	459	93 (20.3)	366 (79.7)	3.5 (2.9 - 3.9)
Subtype				
Systemic	1565	772 (49.3)	793 (50.7)	8.2 (7.4 - 8.9)
Extranodal(MALT)	474	299 (63.1)	175 (36.9)	11.7 (10.6 - 13.2)
First line management				
Watch & wait	1087	573 (52.7)	514 (47.3)	9.2 (8.5 - 10.0)
Chemotherapy	605	298 (49.3)	307 (50.7)	7.9 (6.5 - 8.8)
Radiotherapy	153	122 (79.7)	31 (20.3)	Not reached
H. pylori eradication	83	53 (63.9)	30 (36.1)	Not reached
Supportive/palliative care	84	17 (20.2)	67 (79.8)	0.9 (0.2 - 1.4)
non-haematological co-morbidity	27	8 (29.6)	19 (70.4)	0.4 (0.2 - 3.8)

Figure 11 Overall survival from diagnosis

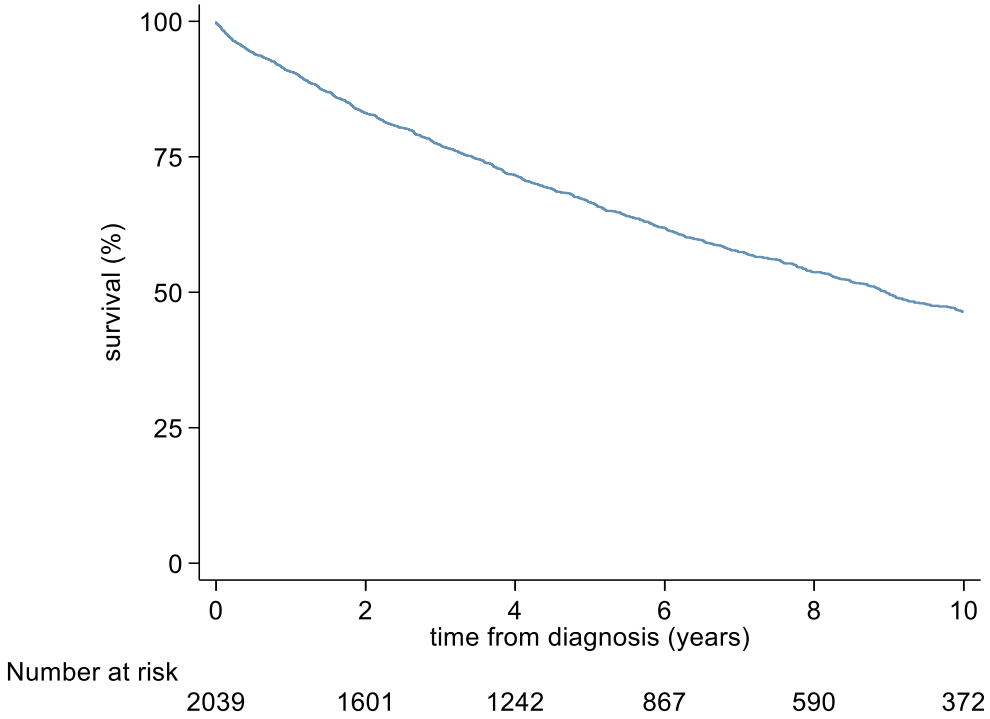


Figure 12 Overall survival from diagnosis by sex

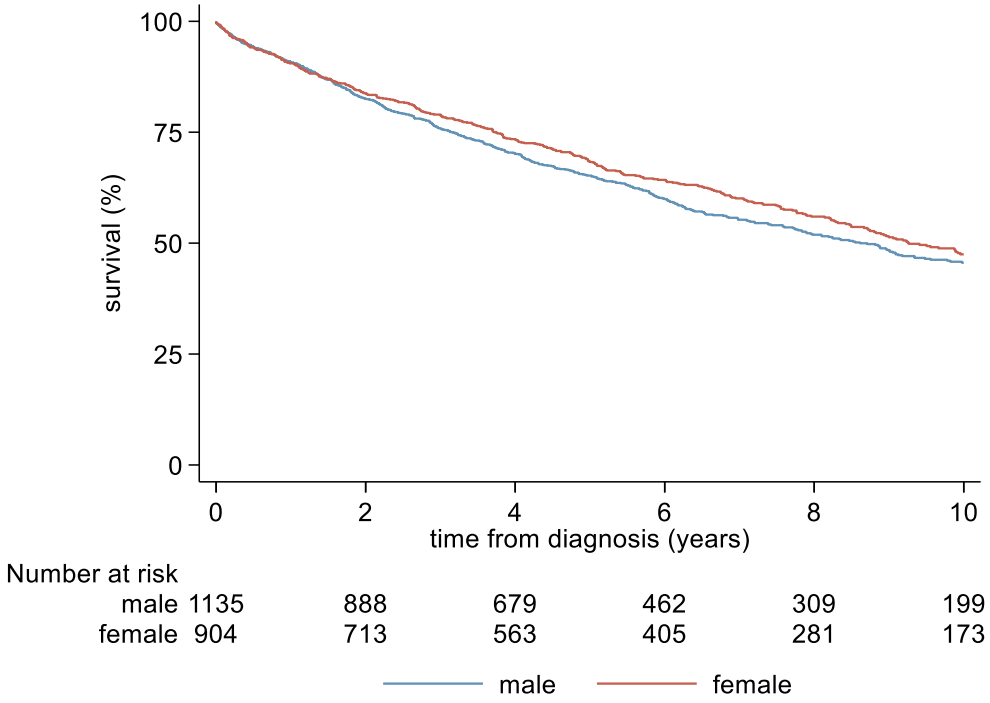


Figure 13 Overall survival from diagnosis by age at diagnosis

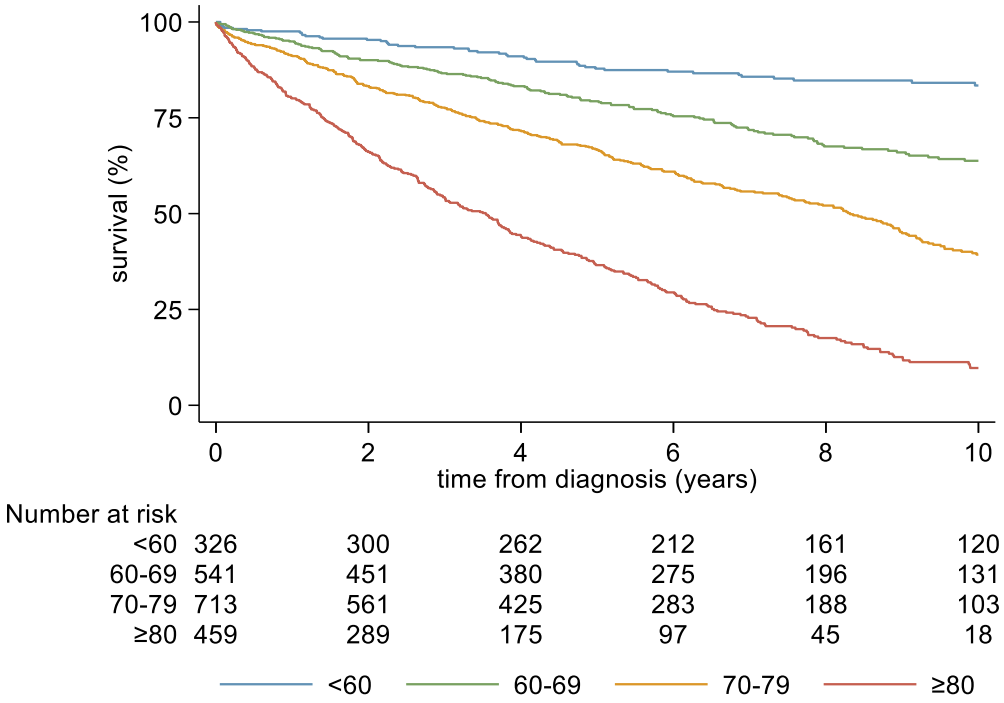


Figure 14 Overall survival from diagnosis by subtype

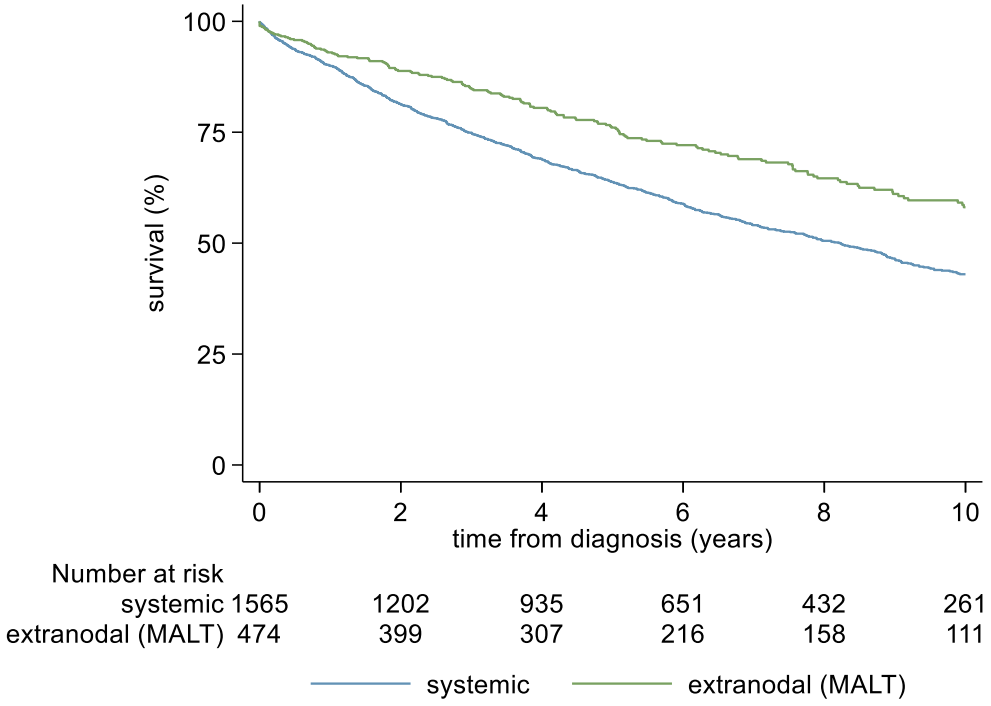
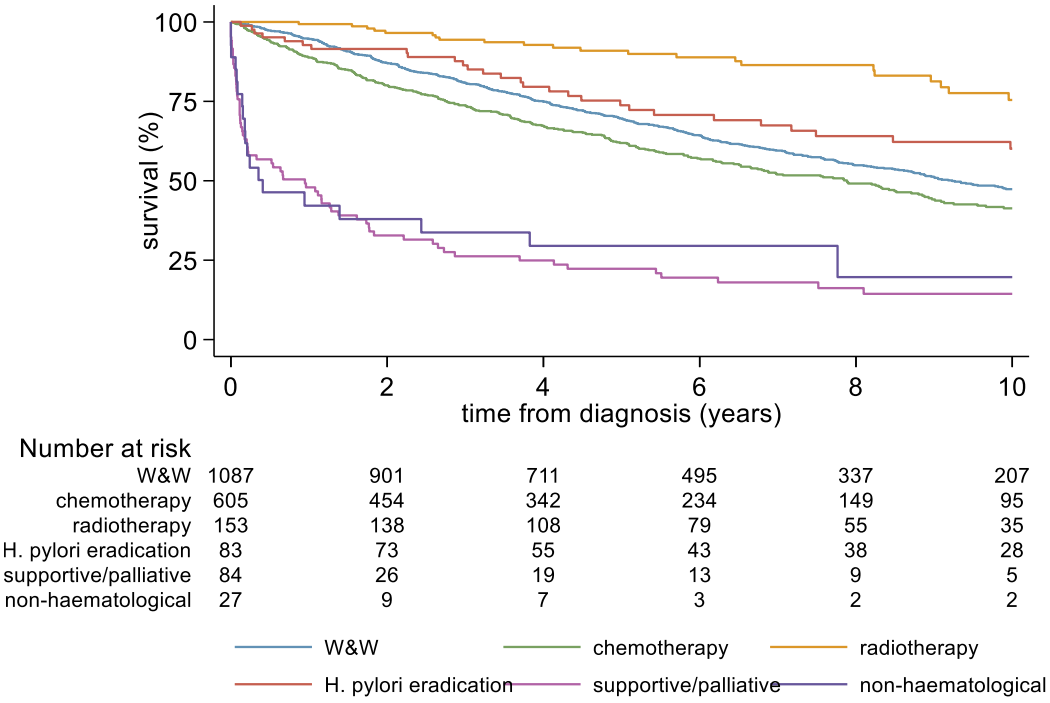


Figure 15 Overall survival from diagnosis by first line management



Overall survival from start of treatment

Table 13 Overall survival from start of treatment by regimen

	n (%)	Status n (row %)		Median survival years (95% CI)
		Alive	Dead	
Total	1008	552 (54.8)	456 (45.2)	8.8 (7.9 - 9.8)
Chlorambucil	252	59 (23.4)	193 (76.6)	4.5 (3.4 - 5.3)
Bendamustine / Rituximab	135	102 (75.6)	33 (24.4)	NR
R-CVP	97	55 (56.7)	42 (43.3)	8.8 (6.4 - NR)
Dexamethasone/Rituximab/Cyclophosphamide	94	65 (69.1)	29 (30.9)	6.9 (5.3 – NR)
Single Agent Rituximab	77	43 (55.8)	34 (44.2)	9.3 (3.1 - NR)
FCR	65	33 (50.8)	32 (49.2)	10.2 (5.6 - NR)
FC	59	38 (64.4)	21 (35.6)	NR
Chlorambucil / Rituximab	29	10 (34.5)	19 (65.5)	5.3 (2.4 - 6.3)
R-CHOP	21	12 (57.1)	9 (42.9)	8.0 (6.7 - NR)
Other Rituximab[1]	7	7 (100.0)	-	NR
Other non-Rituximab[2]	14	5 (35.7)	9 (64.3)	3.3 (0.1 - NR)
Radiotherapy	158	123 (77.8)	35 (22.2)	NR

NR = not reached

[1] VCR (n=4), Rituximab / Prednisolone (n=2), Rituximab / Dexamethasone (n=1)

[2] Bendamustine (n=2), Lenalidomide / Cyclophosphamide / Dexamethasone (n=2), Methotrexate (IT) (n=2), Acalabrutinib (n=1), Bendamustine / Dexamethasone (n=1), C-Z-Dex (n=1), CHOP (n=1), CTDa (n=1), Cyclophosphamide (n=1), Etoposide (n=1), Methotrexate (HD)

Figure 16 Overall survival from start of treatment

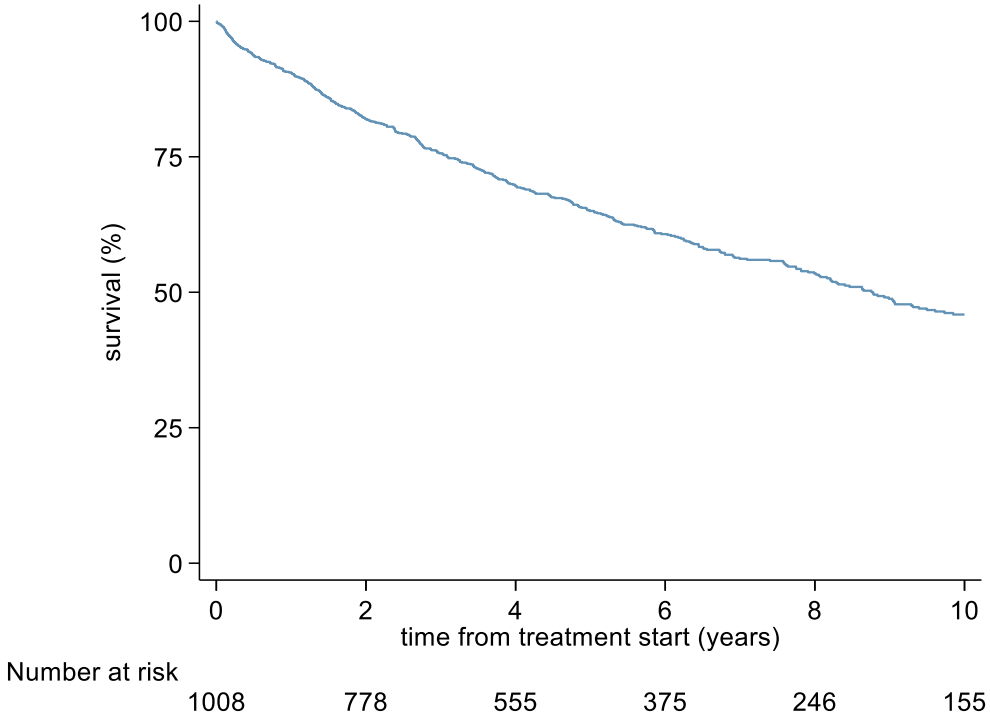


Figure 17 Overall survival from start of treatment by treatment

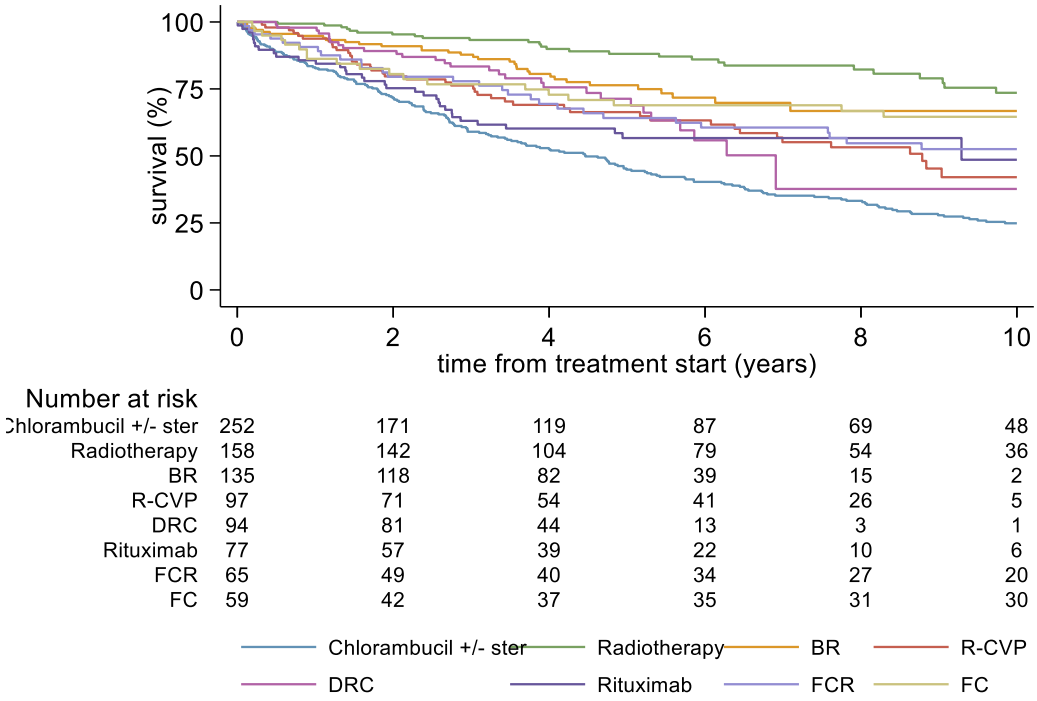


Table 14 Overall survival from start of second line treatment by regimen

	n (%)	Status n (row %)		Median survival years (95% CI)
		Alive	Dead	
Total	278	128 (46.0)	150 (54.0)	5.1 (3.8 - 7.4)
Single Agent Rituximab	54	20 (37.0)	34 (63.0)	4.0 (2.4 - 7.4)
Chlorambucil	33	8 (24.2)	25 (75.8)	2.0 (1.0 - 2.9)
FC	30	9 (30.0)	21 (70.0)	3.8 (2.0 - 12.9)
R-CVP	30	19 (63.3)	11 (36.7)	8.6 (4.9 - NR)
Bendamustine / Rituximab	29	18 (62.1)	11 (37.9)	NR (2.3 - NR)
Ibrutinib	22	13 (59.1)	9 (40.9)	NR (0.9 - NR)
FCR	17	10 (58.8)	7 (41.2)	NR (4.6 - NR)
Dexamethasone/Rituximab/Cyclophosphamide	15	10 (66.7)	5 (33.3)	8.1 (2.8 - NR)
R-CHOP	8	3 (37.5)	5 (62.5)	1.4 (0.1 - NR)
Other Rituximab[1]	10	4 (40.0)	6 (60.0)	6.9 (0.1 - NR)
Other non-Rituximab[2]	20	8 (40.0)	12 (60.0)	4.8 (1.1 - NR)
Radiotherapy	10	6 (60.0)	4 (40.0)	9.5 (0.1 - NR)

NR = not reached

[1] Chlorambucil / Rituximab (n=4), Fludarabine / Rituximab (n=2), Gemcitabine / Dexamethasone / Cisplatin / Rituximab (n=1), IVE / Rituximab (n=1), Velcade / Dexamethasone / Rituximab (n=1), Venetoclax / Rituximab (n=1)

[2] Acalabrutinib (n=5), Bendamustine (n=3), CVP (n=2), Ublituximab / Umbralisib (n=2), Alemtuzumab (n=1), Bendamustine / Methylprednisolone (n=1), Cyclophosphamide / Dexamethasone (n=1), Cyclophosphamide / Prednisolone (n=1), Methotrexate (IT) (n=1), VCD (n=1), Vincristine / Prednisolone (n=1), Zanubrutinib (n=1)

Figure 18 Overall survival from start of second line treatment

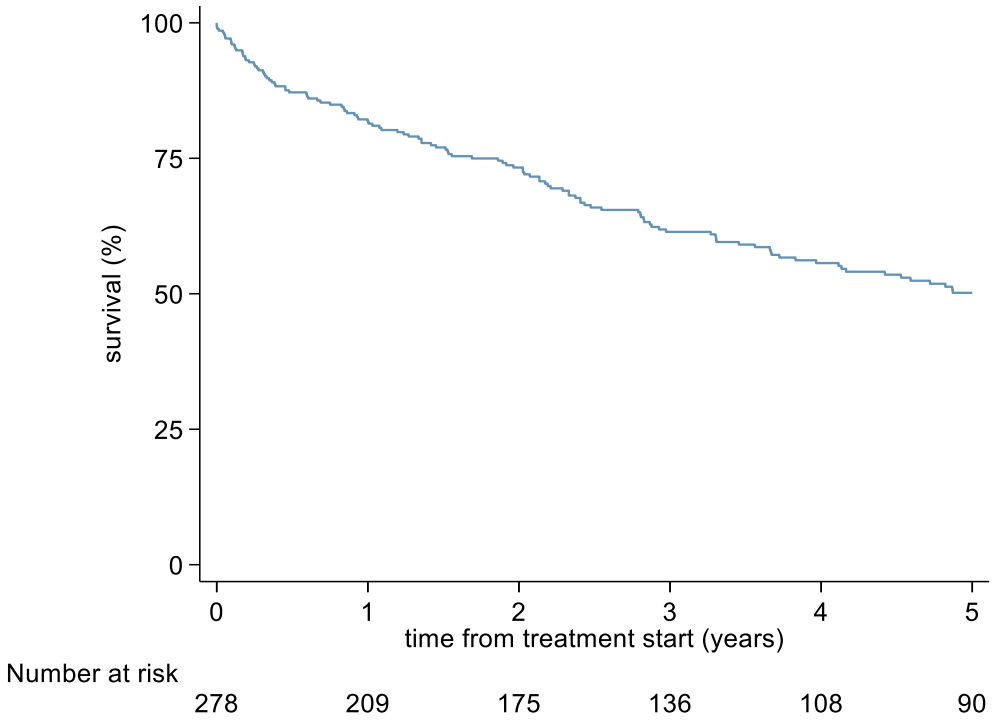
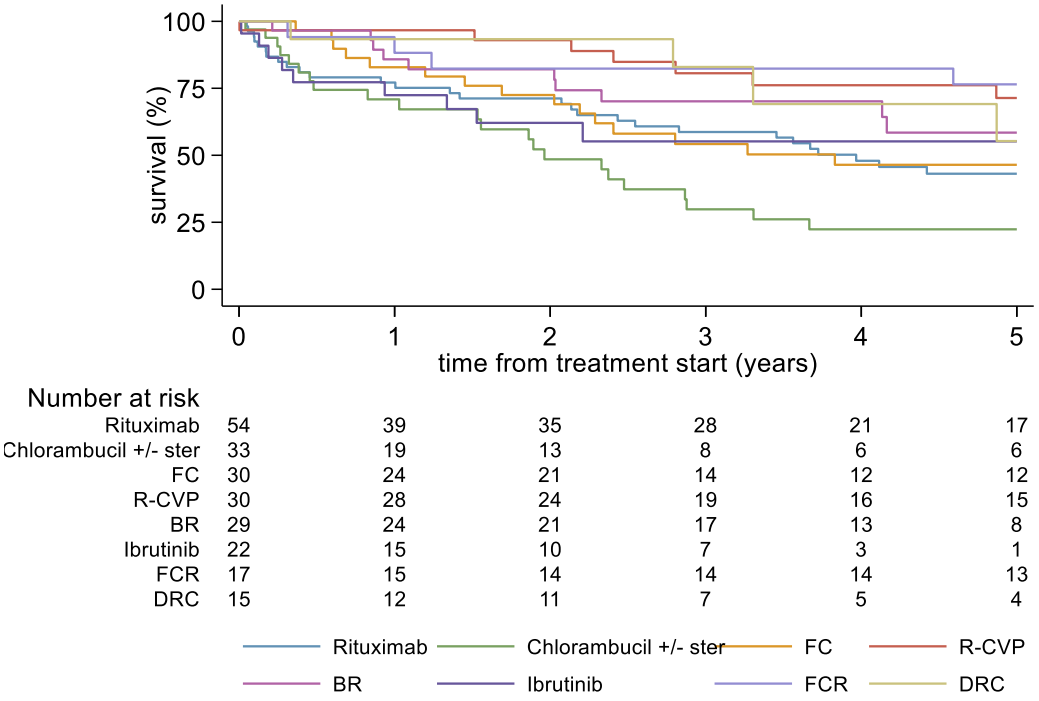


Figure 19 Overall survival from start of second line treatment by treatment



Number at risk

Rituximab	54	39	35	28	21	17
Chlorambucil +/- ster	33	19	13	8	6	6
FC	30	24	21	14	12	12
R-CVP	30	28	24	19	16	15
BR	29	24	21	17	13	8
Ibrutinib	22	15	10	7	3	1
FCR	17	15	14	14	14	13
DRC	15	12	11	7	5	4

Table 15 Overall survival from start of third line treatment by treatment

	n (%)	Status n (row %)		Median survival years (95% CI)
		Alive	Dead	
Total	103	45 (43.7)	58 (56.3)	4.6 (2.4 - 7.1)
Single Agent Rituximab	25	8 (32.0)	17 (68.0)	4.3 (2.1 - 10.2)
Bendamustine / Rituximab	18	13 (72.2)	5 (27.8)	10.6 (6.3 - NR)
R-CVP	10	5 (50.0)	5 (50.0)	7.7 (0.0 - NR)
Ibrutinib	8	7 (87.5)	1 (12.5)	NR (0.9 - NR)
Chlorambucil	7	2 (28.6)	5 (71.4)	2.1 (0.1 - NR)
Other Rituximab[1]	14	4 (28.6)	10 (71.4)	2.1 (0.2 - NR)
Other non-Rituximab[2]	18	5 (27.8)	13 (72.2)	2.1 (0.4 - 4.4)
Radiotherapy	3	1 (33.3)	2 (66.7)	7.1 (0.1 - NR)

NR = not reached

[1] R-CHOP (n=5), Chlorambucil / Rituximab (n=3), Cyclophosphamide / Prednisolone / Rituximab (n=2), FCR (n=2), DRC (n=1), Eltrombopag / Rituximab (n=1)

[2] Fludarabine (n=3), Venetoclax (n=3), Acalabrutinib (n=2), Bendamustine (n=2), CVP (n=2), FC (n=2), Zanubrutinib (n=2), CHOP (n=1), Velcade / Dexamethasone (n=1)

Figure 20 Overall survival from start of third line treatment

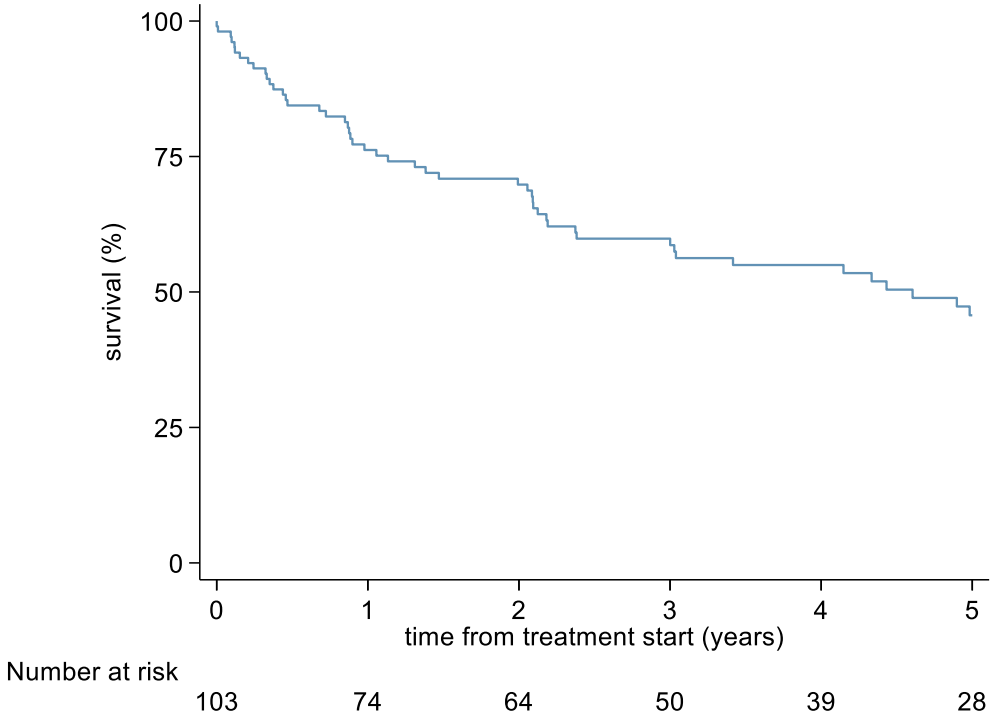
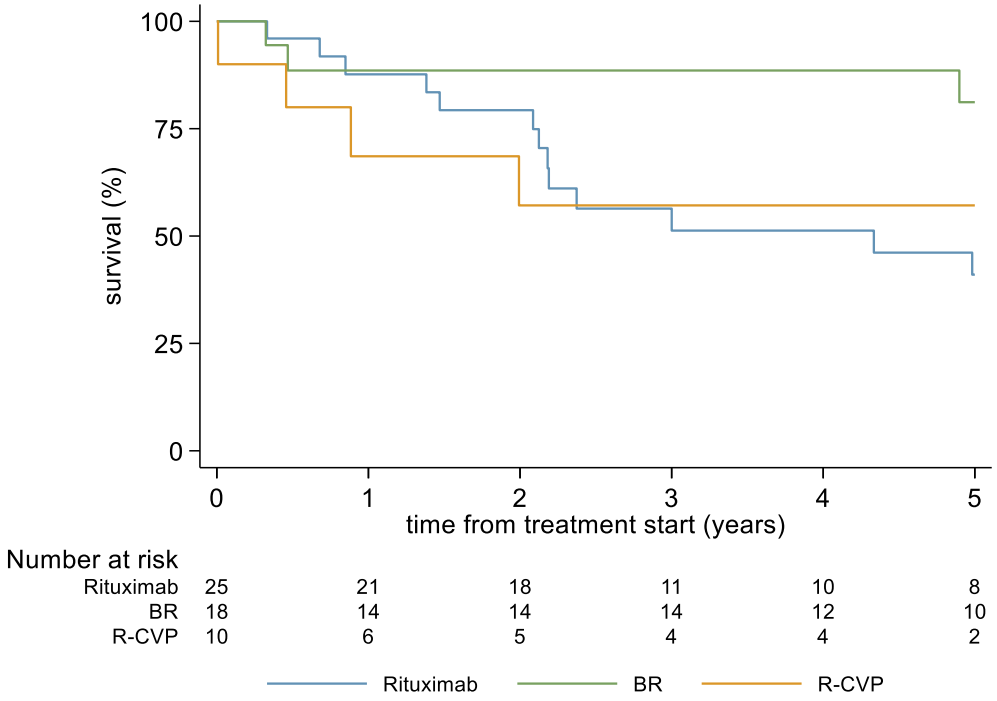


Figure 21 Overall survival from start of third line treatment by treatment



Progression-free survival

Table 16 Progression-free survival from start of treatment by regimen

	n (%)	Progression-free n (row %)		Median PFS years (95% CI)
		Yes	No	
Total	1008	468 (46.4)	540 (53.6)	2.9 (2.6 - 3.3)
Chlorambucil	252	29 (11.5)	223 (88.5)	1.8 (1.4 - 2.0)
Bendamustine / Rituximab	135	104 (77.0)	31 (23.0)	5.7 (4.1 - NR)
R-CVP	97	45 (46.4)	52 (53.6)	2.9 (1.9 - 3.3)
Dexamethasone/Rituximab/Cyclophosphamide	94	56 (59.6)	38 (40.4)	4.3 (2.4 - 5.3)
Single Agent Rituximab	77	37 (48.1)	40 (51.9)	2.4 (1.6 - 4.1)
FCR	65	28 (43.1)	37 (56.9)	3.4 (2.1 - 4.4)
FC	59	13 (22.0)	46 (78.0)	2.1 (1.3 - 4.9)
Chlorambucil / Rituximab	29	14 (48.3)	15 (51.7)	1.6 (1.0 - 3.7)
R-CHOP	21	11 (52.4)	10 (47.6)	6.7 (0.3 - NR)
Other Rituximab[1]	7	3 (42.9)	4 (57.1)	2.6 (0.4 - NR)
Other non-Rituximab[2]	14	3 (21.4)	11 (78.6)	0.2 (0.0 - 0.4)
Radiotherapy	158	125 (79.1)	33 (20.9)	4.0 (2.6 - 5.4)

NR = not reached

[1] VCR (n=4), Rituximab / Prednisolone (n=2), Rituximab / Dexamethasone (n=1)

[2] Bendamustine (n=2), Lenalidomide / Cyclophosphamide / Dexamethasone (n=2), Methotrexate (IT) (n=2), Acalabrutinib (n=1), Bendamustine / Dexamethasone (n=1), C-Z-Dex (n=1), CHOP (n=1), CTDa (n=1), Cyclophosphamide (n=1), Etoposide (n=1), Methotrexate (HD)

Figure 22 Progression-free survival from start of treatment

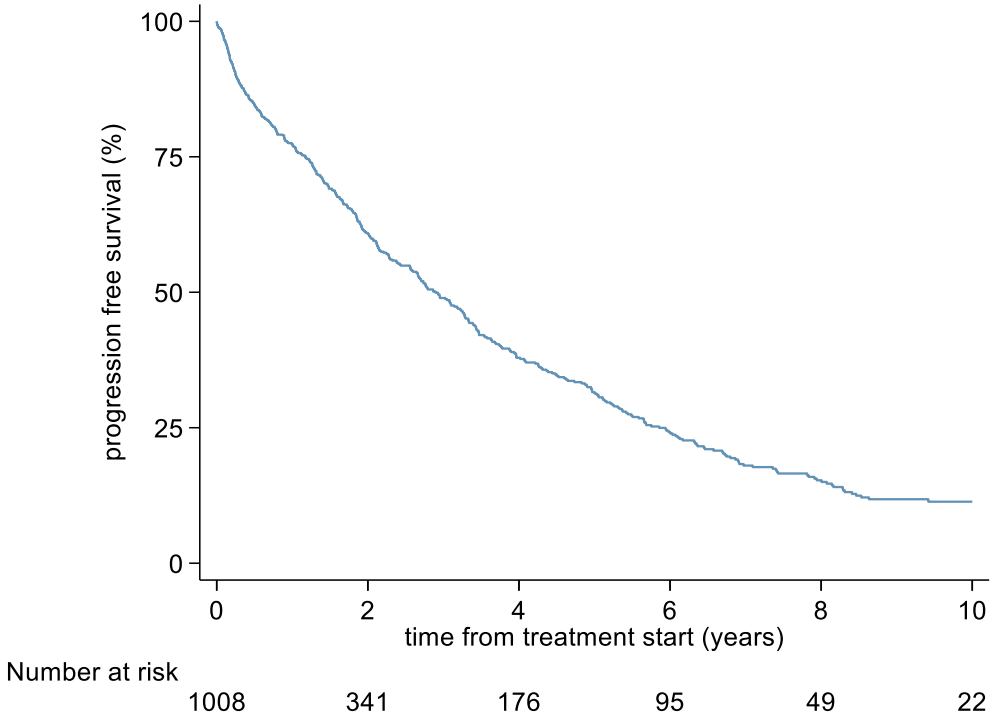


Figure 23 Progression-free survival from start of treatment by treatment

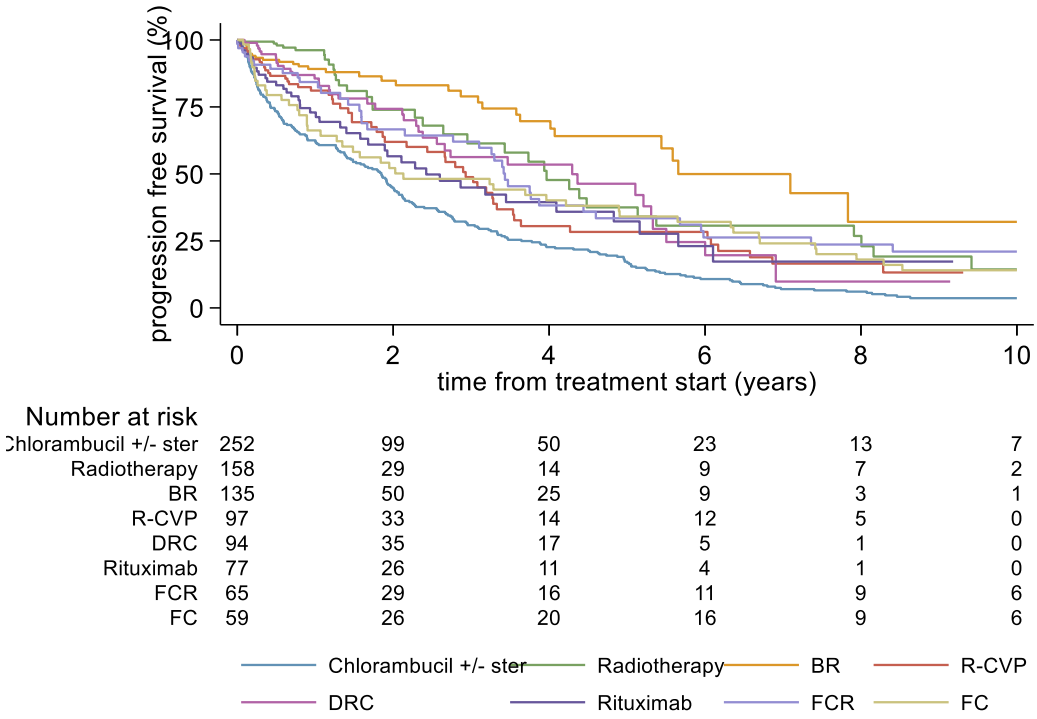


Table 17 Progression-free survival from start of second line treatment by regimen

	n (%)	Progression-free n (row %)		Median PFS years (95% CI)
		Yes	Yes	
Total	278	73 (26.3)	205 (73.7)	1.8 (1.4 - 2.2)
Single Agent Rituximab	54	10 (18.5)	44 (81.5)	1.1 (0.4 - 1.7)
Chlorambucil	33	2 (6.1)	31 (93.9)	1.0 (0.4 - 1.5)
FC	30	1 (3.3)	29 (96.7)	1.7 (0.6 - 2.3)
R-CVP	30	13 (43.3)	17 (56.7)	2.9 (2.1 - 7.4)
Bendamustine / Rituximab	29	11 (37.9)	18 (62.1)	2.3 (1.1 - 4.4)
Ibrutinib	22	10 (45.5)	12 (54.5)	1.3 (0.3 - NR)
FCR	17	9 (52.9)	8 (47.1)	7.9 (1.2 - NR)
Dexamethasone/Rituximab/Cyclophosphamide	15	7 (46.7)	8 (53.3)	3.3 (1.6 - 5.1)
Radiotherapy	10	2 (20.0)	8 (80.0)	2.4 (0.1 - 4.5)
R-CHOP	8	2 (25.0)	6 (75.0)	0.5 (0.1 - NR)
Other Rituximab[1]	10	2 (20.0)	8 (80.0)	1.9 (0.1 - NR)
Other non-Rituximab[2]	20	4 (20.0)	16 (80.0)	1.1 (0.4 - 2.3)

NR = not reached

[1] Chlorambucil / Rituximab (n=4), Fludarabine / Rituximab (n=2), Gemcitabine / Dexamethasone / Cisplatin / Rituximab (n=1), IVE / Rituximab (n=1), Velcade / Dexamethasone / Rituximab (n=1), Venetoclax / Rituximab (n=1)

[2] Acalabrutinib (n=5), Bendamustine (n=3), CVP (n=2), Ublituximab / Umbralisib (n=2), Alemtuzumab (n=1), Bendamustine / Methylprednisolone (n=1), Cyclophosphamide / Dexamethasone (n=1), Cyclophosphamide / Prednisolone (n=1), Methotrexate (IT) (n=1), VCD (n=1), Vincristine / Prednisolone (n=1), Zanubrutinib (n=1)

Figure 24 Progression-free survival from start of second line treatment

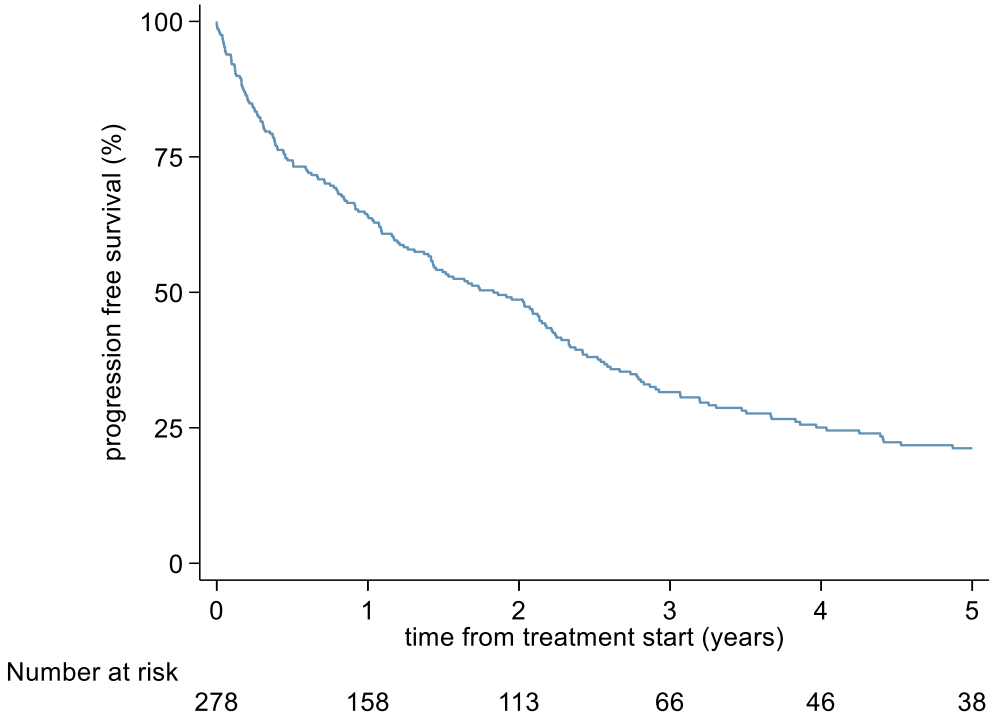
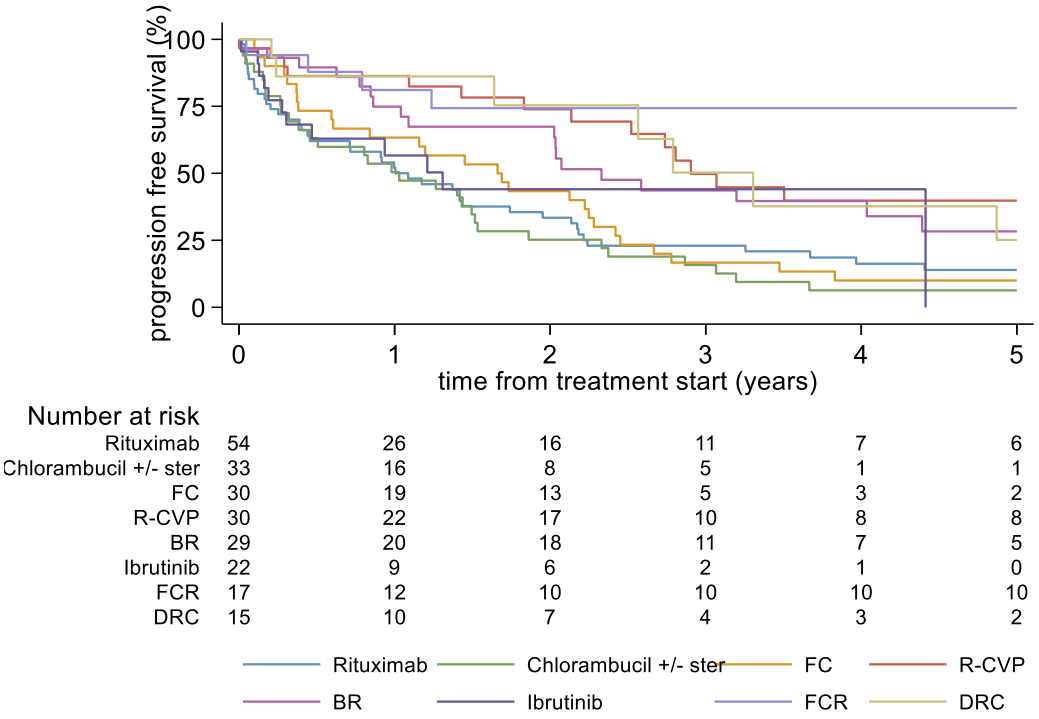


Figure 25 Progression-free survival from start of second line treatment by treatment



Number at risk

Rituximab	54	26	16	11	7	6
Chlorambucil +/- ster	33	16	8	5	1	1
FC	30	19	13	5	3	2
R-CVP	30	22	17	10	8	8
BR	29	20	18	11	7	5
Ibrutinib	22	9	6	2	1	0
FCR	17	12	10	10	10	10
DRC	15	10	7	4	3	2

Table 18 Progression-free survival from start of third line treatment by treatment

	n (%)	Progression-free n (row %)		Median PFS years (95% CI)
		Yes	Yes	
Total	103	26 (25.2)	77 (74.8)	2.1 (1.4 - 2.8)
Single Agent Rituximab	25	4 (16.0)	21 (84.0)	1.9 (0.8 - 4.4)
Bendamustine / Rituximab	18	7 (38.9)	11 (61.1)	4.9 (3.7 - 6.3)
R-CVP	10	2 (20.0)	8 (80.0)	0.9 (0.0 - NR)
Ibrutinib	8	5 (62.5)	3 (37.5)	NR (0.4 - NR)
Chlorambucil	7	1 (14.3)	6 (85.7)	2.0 (0.1 - 2.8)
Other Rituximab[1]	14	3 (21.4)	11 (78.6)	1.1 (0.1 - 3.0)
Other non-Rituximab[2]	18	4 (22.2)	14 (77.8)	1.0 (0.4 - 2.4)
Radiotherapy	3	-	3 (100.0)	2.0 (0.1 - NR)

NR = not reached

[1] R-CHOP (n=5), Chlorambucil / Rituximab (n=3), Cyclophosphamide / Prednisolone / Rituximab (n=2), FCR (n=2), DRC (n=1), Eltrombopag / Rituximab (n=1)

[2] Fludarabine (n=3), Venetoclax (n=3), Acalabrutinib (n=2), Bendamustine (n=2), CVP (n=2), FC (n=2), Zanubrutinib (n=2), CHOP (n=1), Velcade / Dexamethasone (n=1)

Figure 26 Progression-free survival from start of third line treatment

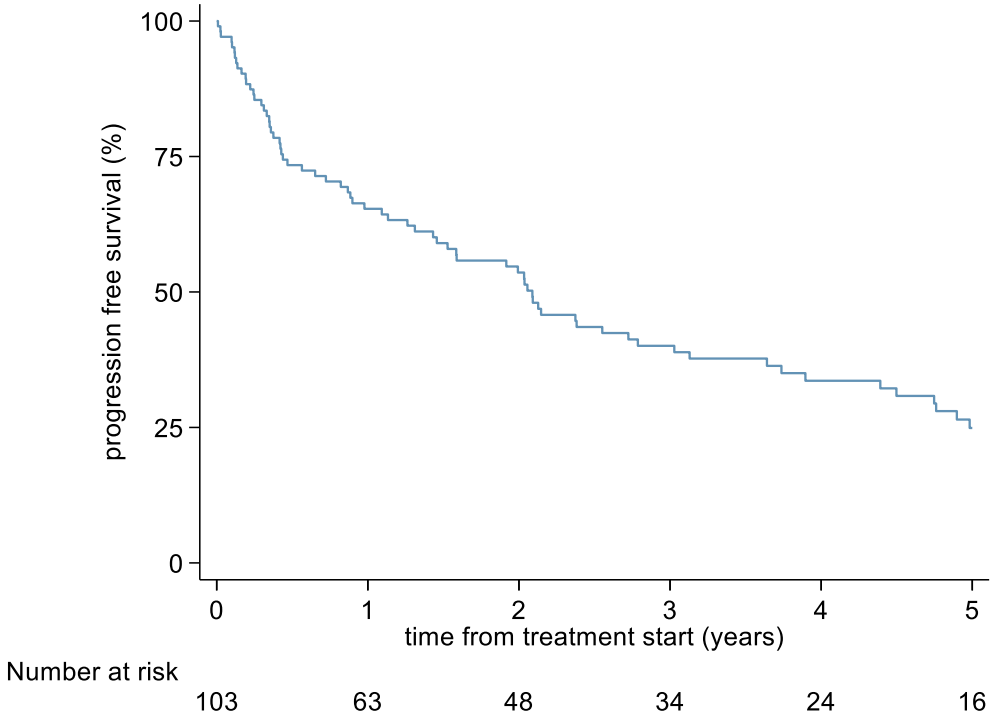
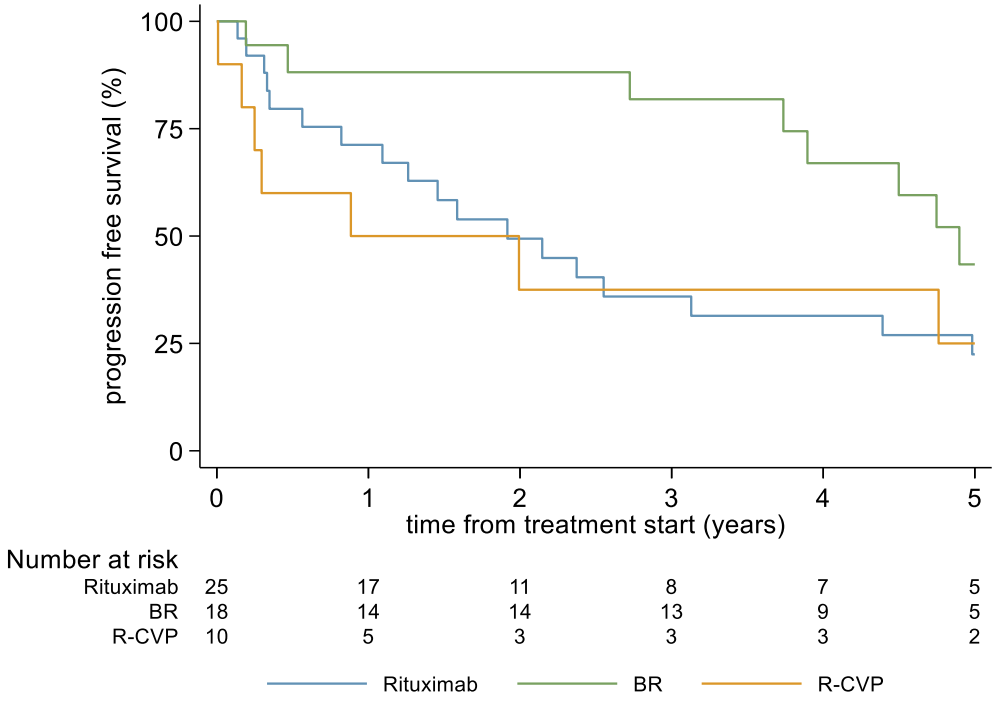


Figure 27 Progression-free survival from start of third line treatment by treatment



Outcomes in relapse/refractory patients previously treated with an anti-CD20 monoclonal antibody

Figure 28 Flow diagram for MZL patients following anti-CD20 monoclonal antibody and subsequently further treated

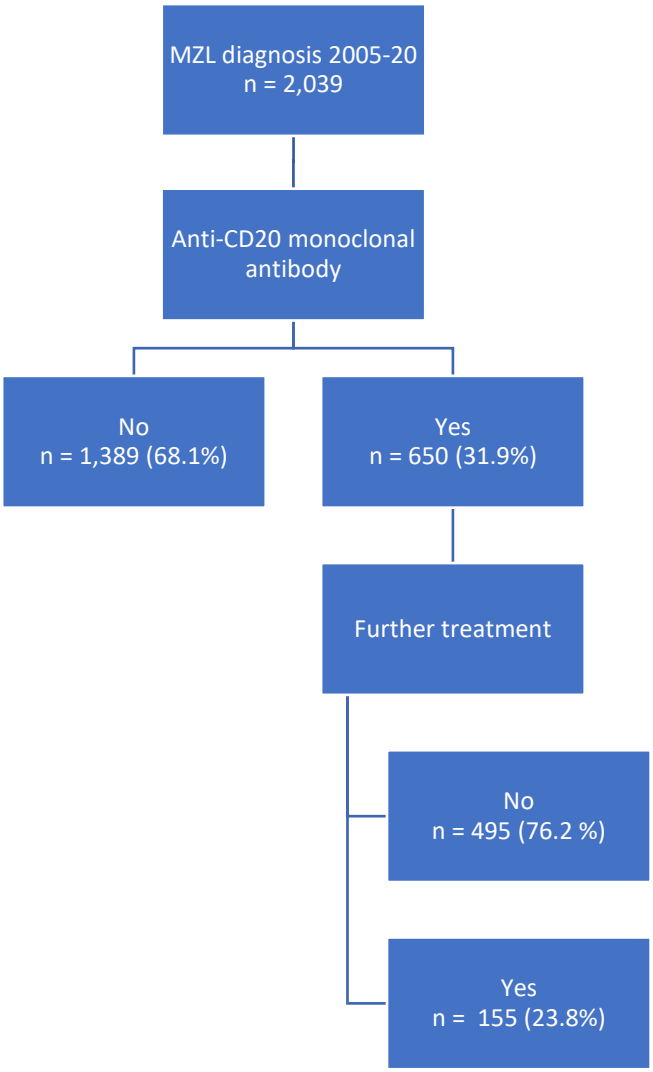


Figure 29 Treatments for patients following treatment with anti-CD20 monoclonal antibodies

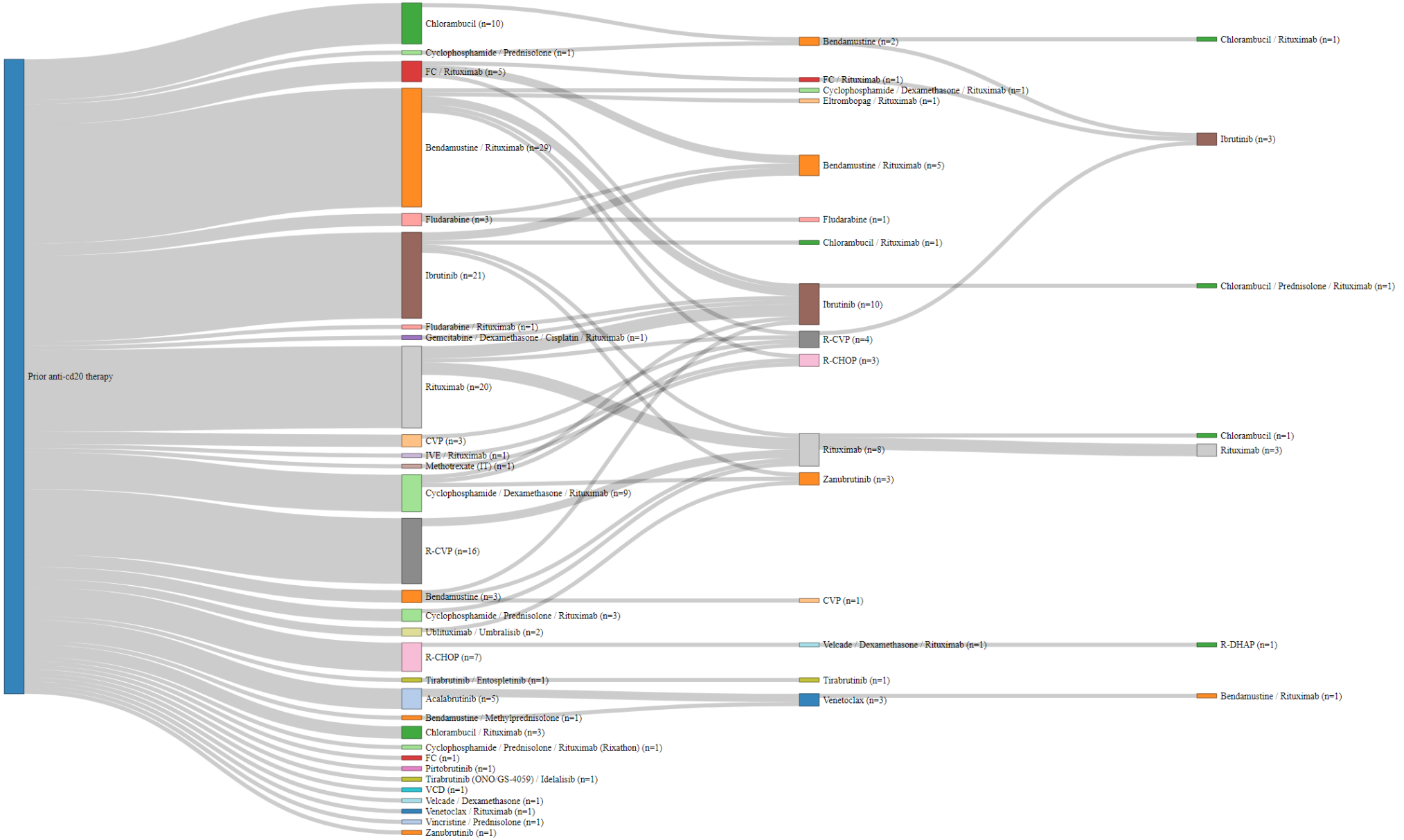


Table 19 Relapse/refractory treatment following anti CD20 monoclonal antibody treatment by sex, age and subtype

	Total	Sex		Age at treatment start		Subtype	
	n (%)	Male	Female	Mean (sd)	Median (min-max)	Systemic	Extranodal (MALT)
Total	155 (100.0)	95 (100.0)	60 (100.0)	73.0 (9.9)	73.2 (40.0 - 90.7)	145 (100.0)	10 (100.0)
Bendamustine / Rituximab	29 (18.7)	21 (22.1)	8 (13.3)	70.2 (6.5)	69.7 (59.3 - 82.9)	26 (17.9)	3 (30.0)
Ibrutinib	21 (13.5)	13 (13.7)	8 (13.3)	73.7 (10.1)	76.7 (51.6 - 88.0)	21 (14.5)	-
Single Agent Rituximab	20 (12.9)	8 (8.4)	12 (20.0)	76.7 (9.2)	77.1 (51.6 - 90.7)	19 (13.1)	1 (10.0)
R-CVP	16 (10.3)	10 (10.5)	6 (10.0)	72.2 (10.0)	73.7 (55.8 - 85.9)	13 (9.0)	3 (30.0)
Dexamethasone/Rituximab/Cyclophosphamide	13 (8.4)	8 (8.4)	5 (8.3)	79.0 (7.4)	79.8 (67.3 - 88.4)	12 (8.3)	1 (10.0)
Chlorambucil	10 (6.5)	6 (6.3)	4 (6.7)	79.3 (9.6)	82.3 (60.4 - 90.0)	10 (6.9)	-
R-CHOP	7 (4.5)	6 (6.3)	1 (1.7)	61.2 (10.7)	60.6 (46.5 - 77.9)	7 (4.8)	-
FCR	6 (3.9)	5 (5.3)	1 (1.7)	68.5 (9.9)	67.7 (56.6 - 84.3)	6 (4.1)	-
Acalabrutinib	5 (3.2)	3 (3.2)	2 (3.3)	67.6 (16.5)	72.6 (40.0 - 83.0)	5 (3.4)	-
Other Rituximab[1]	6 (3.9)	2 (2.1)	4 (6.7)	78.7 (9.1)	78.7 (68.0 - 89.2)	5 (3.4)	1 (10.0)
Other non-Rituximab[2]	22 (14.2)	13 (13.7)	9 (15.0)	71.3 (9.0)	70.5 (52.5 - 88.0)	21 (14.5)	1 (10.0)

[1] Chlorambucil / Rituximab (n=3), Gemcitabine / Dexamethasone / Cisplatin / Rituximab (n=1), IVE / Rituximab (n=1), Venetoclax / Rituximab (n=1)

[2] Bendamustine (n=3), CVP (n=3), Fludarabine (n=3), Ublituximab / Umbralisib (n=2), Bendamustine / Methylprednisolone (n=1), Cyclophosphamide / Prednisolone (n=1), FC (n=1), Methotrexate (IT) (n=1), Pirtobrutinib (n=1), Tirabrutinib / Idelalisib (n=1), Tirabrutinib / Entospletinib (n=1), VCD (n=1), Velcade / Dexamethasone (n=1), Vincristine / Prednisolone (n=1), Zanubrutinib (n=1)

Overall survival from start of relapsed/refractory treatment following anti CD20 monoclonal antibody treatment for all patients

Table 20 Overall survival from start of relapsed/refractory treatment following anti CD20 monoclonal antibody treatment for all patients

	n (%)	Status n (row %)		Median survival years (95% CI)
		Alive	Dead	
Total	155	78 (50.3)	77 (49.7)	4.7 (3.3 - 5.5)
Bendamustine / Rituximab	29	17 (58.6)	12 (41.4)	5.1 (2.0 - NR)
Ibrutinib	21	14 (66.7)	7 (33.3)	NR (1.5 - NR)
Single Agent Rituximab	20	7 (35.0)	13 (65.0)	5.0 (2.1 - NR)
R-CVP	16	8 (50.0)	8 (50.0)	2.8 (0.9 - NR)
Dexamethasone/Rituximab/Cyclophosphamide	13	8 (61.5)	5 (38.5)	3.3 (3.0 - NR)
Chlorambucil	10	3 (30.0)	7 (70.0)	2.0 (0.2 - NR)
R-CHOP	7	2 (28.6)	5 (71.4)	1.4 (0.2 - NR)
FCR	6	4 (66.7)	2 (33.3)	NR (4.6 - NR)
Acalabrutinib	5	2 (40.0)	3 (60.0)	3.7 (1.0 - NR)
Other Rituximab[1]	6	3 (50.0)	3 (50.0)	0.7 (0.1 - NR)
Other non-Rituximab[2]	22	10 (45.5)	12 (54.5)	4.7 (1.1 - NR)

NR = not reached

[1] Chlorambucil / Rituximab (n=3), Gemcitabine / Dexamethasone / Cisplatin / Rituximab (n=1), IVE / Rituximab (n=1), Venetoclax / Rituximab (n=1)

[2] Bendamustine (n=3), CVP (n=3), Fludarabine (n=3), Ublituximab / Umbralisib (n=2), Bendamustine / Methylprednisolone (n=1), Cyclophosphamide / Prednisolone (n=1), FC (n=1), Methotrexate (IT) (n=1), Pirtobrutinib (n=1), Tirabrutinib / Idelalisib (n=1), Tirabrutinib / Entospletinib (n=1), VCD (n=1), Velcade / Dexamethasone (n=1), Vincristine / Prednisolone (n=1), Zanubrutinib (n=1)

Figure 30 Overall survival from start of relapsed/refractory treatment following anti CD20 monoclonal antibody treatment for all patient

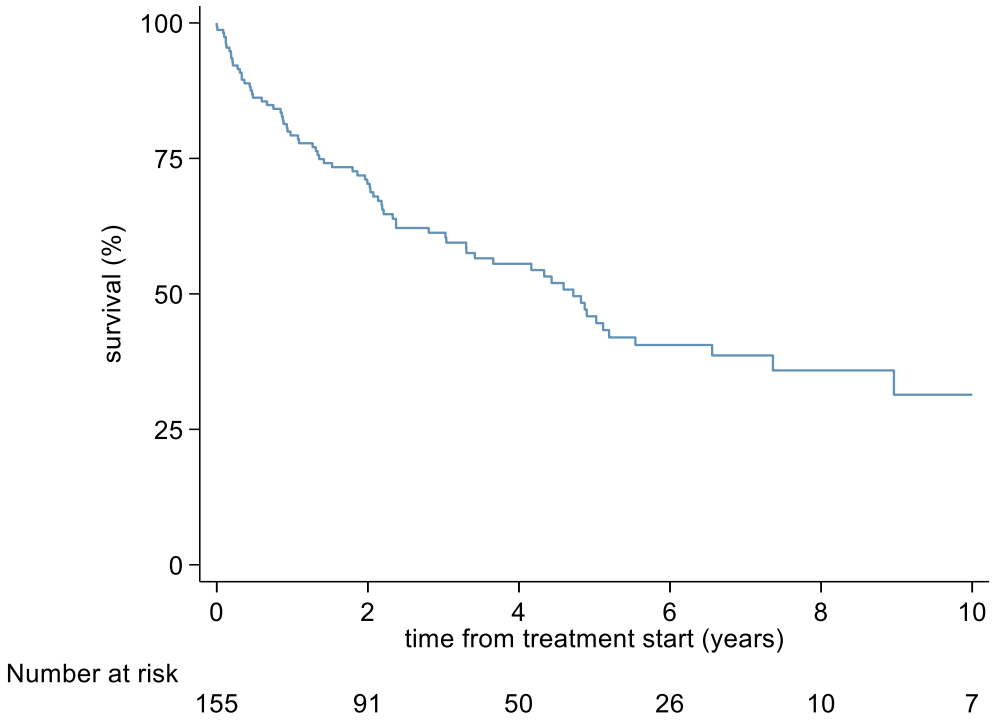
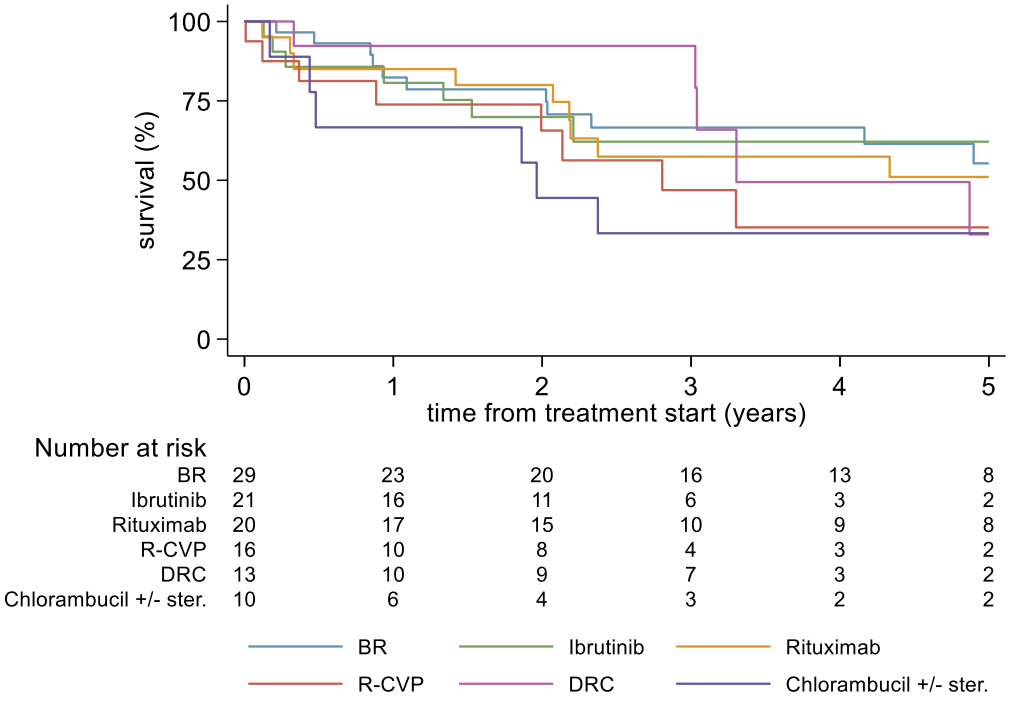


Figure 31 Overall survival from start of relapsed/refractory treatment following anti CD20 monoclonal antibody treatment for all patient by treatment



Number at risk

BR	29	23	20	16	13	8
Ibrutinib	21	16	11	6	3	2
Rituximab	20	17	15	10	9	8
R-CVP	16	10	8	4	3	2
DRC	13	10	9	7	3	2
Chlorambucil +/- ster.	10	6	4	3	2	2

Progression-free survival from start of relapsed/refractory treatment following anti CD20 monoclonal antibody treatment for all patients

Table 21 Progression-free survival from start of relapsed/refractory treatment following anti CD20 monoclonal antibody treatment for all patients

	n (%)	Progression-free n (row %)		Median PFS years (95% CI)
		Yes	No	
Total	155	53 (34.2)	102 (65.8)	2.0 (1.4 - 2.4)
Bendamustine / Rituximab	29	10 (34.5)	19 (65.5)	2.3 (1.1 - 4.4)
Ibrutinib	21	11 (52.4)	10 (47.6)	4.4 (0.5 - NR)
Rituximab	20	7 (35.0)	13 (65.0)	2.1 (0.8 - 7.4)
R-CVP	16	5 (31.2)	11 (68.8)	2.0 (0.4 - 2.8)
Dexamethasone/Rituximab/Cyclophosphamide	13	5 (38.5)	8 (61.5)	2.6 (0.2 - NR)
Chlorambucil	10	3 (30.0)	7 (70.0)	1.9 (0.0 - NR)
R-CHOP	7	2 (28.6)	5 (71.4)	0.4 (0.1 - NR)
FCR	6	1 (16.7)	5 (83.3)	5.3 (0.4 - NR)
Acalabrutinib	5	2 (40.0)	3 (60.0)	1.6 (0.9 - NR)
Other Rituximab[1]	6	1 (16.7)	5 (83.3)	0.5 (0.1 - NR)
Other non-Rituximab[2]	22	6 (27.3)	16 (72.7)	1.7 (0.4 - 3.6)

NR = not reached

[1] Chlorambucil / Rituximab (n=3), Gemcitabine / Dexamethasone / Cisplatin / Rituximab (n=1), IVE / Rituximab (n=1), Venetoclax / Rituximab (n=1)

[2] Bendamustine (n=3), CVP (n=3), Fludarabine (n=3), Ublituximab / Umbralisib (n=2), Bendamustine / Methylprednisolone (n=1), Cyclophosphamide / Prednisolone (n=1), FC (n=1), Methotrexate (IT) (n=1), Pirtobrutinib (n=1), Tirabrutinib / Idelalisib (n=1), Tirabrutinib / Entospletinib (n=1), VCD (n=1), Velcade / Dexamethasone (n=1), Vincristine / Prednisolone (n=1), Zanubrutinib (n=1)

Figure 32 Progression-free survival from start of relapsed/refractory treatment following anti CD20 monoclonal antibody treatment for all patient

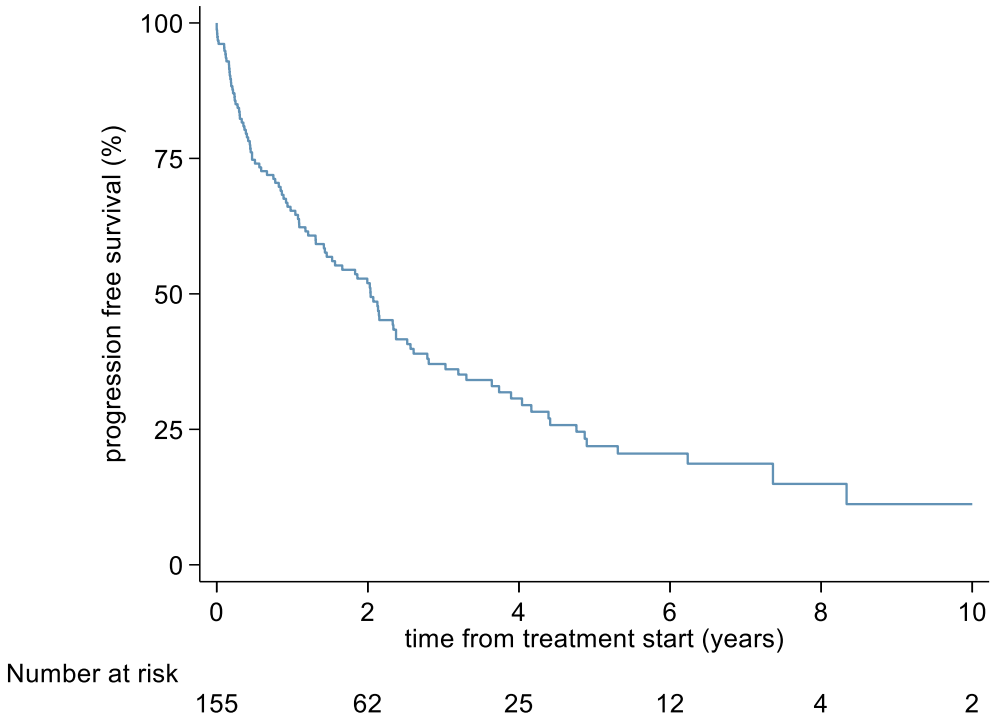
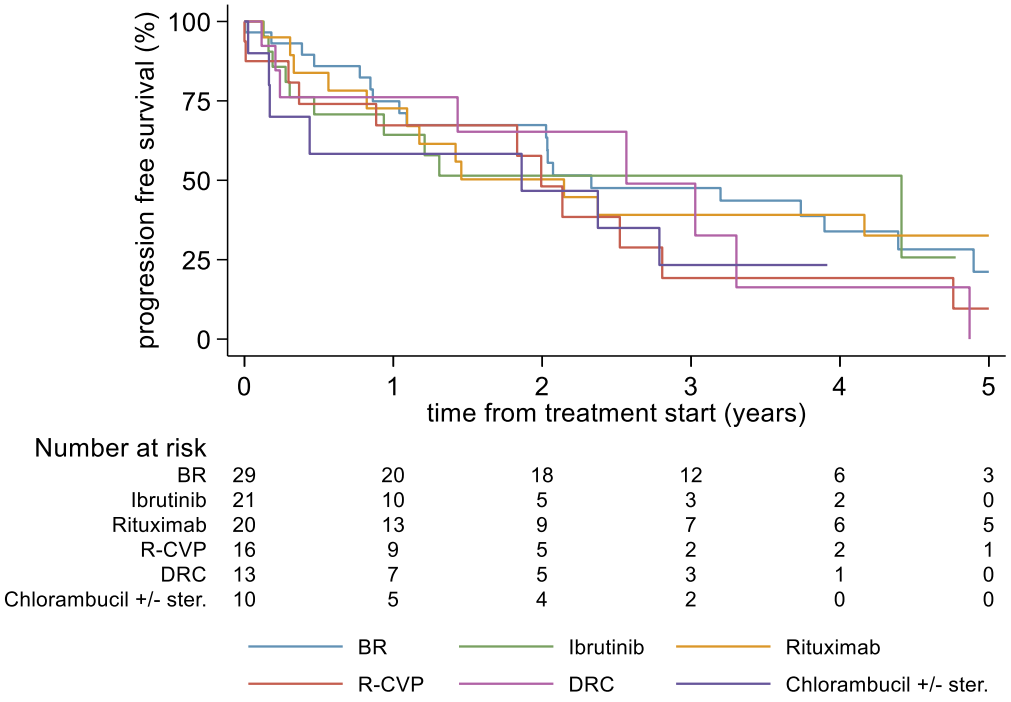


Figure 33 Progression-free survival from start of relapsed/refractory treatment following anti CD20 monoclonal antibody treatment for all patient by treatment



Number at risk

BR	29	20	18	12	6	3
Ibrutinib	21	10	5	3	2	0
Rituximab	20	13	9	7	6	5
R-CVP	16	9	5	2	2	1
DRC	13	7	5	3	1	0
Chlorambucil +/- ster.	10	5	4	2	0	0

Table 22 Baseline characteristics at start of treatment and outcomes for HMRN and participants in the phase 2 study

	HMRN N=90	MAGNOLIA[2] N = 68
Baseline Characteristic:		
2 prior treatment lines (%)	18.9	26.0
≥3 prior treatment lines (%)	2.2	28.0
Refractory to last therapy (%)	25.6	32.0
Age ≥65 years (%)	80.0	60.0
Median age (years)	73.8	70
Mean age (sd) (years)	73.3 (9.2)	67.5 (11.1)
Prior anti-CD20 therapy (%)	100.0	100.0
Time since last therapy (median) months	19.6	21
Time since last therapy (mean, months)	25.0 (23.4)	-
POD24 (%)	51.1	45.0
≥61.5 months from diagnosis (%)	34.4	50
Time from diagnosis (mean, months)	53.2 (40.0)	80.1 (69.3)
Chemotherapy regimen (%):		
Bendamustine / Rituximab	30.0	-
Single Agent Rituximab	13.3	-
R-CVP	11.1	-
Chlorambucil	7.8	-
Dexamethasone/Rituximab/Cyclophosphamide	13.3	-
R-CHOP	4.4	-
FCR	2.2	-
Other rituximab[1]	6.7	-
Other non-rituximab[2]	11.1	-
Outcomes:		
Overall Response Rate (%)	58.8	68.2
In those formally assessed n=69	75.4	-
1-year overall survival (%)	75.2	95.3
1-year progression-free survival (%)	64.9	82.5

[1] Chlorambucil / Rituximab (n=3), Gemcitabine / Dexamethasone / Cisplatin / Rituximab (n=1), IVE / Rituximab (n=1), Venetoclax / Rituximab (n=1)

[2] CVP (n=3), Bendamustine (n=2), Bendamustine / Methylprednisolone (n=1), Cyclophosphamide / Prednisolone (n=1), Fludarabine (n=1), VCD (n=1), Velcade / Dexamethasone (n=1)

[2] Opat S et al. The MAGNOLIA Trial: Zanubrutinib, a Next-Generation Bruton Tyrosine Kinase Inhibitor, Demonstrates Safety and Efficacy in Relapsed/Refractory Marginal Zone Lymphoma. Clin Cancer Res. 2021 Dec 1;27(23):6323-6332. doi: 10.1158/1078-0432.CCR-21-1704. Epub 2021 Sep 15. PMID: 34526366; PMCID: PMC9401507.

Figure 34 Overall survival for HMRN patients from start of first treatment following anti-CD20 monoclonal antibody treatment (treated from 01/01/2014 and excluding ECOG≥3 or missing at diagnosis)

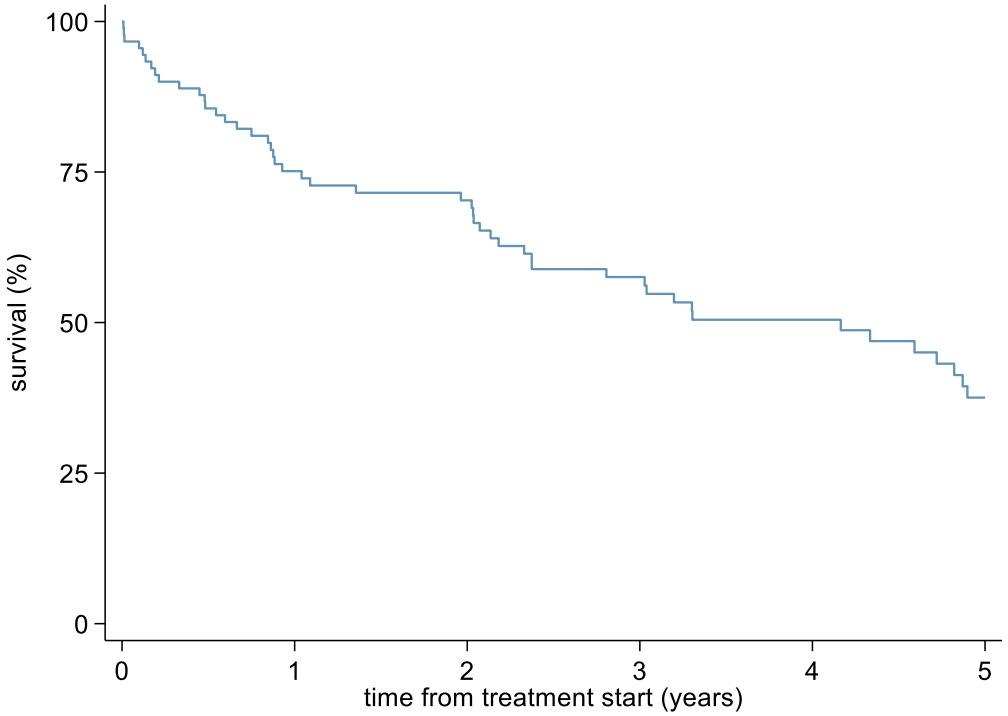


Figure 35 Progression-free survival for HMRN patients from start of first treatment following anti-CD20 monoclonal antibody treatment (treated from 01/01/2014 and excluding ECOG≥3 or missing at diagnosis)

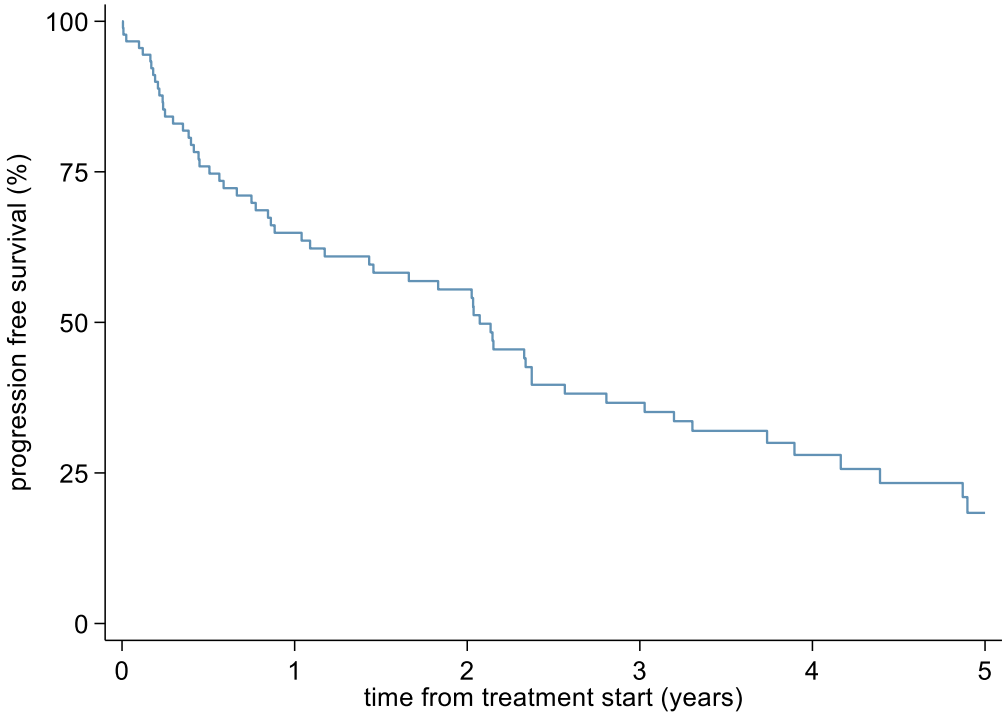


Figure 36 Time to next treatment for HMRN patients from start of first treatment following anti-CD20 monoclonal antibody treatment (treated from 01/01/2014 and excluding ECOG≥3 or missing at diagnosis)