Treatment patterns and outcomes in relapsed/refractory follicular lymphoma: results from the international SCHOLAR-5 study

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Supplemental Information

1 Additional Methods

1.1 Data collection procedures by source

Building the SCHOLAR-5 external cohort

To describe clinical and demographic characteristics and treatment patterns in patients with r/r FL in the real-world setting, and to estimate response rates and time-to-event outcomes among these patients, Kite created the SCHOLAR-5 cohort from multiple data sources, including university hospitals and comprehensive cancer centres in the UK (n=2; Barts and The Christie), France (n=1; Lyon-Sud), Spain (n=1; Vall d'Hebron Institute of Oncology [VHIO]), Portugal (n=1; Instituto Portugues de Oncologia do Porto [IPO-Porto]) and US (n=2; Memorial Sloan Kettering Cancer Center [MSK] and Vanderbilt-Ingram Cancer Center).

These sites were selected because of the suitability of their data, numbers of eligible patients, data availability across core variables of interest, ability to enhance variables through clinical notes, and faster rates of extraction, compared to other sites assessed during the data source identification process. The patient selection period extended from 23 July 2014 to dates specific to each site: 17 July 2019 for IPO, 22 July 2019 for Lyon-Sud, 17 August 2019 for Barts, 4 September 2019 for VHIO, 14 September 2019 for MSK, 13 October 2019 for Christie, and 17 December 2019 for Vanderbilt. Data abstraction occurred on these dates in 2020, but as at least 12 months of potential follow-up was required which required limiting the patient selection dates to 2019. Furthermore, data were collected through to these 2020 dates with history through 23 July 2014 to describe prior lines of treatment.

Data abstraction was conducted locally at each center and an iterative data quality process was used to ensure data were correct, consistent, and optimized for relevant clinical detail. A common data model was created to harmonize the variable names and values across geographies to ensure minimal errors when pooling data from different centers, languages, and electronic records systems. The data collection process involved a rigorous set of logic checks to ensure data were accurate and complete within each patient's record and across each site's submitted records overall.

1. Memorial Sloan Kettering Comprehensive Cancer Center is one of the largest and the oldest Cancer Centers in the world, and it is ranked as the second most important Cancer Center in the United States. The lymphoma program at MSKCC includes more than 20 oncologists focusing exclusively on lymphoma, and a portfolio of more than 100 clinical trials dedicated to lymphoma. The data collection period extended through to 14 September 2020.

2. The Department of Hematology of Hospices Civils de Lyon (HCL) at Lyon Sud Hospital is one of the largest French and European haematological center especially for the management of lymphoma patients. A specific clinical research team conducted more than 100 clinical trials specifically for lymphoid malignancies. The department is an active member of the Lymphoma Study Association (LYSA). The data collection period extended through to 22 July 2020.

3. The Barts Cancer Institute (BCI) was created in 2003, and brought together some of the most eminent cancer research teams in London to the Historic St. Bartholomew's (Barts) Hospital, the oldest hospital in England and the Barts and The London School of Medicine and Dentistry, Queen Mary University of London and is a Cancer Research UK Centre of excellence. BCI forms part of the Cancer Research UK City of London (CoL) Centre, which is a world class hub

for cancer biotherapeutics, together with our partners from three other of the central London Cancer Research UK centres: University College London, King's College London, and The Francis Crick Institute. The data collection period extended through to 17 August 2020.

4. The Christie is a large Comprehensive Cancer Centre in the northwest of England receiving more than 14,000 new patient referrals annually. With the University of Manchester and Cancer Research UK the Christie forms the Manchester Cancer Research Centre (MCRC) and is also a partner in the Manchester Academic Health Science Centre. The Lymphoma Group has a large clinical trial and translational program and a research focused approach to patient care. The data collection period extended through to 13 October 2020.

5. The Vall d'Hebron University Hospital (VHUH) is the second largest hospital in Spain and it covers all medical and surgical specialities. It has more than 1400 beds and treats around 1,200,000 patients per year. Established in 2006, the Vall d´Hebron Institute of Oncology (VHIO) is a leading comprehensive cancer center of excellence where its scientists and research physicians work together as multidisciplinary teams to both accelerate and advance personalized and targeted therapies against cancer. The clinical research unit has conducted more than 400 clinical trials during the last year in oncological and haematological malignancies. The data collection period extended through to 4 September 2020.

6. IPO Porto is the largest Comprehensive Cancer Center in Portugal. Every year it treats around 40,000 patients, 10,000 of whom are new patients, in 11 integrated practice units. Its Clinical Research Unit has conducted more than 80 clinical trials in hematologic malignancies. IPO Porto Research Center also comprises two research units dedicated to real world evidence studies – Management, Outcomes Research and Economics in Healthcare (MOREHealth) Group and Cancer Epidemiology Group. The data collection period extended through to 17 July 2020.

7. Vanderbilt-Ingram Cancer Center is a leader in the prevention, diagnosis and treatment of cancer. The center's world-renowned team of experts provides an integrated, personalized and patient-centered approach to cancer care, including treatment, research, support, education and outreach. From a wide variety of wellness programs to a leading REACH for Survivorship Clinic, patients find support from diagnosis through survivorship. Vanderbilt-Ingram is a National Cancer Institute-designated Comprehensive Cancer Center, one of just two centers in Tennessee and 51 in the country to earn this highest distinction and ranks in the top 10 nationwide for cancer research grant support. The data collection period extended through to 17 December 2020.

Clinical sites 1-6

Data from 6 sites across the US, UK, France, and Spain were collected from electronic medical records. For eligible patients, data were accessed and extracted by appropriately trained analysts or research fellows from the different participating sites. Site selection was based on availability and completeness of data for variables of interest, as well as sufficient patient numbers given agreed inclusion/exclusion criteria. A common data model (CDM) was developed for this study and used to ensure consist variable names and definitions when extracting data.

Clinical site 7: Vanderbilt Medical Centre

Data for the VUMC SD component of the SCHOLAR-5 cohort come from electronic medical records collected through a wholly owned subsidiary of VUMC, Nashville Biosciences. Data from consented patients are de-identified under HIPAA Safe Harbor standards, including removal of identifying fields, manual review of clinical notes, use of global research identifiers, and time-shifting of index date. The study CDM was used to guide manual review. This manual review was performed by the physician trained in the use of the CDM. The most recent, as well as the relevant prior, hematology notes were

identified and used to obtain clinical data. Relevant imaging reports and laboratory measurements were also reviewed and extracted based on the requirements of the CDM. Sub-cohort A patient level key variables included demographics, clinical characteristics (Table S2), therapeutic regimens received, and death or censoring dates. Patient-level line of treatment variables extracted included time varying baseline characteristics, best overall response for each line of therapy received, progression date and treatment start and end dates.

Disease response and progression assessments
Responses were assessed using a variety of methods including computed tomography (CT) scans and Cheson criteria.

1.2 Eligibility criteria for SCHOLAR-5

Overall inclusion criteria for the SCHOLAR-5 cohort were:

1. Patients aged ≥18 years;
2. Patients with histologically confirmed diagnosis of iNHL, with histological subtype limited to FL Grade 1, Grade 2, or Grade 3a or MZL nodal/extranodal based on criteria established by the World Health Organization (WHO) 2016 classification (data from patients with MZL were omitted at the analysis stage);
3. Patients with r/r disease (i.e., r/r iNHL) starting third or higher line of therapy on or after 23rd July 2014 (exact date differed according to individual cohort component protocols). Prior line of therapy with anti-CD20 monotherapy did not count as line of therapy for eligibility.

Patient level Exclusion criteria for the SCHOLAR-5 cohort were:

1. Transformed FL;
2. FL Histological Grade 3b;
3. Prior anti-CD19 CAR T-cell therapy or other genetically modified T-cell therapy;
4. Eligible within 12 months before the last updated version of the database (site specific)

1.3 Variable Definitions

ECOG
The measure of ECOG used as a covariate was an augmented ECOG, meaning that when ECOG was not reported and the Karnofsky's index of performance status was available, ECOG was derived using this score. The methods of imputation used for ECOG are detailed in Section 5 of the section on handling of missing values.

FLIPI
The FLIPI score ranges from 0 to 5 and consists of the five sub-scores for Stage, lactate dehydrogenase (LDH), hemoglobin (HB), age group and number of involved nodal sites. Each sub-score is scored with a score of either 0 or 1, with a score = 1 per criterion if

- Stage = III-IV
- LDH > upper limit of normal (ULN)
- HB <=12 g/dl
- Age > 60 years
- > 4 nodal sites

When FLIPI was not provided explicitly and all of the sub-scores were available, the overall score was derived from its definition.

Previous LoT

The number of previous LoT was assigned according to the number of previous eligible LoT. Eligible LoT differed from LoT assignment from some of the data sources. As such, in all sub-cohorts LoT were reviewed and LoT numbering re-assigned. Radiotherapy on its own, surgery on its own and watch and wait were all ineligible as a line of therapy and not counted towards the prior lines of therapy. These lines of therapy were manually reviewed for reassignment by members of the investigator team.

Relapsed versus refractory

Refractory disease was defined as progressing (defined as PD) during or within 6 months after completion of the most recent prior treatment. Relapsed disease was defined as progressing after CR, PR or SD > 6 months after completion of the most recent prior treatment. Based on these definitions, as set in the SAP, some patients may have progressed and not be identified as relapsed or refractory. For example, a patient does not have a date of completion for the prior treatment. Someone in his or her last line of therapy, was assumed to still be on treatment and was deemed refractory. Cases where the exact classification of whether progressive disease constituted relapsed or refractory disease were not excluded. If patients progressed but could not be differentiated as being relapsed or refractory (e.g., when date of completion of therapy was missing), the patient's LoT was still considered eligible.

POD24

POD24 was a key covariate. In data from real-world clinical practices, POD24 was defined as patients having progressed within 24 months after initiation of first-line anti-CD20 chemotherapy combination therapy. Only patients with a first line of therapy that included an anti-CD20 combined chemotherapy were eligible to be evaluated as POD24. Switching therapy within 24 months was not sufficient to be considered POD24.

The POD24 definition above was applied to Sub-cohort A, but for Sub-cohort B, the definition was solely based on switching treatment within 24 months of initiating first-line chemoimmunotherapy because progression in first-line LoT was not collected. Defining POD24 based on switching treatments should capture all but a few patients meeting the definition above, but should also identify patients that do not meet the definition (e.g., a patient switching treatment for another reason than progression). As such, there is expected to be over-reporting of POD24 in Sub-cohort B and thus an under-correction for the imbalance. Such a bias will be in favor of SCHOLAR-5 rather than ZUMA-5.

Response variables

For each LoT outcomes only included response assessments obtained after the initial treatment and until either PD was noted or subsequent anti-cancer therapy (including stem cell transplant) was initiated. PFS was defined as the time from index date until earliest date of progression or death from any cause. Follow-up was censored if a patient initiated a new LoT and the censoring date was set to the date of the most recent non-progressive tumour assessment. OS was defined as the time from index date to death, with censoring at last recorded date on which the patient was known to be alive for patients with no date of death recorded. A patient with multiple LoTs would have contributed data to the OS analysis for each of their eligible LoT. Time-to-next treatment (TTNT) was defined as the time from index date to initiation of next therapy or date of death, with patients who had neither a date of death or a follow-up treatment censored on the last date of follow up. Outcome variables with partial dates (e.g., only month and year were available) were addressed as described in the supplemental data. Patients were censored at date of transformation if it occurred during follow-up.

1.4 Missing Values

ECOG Performance Missing Data

The Karnofsky's index of performance status (KPS) was converted to ECOG status 0-4 when ECOG was not available or missing[14]. The ECOG 0-4 grade is summarized in Table S2. If the ECOG value was missing for the 6-months period before the index therapy start date and could not be taken from the KPS, it was checked whether the value right before and after the period was available, identical and within the range of 0-1, in which case the ECOG value was set to this stable pre/post value. The identical approach was taken for the KPS being classifiable as either 100% (ECOG=0) or 80-90% (ECOG=1). If the ECOG score could not be derived this way but was > 1 at the last measurement before the index date, the patient was excluded from any line of treatment analysis which occurred later than the ECOG measurement date.

Partial Dates

The following partial dates were imputed as per Table S3:

- Adverse event (AE) start dates
- Medication start dates (including LoT start dates)
- Clinical and laboratory dates:
    - Gene expression assessment dates
    - Laboratory characteristics assessment dates
    - Medical history/Comorbidity diagnosis dates

Additionally, for classifying prior, concomitant and post medications according to the treatment exposure start and end dates, the treatment end dates were imputed the following way:

1) If year and month are available but day were missing, the date was set to the last day of the month.

2) If year was available but day and month were missing, the date was set to December 31.

The LoT end date was defined differently to the treatment exposure end date described above and was always defined as starting date of the next LoT minus one day, while treatment exposure itself could end before the end of the LoT. For the last LoT, no end date was derived.

Imputation rule for partial or missing event dates for time-to-event variables (OS, PFS, TTNT, DoR):

1) If year and month were available but day was missing, the date was set to the last day of the month.

2) If the month was also missing or the date was completely missing, the time-to-event was not calculated.

Imputation rule for partial or missing censoring dates for time-to-event variables (OS, PFS, TTNT, DoR):

1) For partial or missing censoring dates the analogous rule applied, with the censoring date needed to have at least the month and year available, else the last available (imputed) date before the missing censoring date was used.

Imputation rules for partial or missing start dates for time-to-event variables (OS, PFS, TTNT, DoR):

1) If the start day for the calculation was missing, this day was set to the 1st day of the month

2) If the month was also missing or the date was completely missing, the time-to-event was not calculated.

These rules led to conservative time-to-event outcomes for comparison, due to missing data being imputed for the comparator data and imputing either the most advantageous dates for the available treatment options in the real-world setting.

Missing days for age calculations were set to the 15th of the month, and missing days and months for the birth day were set to the 30th of June of the year.

FLIPI Score
If only one sub-score was missing, but the overall FLIPI score was available, the missing sub-score was derived and used for analysis.

1.5 Treatment categories

For analytic purposes, treatment regimens were grouped into the following categories to ease interpretation of results: allogeneic SCT, autologous SCT, anti-CD20 monoclonal antibody monotherapy, anti-CD20 monoclonal antibodies plus bendamustine (CD20+Benda), CD20+CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine and prednisone) like, CD20+CVP (cyclophosphamide, vincristine and prednisone), CD20+fludarabine based, CD20+other chemo, chemotherapy (other), experimental, EZH2i (enhancer of zeste homolog 2 specific inhibitors), R^2 (rituximab and lenalidomide) and other imid-based, PI3K inhibitor based and radioimmunotherapy. The CHOP-like category included primarily CHOP, but also CHEP (etoposide instead of vincristine) and EPOCH (CHOP + etoposide). Other chemotherapy primarily included platinum-based chemotherapies and chlorambucil, but also included a variety of others. Experimental treatments included treatments described as experimental treatments or considered off-label. They included SYK-inhibitors, PD1-inhibitors and BCL2-inhibitors, among others.

2 Additional Results

Table S1. Baseline characteristics at first eligible LoT

	Europe	US	Overall
Sample size	78	50	128
Age (years, median, range)	65.5 (36 - 85)	64 (38-86)	65 (36 - 86)
Age ≥ 65 years -n (%)	43 (55.1%)	24 (48.0%)	67 (52.3%)
Male– no. (%)	41 (52.6%)	32 (64.0%)	73 (57.0%)
Follicular lymphoma subtype – no. (%)			
Grade 1	29 (40.8%)	30 (65.2%)	59 (50.4%)
Grade 2	32 (45.1%)	14 (30.4%)	46 (39.3%)
Grade 3a	10 (14.1%)	2 (4.3%)	12 (10.3%)
*Missing**	*7*	*4*	*11*
Disease stage at diagnosis – no. (%)			
I	4 (7.4%)	2 (4.3%)	6 (6.0%)
II	2 (3.7%)	6 (13.0%)	8 (8.0%)
III	10 (18.5%)	21 (45.7%)	31 (31.0%)
IV	38 (70.4%)	17 (37.0%)	55 (55.0%)
*Missing**	*24*	*4*	*28*
FLIPI at diagnosis – no. (%)			
Low	11 (23.9%)	9 (21.4%)	20 (22.7%)
Medium	13 (28.3%)	21 (50.0%)	34 (38.6%)
High	22 (47.9%)	12 (28.6%)	34 (38.6%)
*Missing**	*32*	*8*	*40*
Relapsed or refractory to previous LoT† – no. (%)			
Relapsed	53 (68.8%)	26 (53.1%)	79 (62.7%)
Refractory	24 (31.2%)	23 (46.9%)	47 (37.3%)
*Missing**	*1*	*1*	*2*
ECOG			
0	21 (29.6%)	15 (50.0%)	36 (35.6%)
1	45 (63.4%)	13 (43.3%)	58 (57.4%)
2	3 (4.2%)	2 (6.7%)	5 (5.0%)
3	1 (1.4%)	0 (0.0%)	1 (1.0%)
4	1 (1.4%)	0 (0.0%)	1 (1.0%)
*Missing**	*7*	*20*	*27*
POD24 - yes (%)	24 (30.8%)	10 (20.0%)	34 (26.6%)
Bone marrow involvement at index date – no. (%)	16 (38.1%)	3 (18.2%)	18 (34.0%)
*Missing**	*36*	*34*	*70*
Prior SCT			
Autologous	22 (28.2%)	1 (2.0%)	23 (18.0%)
Allogeneic	1 (1.3%)	2 (4.1%)	3 (2.3%)
None	55 (70.5%)	47 (93.9%)	102 (79.7%)
*Missing**	*0*	*1*	*1*
Prior anti-CD20 + alkylating agent			
Yes	74 (94.9%)	40 (80.0%)	114 (89.1)%
No	4 (5.1%)	10 (20.0%)	14 (10.9%)
Best response to last line of therapy			
Complete response	35 (44.8%)	18 (36.0%)	53 (41.4%)
Partial response	31 (39.7%)	16 (32.0%)	47 (36.7%)
Stable disease	6 (7.7%)	10 (20.0%)	16 (12.5%)
Progressive disease	6 (7.7%)	6 (12.0%)	12 (9.3%)

	Europe	US	Overall
Sample size	78	50	128
Number of nodal sites – no. (%)			
1	9 (16.1%)	4 (13.8%)	13 (15.3%)
2	9 (16.1%)	6 (20.7%)	15 (17.6%)
3	4 (7.1%)	6 (20.7%)	10 (11.8%)
≥ 4	34 (60.7%)	13 (44.8%)	47 (55.3%)
*Missing**	*22*	*21*	*43*
Size of largest nodal mass – no. (%)			
≥ 7cm	13 (30.2%)	9 (23.1%)	22 (26.8%)
*Missing**	*35*	*11*	*46*
Time from last therapy (months, median, IQR)	21.4 (9.2 – 36.7)	15.2 (4.1 – 31.9)	17.9 (7.7 – 34.6)
First eligible LoT			
3	62 (79.5%)	25 (50.0%)	87 (68.0%)
4	8 (10.3%)	16 (32.0%)	24 (18.8%)
5	5 (6.4%)	5 (10.0%)	10 (7.8%)
6	1 (1.3%)	1 (2.0%)	2 (1.6%)
7	1 (1.3%)	1 (2.0%)	2 (1.6%)
8	0 (0.0%)	1 (2.0%)	1 (0.8%)
9	1 (1.3%)	0 (0.0%)	1 (0.8%)
10	0 (0.0%)	1 (2.0%)	1 (0.8%)
Number of eligible LoT			
1	44 (61.5%)	24 (48.0%)	68 (53.1%)
2	24 (30.8%)	15 (30.0%)	39 (30.4%)
3	6 (7.7%)	6 (12.0%)	12 (9.4%)
4	3 (3.8%)	3 (6.0%)	6 (4.7%)
5	1 (1.3%)	1 (2.0%)	2 (1.6%)
6	0 (0%)	1 (2.0%)	1 (0.8%)

** Missing percentage based on full sample, while percentage within categories calculated from patients non-missing values (therefore, percentages add up to more than 100%).*
† Refractory disease was defined as progressing (defined as PD) during or within 6 months after completion of the most recent prior treatment. Relapsed disease was defined as progressing after CR, PR or SD > 6 months after completion of the most recent prior treatment.
All characteristics are at or within 6 months of the initiation of first eligible LoT in analysis, with the exception of disease stage and FLIPI, which are at diagnosis.
POD24: having progressed within 24 months of first-line anti-CD20 monoclonal antibody and chemotherapy combination; FLIPI: Follicular Lymphoma International Prognostic Index.

Table S2: Baseline characteristics by LoT

	3rd LoT	4th LoT	≥5th LoT
Sample size	87	62	47*
Age (years, median, range)	65 (36-86)	65 (36 – 86)	67 (41 – 89)
Age ≥ 65 years -n (%)	44 (50.6%)	34 (54.0%)	27 (57.4%)
Male– no. (%)	50 (57.5%)	37 (58.7%)	28 (59.6%)
Follicular lymphoma subtype – no. (%)			
Grade 1	31 (38.8%)	28 (48.3%)	24 (55.8%)
Grade 2	37 (46.2%)	23 (39.7%)	16 (37.2%)
Grade 3a	12 (15.0%)	7 (12.1%)	3 (7.0%)
Missing	7	5	4
Disease stage at diagnosis – no. (%)			
I	4 (6.3%)	5 (9.8%)	2 (4.7%)
II	4 (6.3%)	4 (7.8%)	4 (9.3%)

	3rd LoT	4th LoT	≥5th LoT
III	19 (30.2%)	17 (33.3%)	13 (30.2%)
IV	36 (57.1%)	25 (49.0%)	24 (55.8%)
Missing	24	12	4
FLIPI at diagnosis – no. (%)			
Low	13 (19.4%)	12 (27.9%)	7 (18.9%)
Medium	17 (29.3%)	17 (39.5%)	18 (48.6%)
High	28 (39.3%)	14 (32.6%)	12 (32.4%)
Missing	29	20	10
Relapsed or refractory to previous LoT – no. (%)			
Relapsed	58 (67.4%)	25 (40.3%)	22 (46.8%)
Refractory	28 (32.6%)	37 (59.7%)	25 (53.2%)
Missing	1	1	0
ECOG			
0	25 (35.2%)	24 (49.0%)	9 (25.0%)
1	42 (59.2%)	24 (49.0%)	24 (66.7%)
2	2 (2.8%)	1 (2.0%)	3 (8.3%)
3	1 (1.4%)	0 (0.0%)	0 (0.0%)
4	1 (1.4%)	0 (0.0%)	0 (0.0%)
Missing	16	14	11
POD24 - yes (%)	30 (34.5%)	18 (28.6%)	6 (12.8%)
Bone marrow involvement at index date – no. (%)	13 (36.1%)	9 (42.9%)	4 (21.1%)
Missing	51	42	28
Prior SCT			
Autologous	19 (21.8%)	15 (24.2%)	6 (12.8%)
Allogeneic	0 (0.0%)	0 (0.0%)	3 (6.4%)
None	68 (78.2%)	47 (75.8%)	38 (80.9%)
Missing	0	1	0
Prior anti-CD20 + alkylating agent			
Yes	79 (90.8%)	55 (87.3%)	43 (91.5%)
No	8 (9.2%)	8 (12.7%)	4 (8.5%)
Best response to last line of therapy			
Complete response	38 (43.7%)	18 (28.6%)	8 (17.0%)
Partial response	30 (34.5%)	16 (25.4%)	15 (31.9%)
Stable disease	10 (11.5%)	3 (4.8%)	13 (27.7%)
Progressive disease	9 (10.3%)	26 (41.3%)	11 (23.4%)
Number of nodal sites – no. (%)			
1	10 (16.1%)	10 (25.0%)	2 (6.9%)
2	11 (17.7%)	8 (20.0%)	1 (3.4%)
3	9 (14.5%)	3 (7.5%)	2 (6.9%)
≥ 4	32 (51.6%)	19 (47.5%)	24 (82.8%)
Missing	25	23	18
Size of largest nodal mass – no. (%)			
≥ 7cm	16 (29.1%)	4 (8.9%)	7 (25.9%)
Missing	32	18	20
Time since diagnosis (months, median, IQR)	81.8 (42.7 – 116.4)	97.3 (64.6 – 129.4)	136.3 (92.6 – 177.8)
Time from last therapy (months, median, IQR)	18.0 (7.3 – 31.9)	9.0 (2.4 – 19.9)	7.7 (1.4 – 20.5)

** The first eligible line ≥5 was used for each patient. The sample contained 36 patients at 5th LoT, 6 patients at 6th LoT, 2 at 7th LoT, and one patient at 8th, 9th, and 10th LoT.*

Table S3: Treatment regimen by LoT for eligible patients, separated by US and Europe.

	LoT 1	LoT 2	LoT 3	LoT 4	LoT 5	LoT 6	LoT 7	LoT 8	LoT 9	LoT 10	LoT 11
US											
Allogeneic SCT				2	3	3			1		
Autologous SCT		1									
CD20 mono	12	20	13	3	3		1				
CD20+Benda	4	9	8	5	6	2					
CD20+CHOP like	21	2	4	2	2	1	1				
CD20+CVP	6	1	1	1		2					
CD20+Fludarabine_based	1	2									
CD20+Other_Chemo		5	6	6	2	1	2	1	1		
Chemotherapy	1	1	2	1		1		2	1	1	
Experimental	4	3	6	8	5	2	3	1		1	
imid based		2	4	3	4	2					
PI3Ki based		1	3	8	4	2					
Radioimmunotherapy	1	3	3	2							
Europe											
Allogeneic SCT			3		1						
Autologous SCT	1	20	11	2							
CD20 mono	4	5	4	1	2	2					1
CD20+Benda	2	14	16	12	1	1	1		1		
CD20+CHOP like	52	9	2	3	2						
CD20+CVP	11	3	2								
CD20+Fludarabine_based			3								
CD20+Other_Chemo	1	14	7	2	3	1		1		1	
Chemotherapy	7	9	8	9	3		2				
Experimental			8	7	4	2		1			
EZH2i			2			1					
imid based		1	4	2	6	3	2				
PI3Ki based		2	8	7	4	1					
Radioimmunotherapy		1		1							
TOTAL	**128**	**128**	**128**	**87**	**55**	**27**	**12**	**6**	**4**	**3**	**1**

Treatment by line of therapy including all LoT of eligible patients. Experimental category does not include recently accepted treatments (PI3K-δ inhibitors, R^2, and EZHi), even if they were not approved at the time of the study. Radiotherapy alone was not considered an eligible line of therapy.
Benda - bendamustine; CD20 - anti CD20 monoclonal antibodies; CHOP - cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP - cyclophosphamide, vincristine, prednisolone;
EZH2i = Enhancer of zeste homolog 2 specific inhibitors, IMiD = immunomodulatory drugs;
LoT = line of therapy; R^2 = rituximab and lenalidomide; SCT = stem cell transplant; PI3Ki = phosphoinositide 3-kinase inhibitor.

Table S4: Treatment regimen including only LoTs included in the analysis set.

	LOT 3	LOT 4	LOT 5	LOT 6	LOT 7	LOT 8	LOT 9	LOT 10
US								
Allogeneic SCT			2	2			1	
Autologous SCT								
CD20 mono	5	3	1		1			
CD20+Benda	4	3	5	1				
CD20+CHOP like	1	2		1				
CD20+CVP				1				
CD20+Fludarabine_based								
CD20+Other_Chemo	4	5	1	1		1	1	
Chemotherapy	2	1		1		1		1
Experimental	3	6	4	2	3	1		1
EZH2i								
imid based	3	2	3	2				
PI3Ki based	3	7	2	1				
Radioimmunotherapy								
Europe								
Allogeneic SCT	3							
Autologous SCT	11	1						
CD20 mono	1	1	2	1				
CD20+Benda	14	6	1	1	1		1	
CD20+CHOP like	1	3	2					
CD20+CVP	1							
CD20+Fludarabine_based	2							
CD20+Other_Chemo	4	2	2					
Chemotherapy	6	6	1					
Experimental	6	6	3	1		1		
EZH2i	2			1				
imid based		1	4	2	5	3	2	
PI3Ki based		2	7	6	2	1		
Radioimmunotherapy		1		1				
TOTAL	**87**	**62**	**36**	**20**	**7**	**4**	**3**	**2**

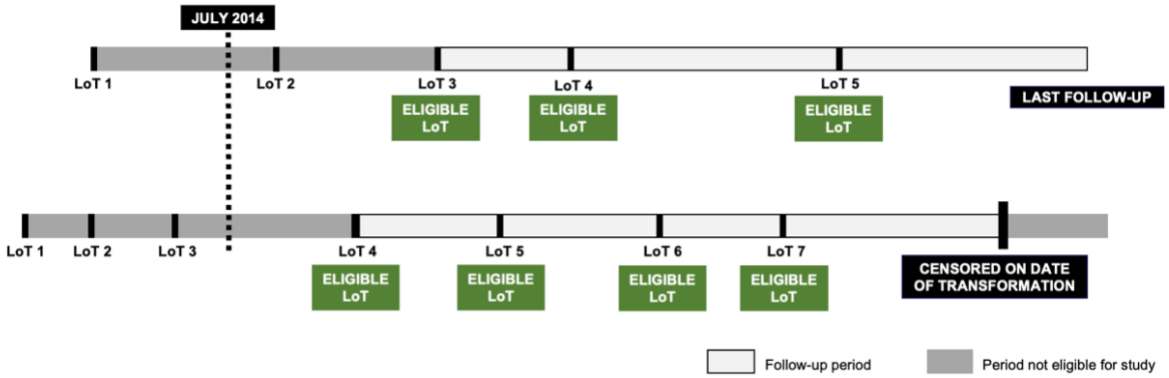
Treatment regiments by line of therapy, including only the eligible lines that were included in the analyses. Experimental category does not include recently accepted treatments (PI3K-δ inhibitors, R^2, and EZHi), even if they were not approved at the time of the study. Radiotherapy alone was not considered an eligible line of therapy.
Benda - bendamustine; CD20 - anti CD20 monoclonal antibodies; CHOP - cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP - cyclophosphamide, vincristine, prednisolone;
EZH2i = Enhancer of zeste homolog 2 specific inhibitors, IMiD = immunomodulatory drugs; LoT = line of therapy; R^2 = rituximab and lenalidomide; SCT = stem cell transplant; PI3Ki = phosphoinositide 3-kinase inhibitor.

Table S5: Clinical outcomes by LoT when including radiotherapy as a LoT

		3rd LoT	4th LoT	≥ 5th LoT
Response outcomes (best)				
ORR	N responders % (95% CI)	60/87 69.0% (58.1 – 78.5)	38/61 62.3% (49.0 – 74.4)	37/87 43.1% (31.6 – 55.4)
CR	N responders % (95% CI)	40/87 46.0% (35.2 – 57.0)	20/61 32.8% (21.3 – 46.0)	18/87 20.3% (11.4 – 33.4)
Time-to-event outcomes				
		N = 92	N = 65	N = 56
OS	Median months (95% CI)	67.6 (59.5 – NR)	60.1 (43.5 – NR)	42.8 (18.9 – NR)
	18m % (95% CI)	87.2 (80.4 – 94.6)	81.9 (72.8 – 92)	63.7 (51.8 – 78.3)
	24m % (95% CI)	84.6 (77.2 – 92.7)	74.2 (63.6 – 86.5)	59.3 (47.2 – 74.5)
	36 months % (95% CI)	80.23 (71.9 – 89.5)	65.0 (53.2 – 79.5)	51.9 (39.4 – 68.2)
	60 months % (95% CI)	60.2 (47.5 – 76.4)	52.5 (38.1 – 72.4)	43.1 (29.5 – 62.9)
PFS	Median months (95% CI)	11.2 (9.9 – 18.9)	11.0 (6.8 – 16.7)	3.9 (3.0 – 7.8)
	18m % (95% CI)	36.0 (25.4 – 51.1)	25.2 (14.6 – 43.6)	9.1 (3.8 – 21.9)
	24m % (95% CI)	19.1 (10.8 – 337)	13.1 (5.5 – 31.0)	6.1 (2.4 – 15.4)
	36 months % (95% CI)	15.9 (8.1 – 31.1)	6.5 (1.8 – 24.1)	--
	60 months % (95% CI)	--	--	--
TTNT	Median months (95% CI)	21.6 (16.3 – 40.7)	17.9 (15.2 – 28.)	7.2 (5.5 – 16.1)
	18m % (95% CI)	57.3 (47.7 – 68.9)	49.0 (37.6 – 63.8)	32.2 (23.2 – 44.7)
	24m % (95% CI)	44.7 (35.0 – 57.2)	39.0 (28.0 – 54.4)	28.4 (20.2 – 40.0)
	36 months % (95% CI)	40.3 (30.7 – 52.9)	29.2 (18.8 – 45.3)	22.4 (14.3 – 35.3)
	60 months % (95% CI)	21.8 (12.1 – 39.4)	20.4 (10.4 – 40.1)	--

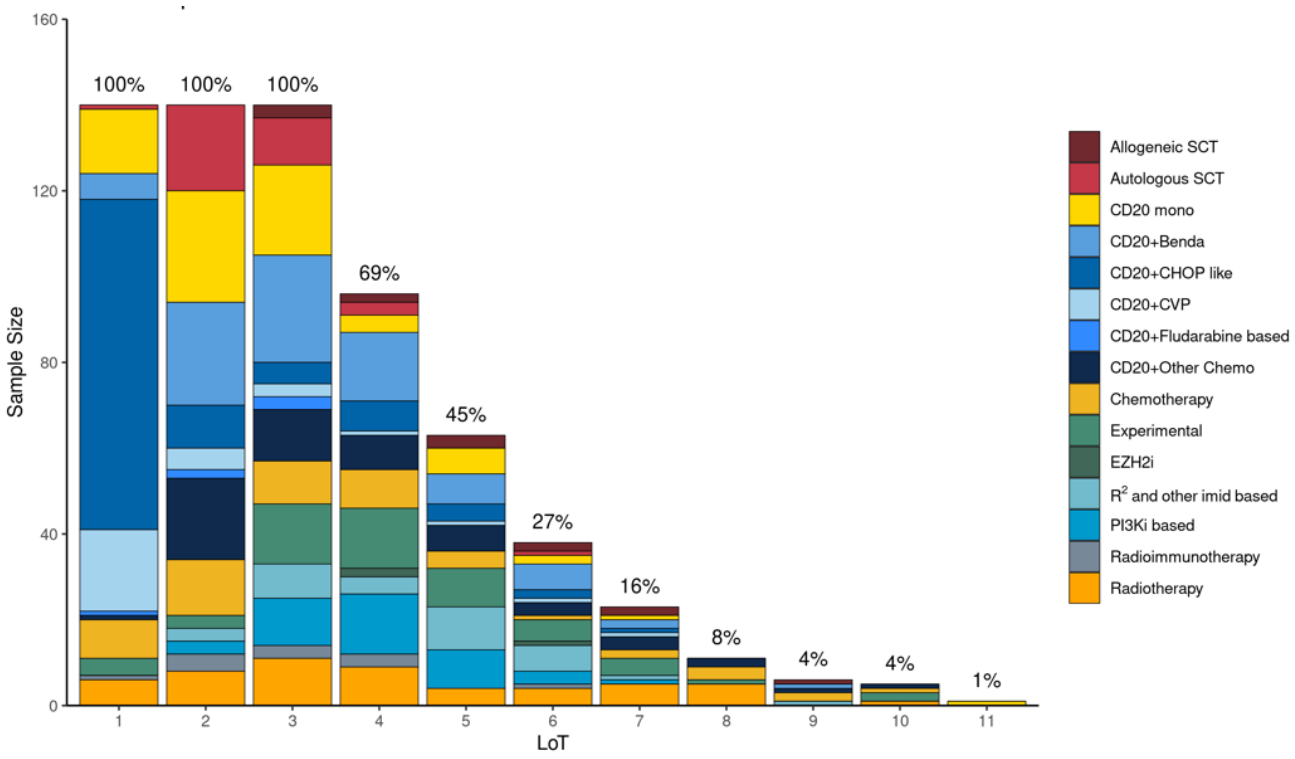
** For ≥5 LoT, multiple LoTs could be included per participant, with the exception of OS which included only the first eligible line per patient. CI: confidence interval; m: months; LoT: Line of therapy; ORR: Overall response rate; CR: Complete response; OS: Overall survival; PFS: Progression-free survival; TTNT, Time-to-next treatment. --, data not available due to last patient being censored or having an event prior to this timepoint.*

Figure S1: LoT eligibility for two example patients



Eligible lines occurred after 23 July 2014, when idelalisib was approved for the treatment of r/r FL in US and Europe. LoT, line of treatment.

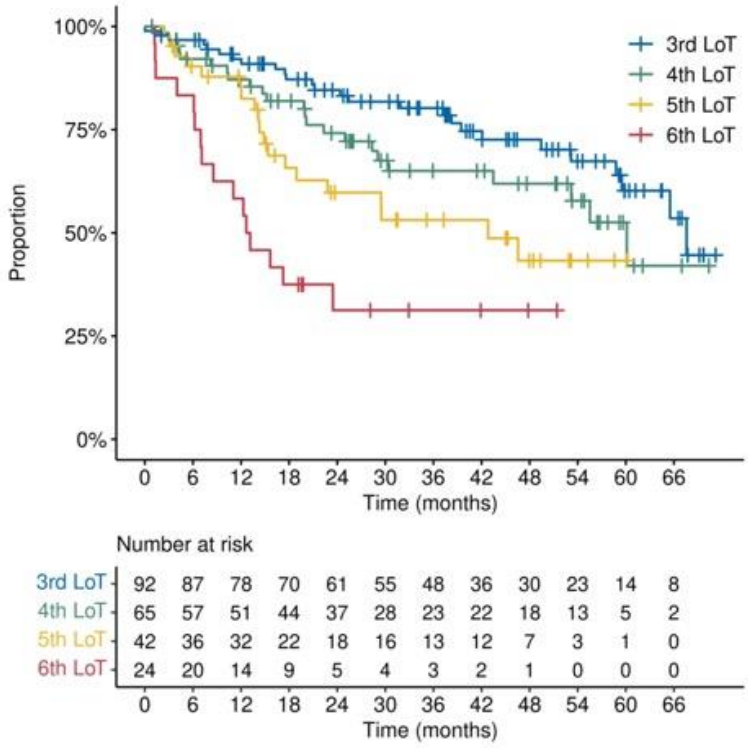
Figure S2 : Treatment patterns across all LoTs when radiotherapy alone is included



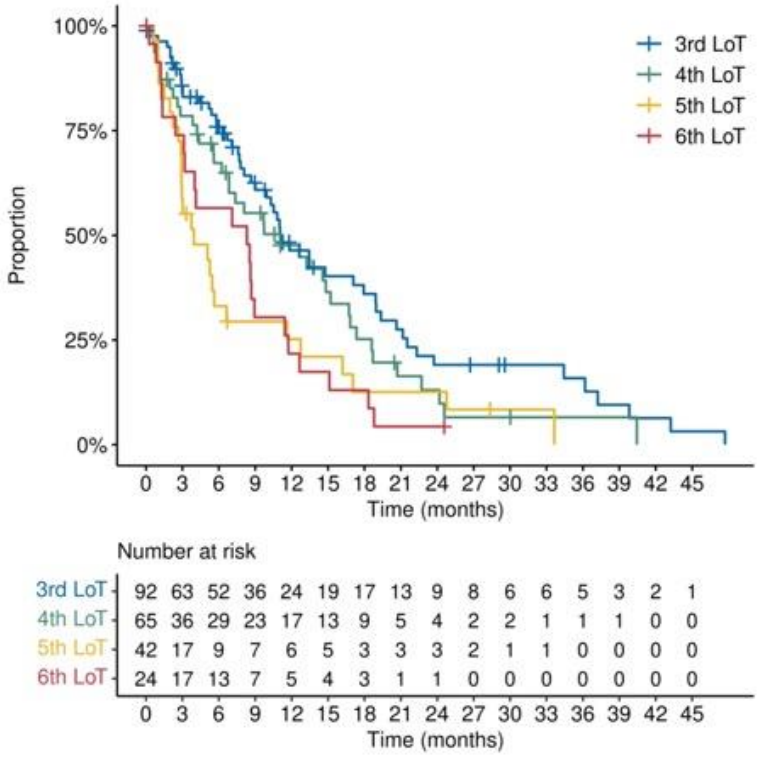
Experimental category does not include recently accepted treatments (PI3K-δ inhibitors, R^2, and EZH2i), even if they were not approved at the time of the study.. The percentage values represent the proportion of patients who contribute to each LoT.

Figure S3: Survival curves by LoT when radiotherapy is an eligible LoT

a. Overall survival



b. Progression-free survival



c. Time-to-next treatment