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

Short title: International SCHOLAR-5 Study

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Running head: SCHOLAR-5 – Unmet needs in r/r FL

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Conflicts of Interest

PG: Consultant or advisory board: Astra-Zeneca, Daiichi Sankyo. **MLP:** Consultant or advisory role: Novartis, Kite, PCYC, BeiGene; Stock ownership: Seres, Notch; Research funding: Seres; Other remuneration: Patents, royalties, other IP: Juno, Seres, Wolters Kluwer. **HG:** Consultant or advisory role: Gilead Sciences, Celgene, Roche; Honoraria - Gilead, Janssen, Celgene; Travel grants: Roche, Gilead Sciences, Celgene, Takeda. **SB:** Consultant or advisory role: Jansen, Celgene, Roche. **AP:** Employment or leadership position - Kite, A Gilead company; Stock ownership - Kite, A Gilead company. **MN:** Employment or leadership position - Kite, A Gilead company; Stock ownership - Kite, A Gilead company. **SK:** Employment or leadership position: RainCity Analytics; Research funding: RainCity Analytics has received funds from for-profit healthcare companies for research. **KD:** Employment or leadership position: Delta Hat. **AH:** Employment or leadership position: Delta Hat. **LM:** Employment or leadership position - Kite, A Gilead company. **EHLO:** Employment or leadership position: RainCity Analytics. **JTS:** Employment or leadership position: Kite, A Gilead Company, Stock ownership: Gilead Sciences. **SWW:** Consultant or advisory role: Kite Pharma, Amgen, Allergan. **MTR:** No conflicts of interests pertinent to the abstract to be declared. **JR:** Consultant or advisory role: Takeda, ADCT, BMS, Novartis, KitePharma; Stock ownership: ADCT & AZ (spouse); Honoraria: Takeda, ADCT, BMS, Novartis, KitePharma; Other remuneration: Speaker's bureau and expert testimony: Takeda, ADCT. SB: Employment or leadership position - Kite, A Gilead company; Stock ownership - Kite, A Gilead company. **JG:** Consultant or advisory role: AZ; Research funding: Janssen, AZ.

Data Sharing Statement

All data are confidential. They can be made available upon approval of a research proposal and signed data access agreement.

ABSTRACT

The SCHOLAR-5 study examines treatment patterns and outcomes of real-world follicular lymphoma (FL) patients on 3rd line of treatment (LoT) or higher, for whom existing data are limited. SCHOLAR-5 is a retrospective cohort study using data from adults (≥ 18 years) with grade 1-3a FL, initiating ≥3rd LoT after June 2014 at major lymphoma centers in the United States (US) and Europe. Objective response rate (ORR), complete response (CR), progression free survival (PFS) and overall survival (OS) were analyzed by LoT. Time-to-event outcomes were assessed using Kaplan-Meier methods. Of 128 patients, 87 initiated 3rd LoT, 63 initiated 4th LoT, and 47 initiated 5th LoT. At 1st eligible LoT, 31% progressed within 24-months of 1st LoT anti-CD20 combination therapy, 28% had prior autologous stem-cell transplantation, and 31% were refractory to the previous LoT. The most common regimen in each LoT was chemoimmunotherapy; however, experimental drugs were increasingly used at later LoTs. In the US, anti-CD20 monotherapy was more common at ≥3rd LoT compared to Europe, where stem cell transplants were more common. ORR at 3rd LoT was 68% (CR 44%), but decreased after each LoT to 37% (CR 22%) in ≥5 LoT. Median OS and PFS at 3rd LoT were 68 and 11 months, respectively, and reduced to 43 and 4 months at ≥5 LoT. Treatments were heterogenous at each LoT in both the US and Europe. Few FL patients achieved complete response in later LoT, and duration of response and survival diminished with each subsequent line.

INTRODUCTION

Indolent non-Hodgkin lymphoma (iNHL) is a slow growing disease constituting approximately one-third of malignant lymphomas in the United States (US) and Europe.[1] Follicular lymphoma (FL) is the most common subtype of iNHL.[2] Despite high initial response rates to front-line treatment, including chemoimmunotherapies such as R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine and prednisone),[3] FL is largely considered to be incurable with standard therapies, and a majority of patients experience multiple relapses in their lifetimes.[4] Moreover, the durability of remission with available treatments decreases with each subsequent line of therapy (LoT).[5-7]

The treatment of relapsed/refractory (r/r) FL, as outlined in National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines,[8, 9] contains a broad range of options. Among these treatments, autologous stem-cell transplantation (ASCT) may be associated with improved progression-free survival (PFS) in r/r FL, but the benefit for overall survival (OS) is less well-defined.[10] No study has prospectively assessed the utility of ASCT in the rituximab era. Rituximab-based therapies, including R^2 (rituximab + lenalidomide)[11] and R-BR (rituximab + bendamustine), [12] are associated with benefits in PFS. Some newer r/r FL therapies have also shown benefits in PFS, including PI3K (phosphoinositide 3-kinase) inhibitors (e.g., idelalisib) [13, 14] and EZH2 (Enhancer of zeste homolog 2 specific) inhibitors.[15] Nonetheless, PFS benefits with these agents tend to not be durable. More recently, anti-CD19 chimeric antigen receptor (CAR) T-cell therapy has demonstrated promising and durable clinical responses in r/r FL,[16] and received regulatory approval by the US Food and Drug Administration (FDA) for this indication.

Due to the variety of treatments available, and the historical lack of a clearly superior treatment for r/r FL, there is substantial variability in the treatment patterns of these patients, especially in later LoTs. Retrospective cohort data from the US and a recent systematic review and meta-analysis have shown that a wide range of treatment regimens are used for r/r FL patients at each LoT, and that, despite a plethora of treatment options, survival rates decrease with each subsequent LoT.[5,17] The existing literature, however, primarily reports the experience in the US and typically span as far back as the early 2000s, which may not be reflective of care today. The impact, if any, of differences in the routine care and resulting clinical outcomes of r/r FL patients in the US and Europe are not yet fully described.[18, 19]

SCHOLAR-5 is a retrospective cohort study that was conducted at major lymphoma centers in the US and Europe, and as such, provides a broad perspective on available treatment options and associated outcomes in those geographies.[20] While SCHOLAR-5 was designed in part to create an external control group against which to compare axicabtagene ciloleucel (axi-cel) results from the pivotal r/r FL ZUMA-5 trial, it also provides unique insights into real-world treatment patterns and outcomes among r/r FL patients in later LoT. The current study, therefore, analyzed SCHOLAR-5 data to describe patient prognostic factors, treatment patterns, and clinical outcomes in the recent, pre-CAR T-cell therapy landscape for r/r FL patients after two or more prior lines of therapy. Additionally, we describe regional differences in patient characteristics, treatments, and outcomes.

METHODS

Design and setting

SCHOLAR-5 is an international, multi-center, retrospective cohort study. Data were obtained through chart reviews of patient records from seven institutions in five countries (Barts Cancer Institute and the Christie NHS Foundation Trust, UK; the Centre Hospitalier Lyon-Sud, France; the Vall d'Hebron Institute of Oncology, Spain; the Instituto Portugues de Oncologia do Porto, Portugal; and the Memorial Sloan Kettering Cancer Center and Vanderbilt Medical Center in the US). These sites were selected based on the numbers of eligible patients, data availability across variables of interest, ability to enhance key variables through manual review of clinical notes, and speed of data abstraction. All data were de-identified and data abstraction processes were identical across all sites. Investigators abided by the general ethical principles outlined in the Declaration of Helsinki and, where necessary, obtained approval from the Independent Review Board(s)/Ethics Committee(s). Additional information on the data sources and data abstraction are provided in the Supplement 1.1.

Study population and follow-up

To meet eligibility for SCHOLAR-5, patients had to be aged ≥18 years with r/r FL grade 1-3a. Each patient was to be initiating 3rd LoT or higher after June 2014. Only patients with biopsy-proven absence of transformation were eligible for inclusion. Patients whose disease transformed during the study period contributed data up until the date of transformation. Patients with prior anti-CD19 or other genetically modified CAR T-cell therapy were excluded, as were patients who met inclusion criteria <12 months before the data collection date (i.e., had <12 months of potential follow-up). See Online Supplement Section 1.2-1.3 for additional details.

Key endpoints

Outcomes of interest were objective response rate (ORR; complete response + partial response), complete response (CR), OS, PFS and time to next treatment (TTNT). Response was determined either by Lugano 2014 criteria or computed tomography (CT) scans using the revised International working group classification.[4] POD24, a key baseline characteristic, was defined as patients having progressed within 24 months after initiation of first-line anti-CD20 chemotherapy combination therapy.

Statistical methods

Analyses were carried out by LoT. All eligible LoT from each patient were included in the analysis. The primary analysis considered only systemic therapies as independent LoTs. A sensitivity analysis was performed to consider radiotherapy alone as an independent LoT. Data were sufficient to report results separately for 3rd and 4th LoT, but data for 5th LoT and higher were combined for analysis due to small sample size. For response outcomes, 95% confidence intervals were calculated on percentages using the Clopper-Pearson method. For the analysis of ≥5th LoT results, random-effects were used to account for multiple LoT per patient in the calculation of point estimates and confidence intervals. For time-to-event outcomes, the Kaplan-Meier (KM) method was used to construct survival curves, from which median survival, 18-month and 24-month proportions were estimated. As with response outcomes, random intercepts were included in the ≥5th LoT analysis for PFS and TTNT to account for multiple LoT and associated outcomes per patient. For OS, only the first eligible ≥5th LoT was included, due to the shared event across lines LoT. For plotting, KM curves were calculated separately for 5th and 6th LoT. All analyses were conducted in R version 3.6.3 using the *survival* package.

RESULTS

Data from 184 patients with r/r non-Hodgkin lymphoma, including 160 r/r FL patients, were included in the SCHOLAR-5 cohort. **Figure 1** illustrates the selection process by showing the counts at each step at the Memorial Sloan Kettering Cancer Center site. Of the 1100 patients in that site's database, 54 patients met all selection criteria for SCHOLAR-5. The most common reasons for exclusions were patients not having initiated 3rd LoT or higher, followed by patients not having initiated their most recent LoT after 23rd July 2014. The latter was the threshold used to identify the modern treatment era, as defined by the regulatory approval of idelalisib – the first PI3K inhibitor. This flow chart highlights that the relatively modest number of patients obtained from large centers such as MSK was due to the application of our pre-defined selection criteria rather than to preferential selection, and is representative of the patient selection process at the other contributing centers.

Of the 160 FL patients identified as potentially eligible across all sites, 128 remained after the final data alignment, and these patients contributed a total of 222 eligible lines of systemic therapy. **Figure 2** illustrates the effect of each criterion applied in this final data alignment phase. The most common reasons for exclusion were presence of marginal zone lymphoma histology and having fewer than 2 prior LoTs after re-alignment with the study LoT definition. Sixteen patients did not have an eligible $\geq 3^{rd}$ LoT therapy, with most of them failing to initiate 3rd LoT after the threshold date. Rates of exclusion were similar between the US and Europe.

Baseline characteristics at the first eligible LoT for the included patients are shown in **Table 1** for the population overall as well as separated by geography. Thirty nine percent (39%) of patients were from the US, 20% from France, 17% from the UK, 14% from Spain, and 10% from

Portugal. Baseline patient characteristics were comparable between Europe and the US. A higher proportion of patients in Europe had an eligible 3rd LoT, compared to the US and more patients in Europe had received SCT prior to their first eligible LoT. Most patients had Grade 1 or 2 FL and stage III-IV disease. Additionally, 30.8% of patients were POD24 (defined by progression of disease within 24 months from initiating first-line anti-CD20 combination therapy). Despite multiple data curation efforts, several variables were not consistently reported in the study database, including the Follicular Lymphoma International Prognostic Index (FLIPI), bone marrow involvement, and the number of nodal sites. Of note, data curation efforts were successful in improving the reporting of multiple variables, most notably the Eastern Cooperative Oncology Group (ECOG) performance scores (derived from other performance scores) and FLIPI (derived from the reporting of its components). The less consistently reported variables may simply be less often collected in the routine clinical practice setting. See Online Supplementary **Table S1** for additional baseline characteristics, and **Table S2** for baseline characteristics separated by LoT. Of note, the proportion of refractory patients increased from 32.6% at 3rd LoT, to 59.7% at 4th and 53.2% at ≥5th LoT, and median time from last therapy reduced from 18.0 months at 3rd LoT, to 9.0 and 7.7 months at 4th and ≥5th LoT.

Treatment patterns

Figure 2 presents the treatment patterns for the overall cohort across all LoTs, (**panel A**), and then separated by geography for 3rd and 4th LoT (**panels B** and **C**). The majority of first-line regimens were chemoimmunotherapy, with anti-CD20 + CHOP-like (e.g., R-CHOP) being the most frequently used regimen. The relative frequency of this regimen declined through subsequent LoT. Nevertheless, chemoimmunotherapy regimens remained common among 2nd LoT patients. There was a large diversity of treatments in 3rd LoT and beyond, suggesting a lack

of a standard approach among later line r/r FL patients. This was further emphasized by the larger number of patients using experimental regimens at 3rd LoT and higher, and the later-line use of treatments often reserved for first-line treatment (e.g., anti-CD20 monotherapy and chemoimmunotherapy). Online Supplementary **Table S3** provides further details of treatment patterns, and Online Supplementary **Figure S2** and **Table S4** present treatment patterns from the sensitivity analysis, where radiotherapy alone was considered an eligible LoT.

Figure 3b shows a divergence in treatment patterns between the US and Europe. At 3rd LoT, patients in the US, compared to Europe, were more likely to be prescribed CD20 monotherapy (20% vs. 2%) and R^2 and other imid-based treatments (12% vs 6%). By contrast patients in Europe were more likely to receive SCT (autologous: 18% vs 0%, allogeneic: 5% vs. 0%). Rates of PI3Ki, experimental, chemotherapy alone, and anti-CD20 combination therapy were similar across geographies. At 4th LoT (**Figure 3c)**, 21% and 18% of regimens were experimental in the US and Europe, respectively, a greater proportion than at 3rd LoT. In Europe, 18% of 4th LoT regimens were chemotherapy alone, compared to 3% in the US. In the sensitivity analysis in which radiotherapy was an eligible independent LoT (i.e., when not restricting LoT to systemic therapy), the treatment patterns as a whole were generally similar to those seen in the primary analysis (i.e., LoT defined by systemic therapies) and the same conclusions are drawn.

Clinical outcomes by LoT

Results of the endpoint analyses are presented in **Table 2**. ORR was 68.3% at 3rd LoT, decreasing to 62.7% at 4th LoT and 37.2% at 5th LoT. Similarly, CR decreased from 43.9% at 3rd LoT to 21.5% at ≥5th LoT. OS at 24 months was 83.7% at 3rd LoT, decreasing to 72.7% at 4th LoT and 54.3% at ≥5th LoT. By 60 months, OS was 62.6% at 3rd Lot, 52.4% at 4th lot, and 38.0%

at ≥5th LoT, although we note that data at this later timepoint were based on limited number of patients. The decreasing estimated probabilities of OS with each subsequent LoT is highlighted in **Figure 4a** as the survival lines for later LoTs clearly lie below those corresponding to earlier LoT. While the choice to focus on systemic LoT had minimal impact on the treatment patterns, it did have a meaningful impact on endpoint analysis. The sensitivity analysis re-defining LoT to include radiotherapy alone as an independent LoT resulted in estimates of OS increasing **(supplemental Table S5)** but the patterns remained the same. Note that given the date threshold used for LoT eligibility, a median OS beyond 72 months was not estimable.

Despite the generally long survival times, particularly in the lower LoT, PFS at 24 months was 16.8% for 3rd LoT, 10.4% for 4th LoT, and 7.9% at ≥5th LoT (**Figure 4b**). There were no clear trends for PFS and OS when examining the 5th and 6th LoT separately. This is partially a reflection of the much sharper decline in the proportion of progression-free patients relative to the decline in overall survival. PFS shows only modest durability of response at the 3rd and 4th LoT. These results also highlight the lack of durable response in later LoT. Similarly, TTNT tended to have increasing probabilities of faster events with increasing lines; however, just as the 5th and 6th LoT were less distinguishable for PFS, 3rd and 4th line were close to one another for TTNT.

DISCUSSION

Treatment patterns and clinical outcomes observed in the international SCHOLAR-5 study – a large, contemporary cohort of later line r/r FL patients – demonstrate an important unmet need in real-world treatment of this vulnerable population. Importantly, this study demonstrates that there is no clear consensus for treatment choice in later lines, with a multiplicity of treatments used in each region, and experimental treatments more commonly utilized in later lines in both the US and Europe. Despite excluding cases of transformation, these findings from the SCHOLAR-5 r/r FL cohort suggest the likelihood, quality, and duration of clinical response decreases with each subsequent LoT, regardless of the type of treatment or geographic region. In other words, available therapies leave an unmet need for some patients with r/r FL who require therapy beyond 2nd line.

SCHOLAR-5 can be contextualized with respect to five recently published r/r FL patient cohorts; however, direct comparisons between patient cohorts can be challenging and should be interpreted with caution. Three cohorts were published prior to SCHOLAR-5, including single-center cohorts from the US (Batlevi et al, 2020) and Japan (Fuji et al, 2020) and a large multicenter cohort from the US (Link et al, 2019).[5, 6, 21] Two additional multicenter cohort studies were conducted at approximately the same time as SCHOLAR-5, namely the ReCORD-FL and LEO CReWE cohorts.[22, 23] There were similarities across all of the patient cohorts. The complete response observed in SCHOLAR-5, 43.9% and 27.1% at 3rd and 4th LoT respectively, are comparable to those published for the Japanese cohort (42.1% and 23.8% at 3rd and 4th LoT, respectively),[21] for ReCORD-FL (37.4% and 32.0% at 3rd and 4th LoT, respectively), and for LEO CReWE (45% at 3rd LoT). For PFS, medians from the five patient cohorts ranged from 10 to 19 months at 3rd LoT and 5 to 12 months at 4th LoT, compared to 11 and 10 months,

respectively, in SCHOLAR-5. [5, 6, 21] The comparison for median OS was more challenging given the shorter follow-up in SCHOLAR-5 (up to 7 years, which was shorter than the anticipated median OS for 3rd LoT patients) due to the restricted time period (2014-2020). The similarity in results between the SCHOLAR-5 and patient cohorts going back to the early 2000s suggests that contemporary treatments (those approved in the 2014-2020 study period) may not offer as significantly improved outcomes over treatments available prior to the introduction of idelalisib. The general alignment of results from SCHOLAR-5, conducted in the US and Europe, to those from the literature (US,[5, 6] Europe,[23] and Japan[21]), suggest that OS and PFS results in r/r FL patients are similar across these regions. In addition, the inverse relationship between length of overall survival and number of LoTs (i.e., shorter survival at higher LoTs) in SCHOLAR-5 is consistent with the trends documented in previously reported cohort studies. In contrast to the other cohorts, LEO-CReWE had a much larger proportion of 3rd LoT patients (94% of patients).[22] Among those 3rd LoT patients, median survival was 169 months, which is higher than results from all the other cohorts, including SCHOLAR-5. It is unclear why median survival in this cohort was notably higher than in the contemporary cohorts.

In this cohort, treatment patterns differed between the US and Europe. Treatment guidelines, product availability (regulatory approvals/reimbursement policies), and physician behavior, can all cause differences in treatment patterns. Timing and availability of novel therapies may differ between the US and Europe, for example access to lenalidomide in r/r FL was highly variable across countries based on regulatory approval and reimbursement, which will have influenced the frequency of this regimen.

The treatment landscape for r/r FL continues to evolve, and the need for treatments in this population that will improve survival outcomes, and lead to more durable remission, remains. Based on retrospective studies, autologous SCT may improve progression-free survival for select patients with r/r FL;[10] however, our data show that this treatment is only used in a small subset of 2L+ patients. Outcomes for relapsed/refractory patients remain poor, despite the availability of EZH2 inhibitors, and immunomodulatory agents, and a limited number of Pi3K inhibitors, with only one being marketed in the US. Moreover, none of these options have demonstrated prolonged periods of durable responses in the majority of patients.[13, 15] Since SCHOLAR-5 was completed, the US FDA granted accelerated approval of axicabtagene ciloleucel, a CAR T-cell therapy, for the treatment of adults with r/r FL after two or more lines of treatment. This approval underscores the critical need for treatments that have the potential to offer durability for patients with r/r FL, a population for whom the prognosis with conventional therapies worsens with each subsequent LoT.

This study adds to a small but growing number of studies that provide insights into the recent treatment landscape and associated outcomes for patients with r/r FL. An important strength of this study was the requirement for biopsy-proven absence of transformation which reduced the potential for misclassification that would have occurred by including patients with transformed FL in the cohort. In addition, as a multi-center and international cohort study, the findings from SCHOLAR-5 can be more generalizable to a wider population as compared to a single-center or single-country study. This study not only describes treatment patterns and outcomes within a substantially sized r/r FL cohort, but also provides insights into treatments and outcomes amongst the US and participating European countries. The insights are based solely on descriptive statistics, similar to the study by Casulo et al.[22], given that the modest sample size

and heterogeneous choices of therapy in 3rd LoT or higher do not lend themselves to statistical testing.

As SCHOLAR-5 data were collected retrospectively and from clinical practice databases, missing or incomplete data were expected. To reduce the impact of this limitation, trained analysts and clinical teams at participating sites curated and enriched the data by reviewing discrepancies, outliers and missing values on key data points, and completing additional data collection, including from review of unstructured data, where possible. As expected in real-world data documenting care provided over several years across many centers, different classification methods were used to assess disease response, and these differences likely introduce more variability into the results as compared to results obtained from the prospective clinical trial setting where procedures, visits, and assessments are outlined per protocol guidance.

As can be seen by the flow diagram for patient selection at MSK (**Figure 1**), strict, clinically-sound criteria were used to identify patients for the SCHOLAR-5 cohort. The benefit of this rigorous selection process is improved likelihood of accurately identifying r/r FL patients who received multiple LoTs for SCHOLAR-5, a patient population who would likely have been amongst the eligible population for treatments, such as CAR T-cell therapies, that have been recently approved in the US and Europe. However, the downside of these strict inclusion criteria, including the required recency of the treatments, and the exclusion of cases of transformation, is that the final sample size was lower than was expected at the outset of the study. As such, relatively few patients had fifth line of therapy or higher. Whilst this precluded the breakdown of outcomes by treatment, it also demonstrated that this population represents patients with a rare disease. The MSK flow diagram also provides insights into the modest resulting sample size for SCHOLAR-5, which is consistent with that reported in other related or

similar studies. A similarly modest patient population was also observed in the recently published RECORD-FL control cohort,[23] where 143 patients initiating 3rd LoT or higher as far back as 2000 were included. In a sub-group analysis that matched the SCHOLAR-5 study period, only 60 initiated 3rd LoT or higher. SCHOLAR-5 patient selection also aligns with the recruitment rate of ZUMA-5.

By restricting our study to a more contemporary setting, we limited the follow-up time for patients within an indolent population. This shorter follow-up time complicates the estimation of median OS, which is expected to be longer than our maximum follow-up time. This in turn impedes naïve comparisons to other patient cohorts. In addition, patients treated with CAR-T were excluded from this cohort due to the lack of data during this observation period.

In conclusion, SCHOLAR-5, an international retrospective cohort of r/r FL patients from seven major lymphoma centers in the US and Europe, highlights the lack of a definitive standard of care for r/r FL patients. Despite inclusion of new and experimental treatments (excluding CAR T-cell therapies) that were available during the study period, fewer patients had a documented clinical responses in later lines of therapy, and the duration of treatment response diminished with each subsequent line. Newly approved therapies, such as CAR T-cell therapies, have shown efficacy in the trial setting, and future studies will be needed to assess their impact in addressing the need for improved response and survival among r/r FL patients in the routine care setting.

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Table 1. 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			
0-1	66 (93.0%)	28 (93.3%)	94 (93.0%)
2-4	5 (7.0%)	2 (6.7%)	7 (7.0%)
*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%)
Size of largest nodal mass – no. (%)			
≥ 7cm	13 (30.2)	9 (23.1%)	22 (26.8%)
*Missing**	*35*	*11*	*46*

** 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 2. Clinical outcomes by LoT

		3rd LoT	4th LoT	≥ 5th LoT
Response outcomes (best)				
ORR	N responders % (95% CI)	56/82 68.3% (57.1 – 78.1)	37/59 62.7% (49.1 – 74.9)	24/65 37.2% (25.2 – 51.1)
CR	N responders % (95% CI)	36/82 43.9% (33.0 – 55.3)	16/59 27.1% (16.4 – 40.3)	14/65 21.5% (13.2 – 33.2)
Time-to-event outcomes				
		N = 87	N = 63	N = 47*
OS	Median months (95% CI)	67.6 (60.1 – NE)	NR (30.4 – NE)	42.8 (15.3 – NE)
	18 months % (95% CI)	86.5 (79.4 – 94.3)	83.1 (74.0 – 93.2)	59.5 (46.6 – 76.0)
	24 months % (95% CI)	83.7 (76.0 – 92.3)	72.7 (61.7 – 85.7)	54.3 (41.2 – 71.5)
	36 months % (95% CI)	77.8 (68.9 – 87.8)	60.7 (48.3 – 76.3)	51.3 (38.1 – 69.0)
	60 months % (95% CI)	62.6 (50.1 – 78.2)	52.4 (38.4 – 71.6)	38.0 (22.6 – 63.9)
PFS	Median months (95% CI)	11.0 (9.0 – 17.9)	9.7 (6.2 – 16.7)	3.9 (3.0 – 8.5)
	18 months % (95% CI)	33.5 (23.1 – 48.6)	23.1 (12.7 – 41.8)	9.9 (4.3 – 22.8)
	24 months % (95% CI)	16.8 (9.1 – 31.0)	10.4 (3.8 – 28.6)	7.9 (3.1 – 20.2)
	36 months % (95% CI)	13.4 (6.3 – 28.5)	6.9 (1.9 – 25.2)	--
	60 months % (95% CI)	--	--	--
TTNT	Median months (95% CI)	20.1 (15.7 – 40.0)	17.9 (14.9 – 24.2)	7.1 (4.3 – 17.4)
	18 months % (95% CI)	53.3 (43.4 – 65.5)	48.9 (37.2 – 64.1)	33.1 (22.7 – 48.3)
	24 months % (95% CI)	41.8 (32.0 – 54.5)	36.1 (25.1 – 52.0)	31.5 (21.5 – 46.0)
	36 months % (95% CI)	37.3 (27.8 – 50.1)	28.3 (17.9 – 44.8)	25.1 (15.0 – 41.8)
	60 months % (95% CI)	23.2 (13.9 – 38.9)	19.8 (10.0 – 39.4)	--

** For ≥5 LoT, 72 eligible lines from 47 patients were included in the analysis, with the exception of OS which included only the first eligible line per patient. CI: confidence interval; 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.*

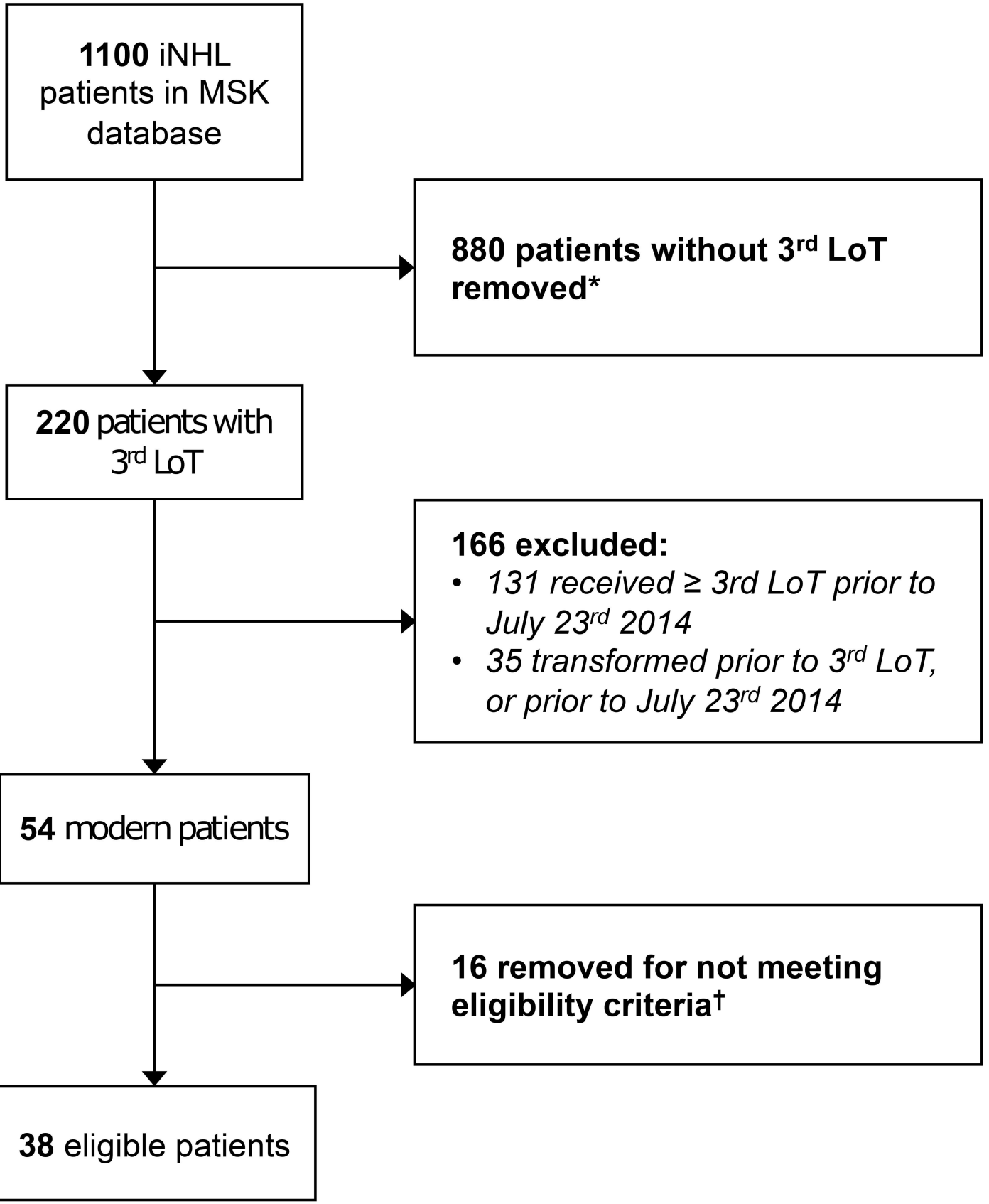
Figure legends

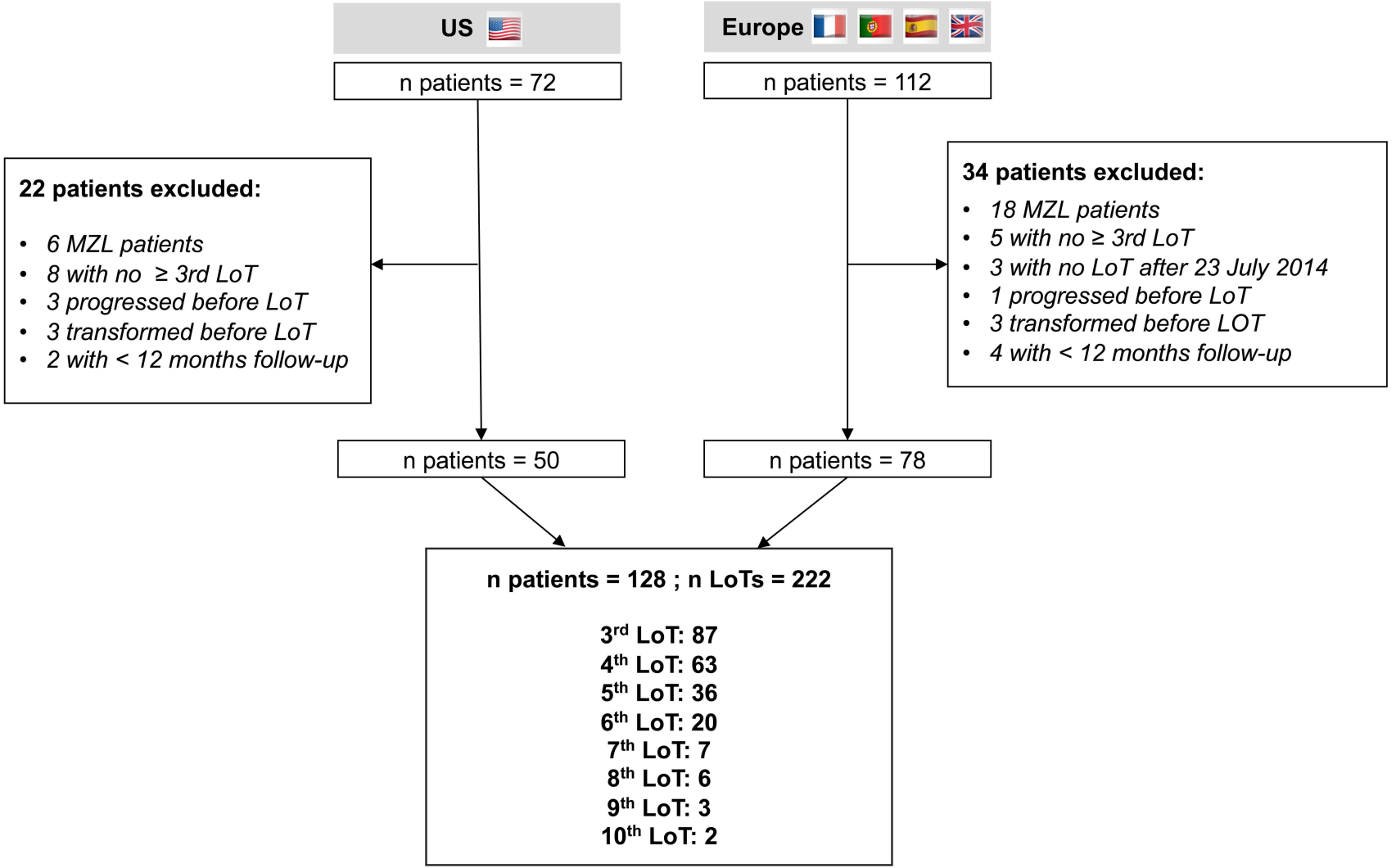
Figure 1: Flowchart of patient selection at Memorial Sloan Kettering Cancer Center.
† Eligibility criteria were patients aged ≥18 years; with histologically confirmed diagnosis of iNHL, with histological subtype limited to FL Grade 1, Grade 2, or Grade 3a based on criteria established by the World Health Organization (WHO) 2016 classification; with r/r disease (i.e., r/r iNHL). Patients with transfomed FL, FL Histological Grade 3b, prior anti-CD19 CAR T-cell therapy or other genetically modified T-cell therapy were excluded. Patient were only included if eligible within 12 months before the last updated version of the sites database

Figure 2: Flowchart of patient and LoT exclusion by continent.
Sixty patients contributed multiple LoT to the analysis set, with these patients contributing a median of 2 LoT (range: 2 – 6). FL, follicular lymphoma; LoT, line of treatment.

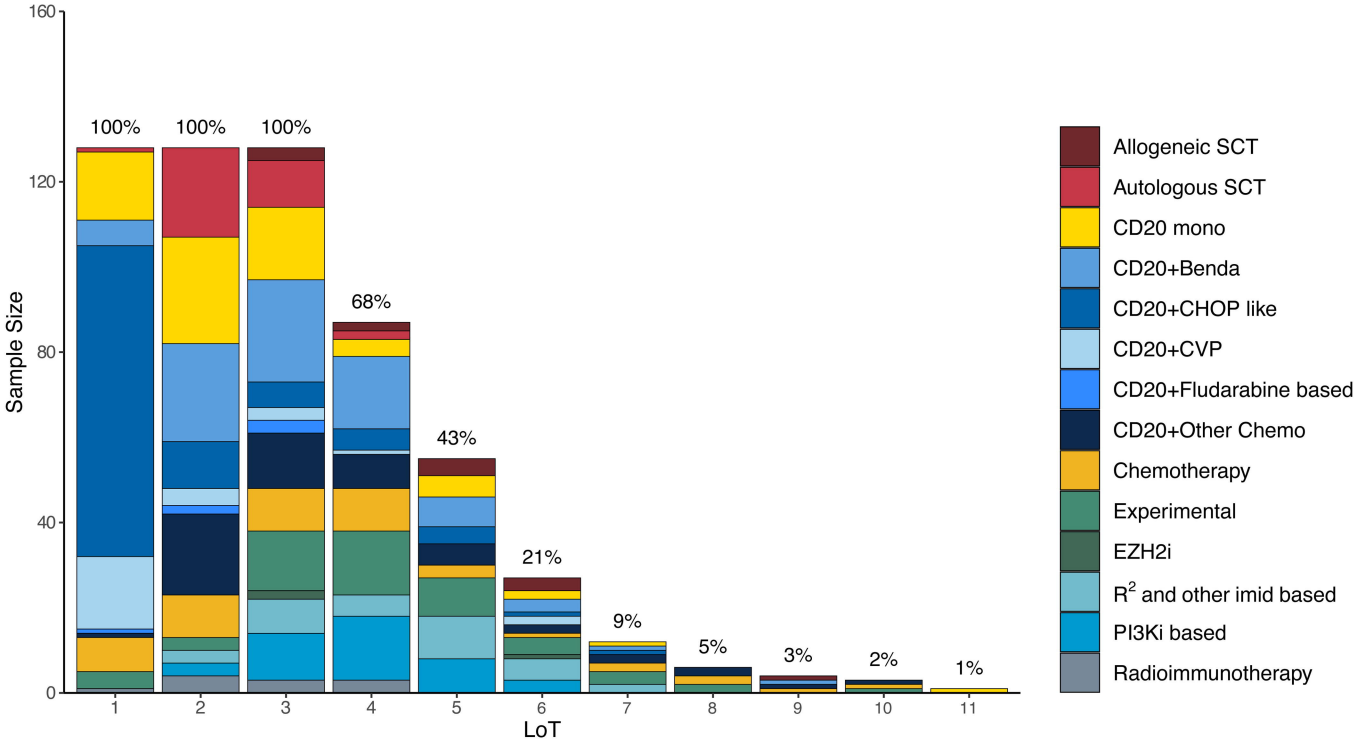
Figure 3: Treatment patterns
Experimental category does not include recently accepted treatments (PI3K-δ inhibitors, R^2, and EZH2i), even if they were not approved at the time of the study.
A. Treatments received by eligible patients, by LoT. The percentage values represent the proportion of patients who contribute to each LoT. B. Eligible third LoT by continent. C. Eligible fourth LoT by continent. Note that panel A includes treatments received prior to the approval of idelalisib, whereas panels B and C include only treatments received after 23rd July 2014.
Benda - bendamustine; CD20 - anti CD20 monoclonal antibodies; Chemo, chemotherapy; CHOP - cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP - cyclophosphamide, vincristine, prednisolone; EZH2i = Enhancer of zeste homolog 2 specific inhibitors, IMiD = immunomodulatory drugs; R^2 = rituximab and lenalidomide; SCT = stem cell transplant; PI3Ki = phosphoinositide 3-kinase inhibitor.

Figure 4: Survival curves by LoT
A. Overall survival and B. progression free survival by LoT. Blue, third LoT; green, fourth LoT; yellow, fifth LoT; red, sixth LoT.


1100 iNHL patients in MSK database
880 patients without 3rd LoT removed*
220 patients with 3rd LoT
166 excluded:
• 131 received ≥ 3rd LoT prior to July 23rd 2014
• 35 transformed prior to 3rd LoT, or prior to July 23rd 2014
54 modern patients
16 removed for not meeting eligibility criteria†
38 eligible patients

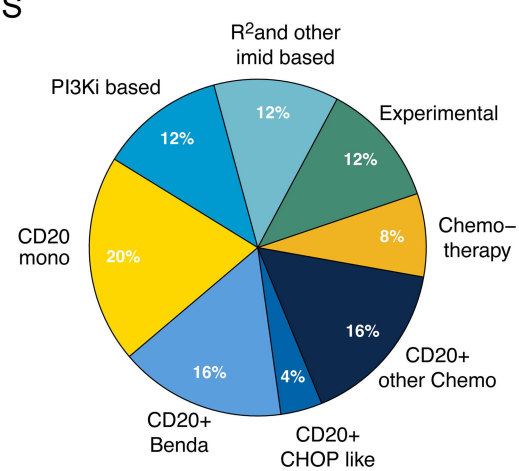

US
n patients = 72
22 patients excluded:
6 MZL patients
8 with no ≥ 3rd LoT
3 progressed before LoT
3 transformed before LoT
2 with < 12 months follow-up
n patients = 50
Europe
n patients = 112
34 patients excluded:
18 MZL patients
5 with no ≥ 3rd LoT
3 with no LoT after 23 July 2014
1 progressed before LoT
3 transformed before LOT
4 with < 12 months follow-up
n patients = 78
n patients = 128 ; n LoTs = 222
3rd LoT: 87
4th LoT: 63
5th LoT: 36
6th LoT: 20
7th LoT: 7
8th LoT: 6
9th LoT: 3
10th LoT: 2

A. Treatment patterns across all LoTs

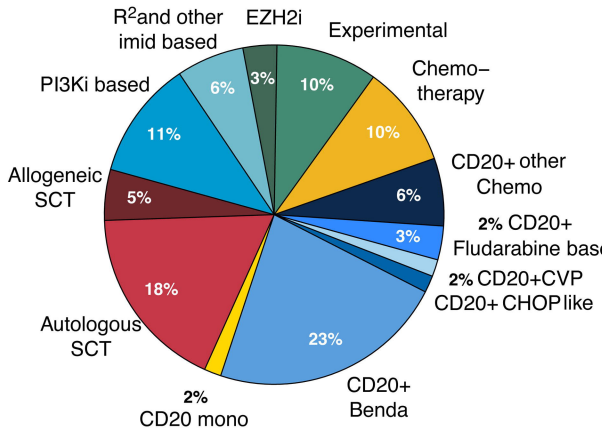


B. Third-line treatments in the anlaysis set

US

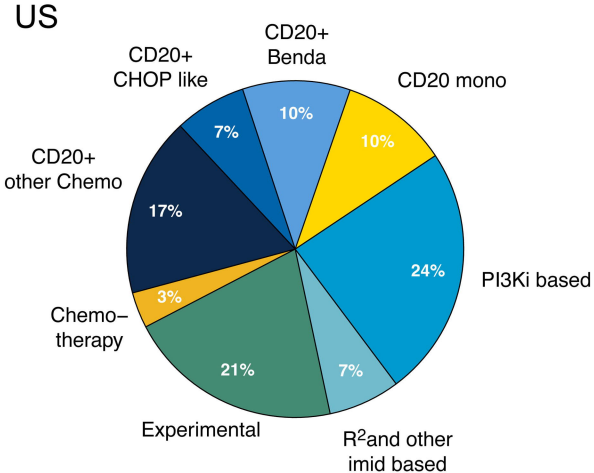


Europe

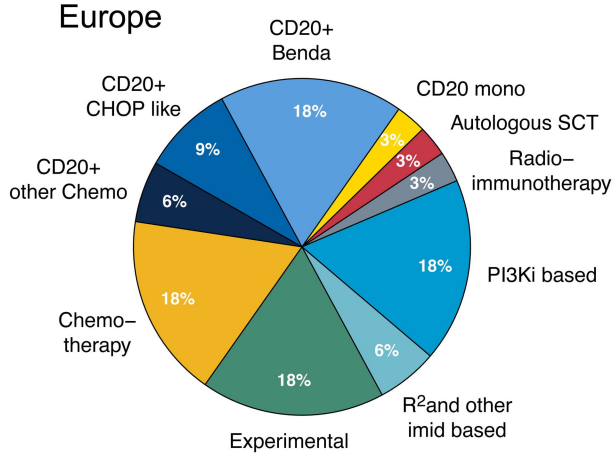


C. Fourth-line treatments in the anlaysis set

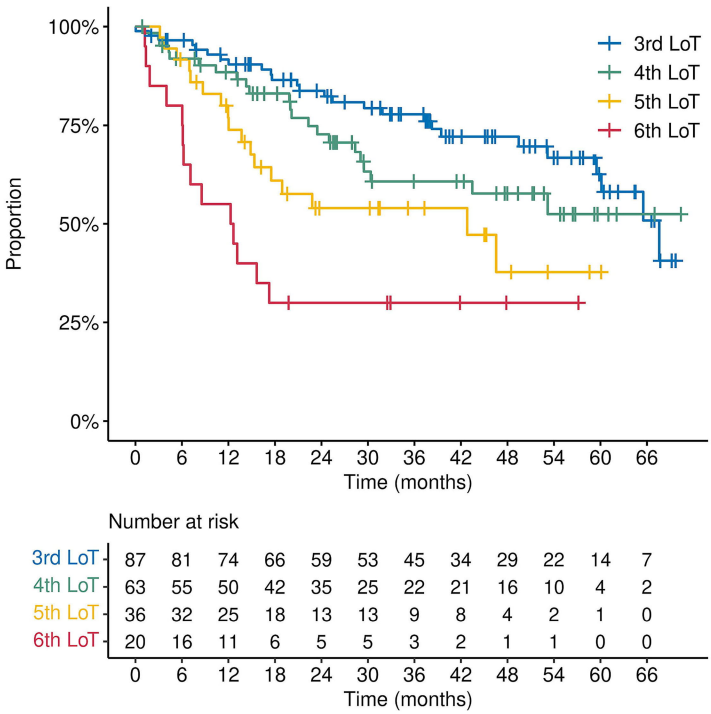
US



Europe



A. Overall survival

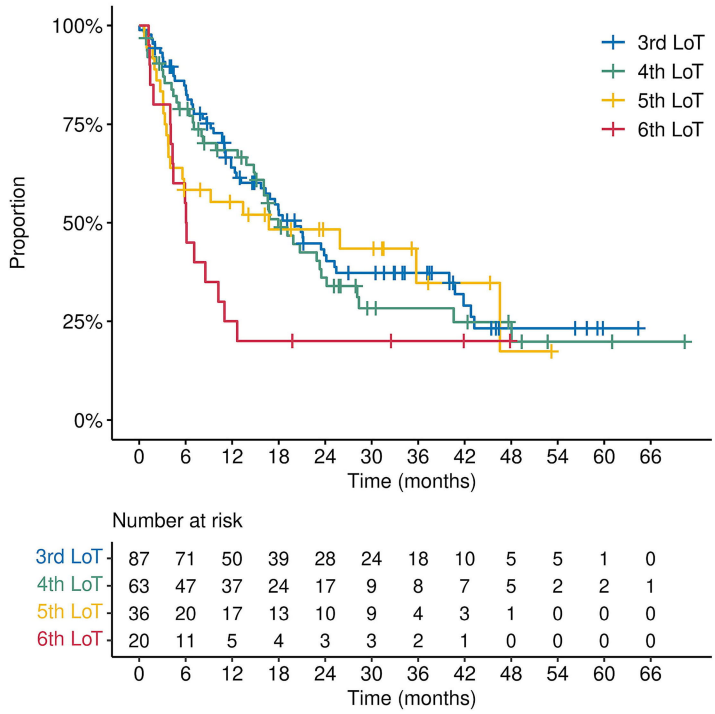


Number at risk

	0	6	12	18	24	30	36	42	48	54	60	66
3rd LoT	87	81	74	66	59	53	45	34	29	22	14	7
4th LoT	63	55	50	42	35	25	22	21	16	10	4	2
5th LoT	36	32	25	18	13	13	9	8	4	2	1	0
6th LoT	20	16	11	6	5	5	3	2	1	1	0	0

Time (months)

C. Time to next treatment

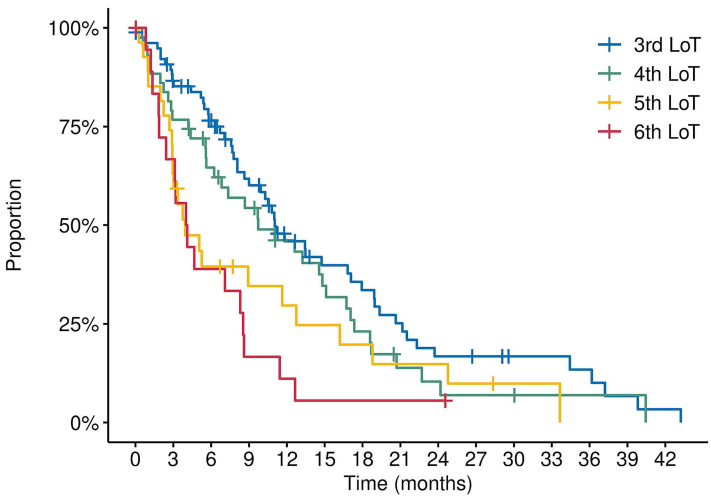


Number at risk

	0	6	12	18	24	30	36	42	48	54	60	66
3rd LoT	87	71	50	39	28	24	18	10	5	5	1	0
4th LoT	63	47	37	24	17	9	8	7	5	2	2	1
5th LoT	36	20	17	13	10	9	4	3	1	0	0	0
6th LoT	20	11	5	4	3	3	2	1	0	0	0	0

Time (months)

B. Progression-free survival



Number at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
3rd LoT	87	62	52	37	24	19	16	12	8	7	5	5	4	2	1
4th LoT	63	33	26	21	16	12	8	4	3	2	2	1	1	1	0
5th LoT	36	17	10	7	6	5	4	3	3	2	1	1	0	0	0
6th LoT	20	12	7	3	2	1	1	1	1	0	0	0	0	0	0

Time (months)

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**

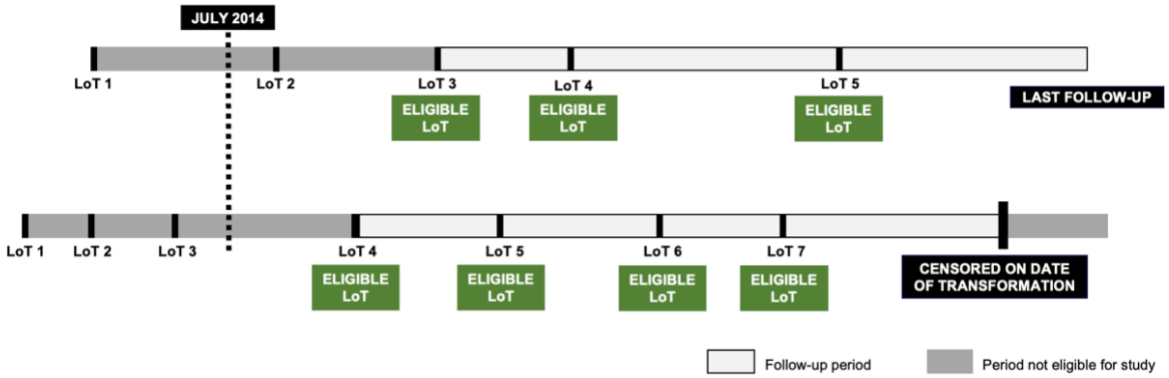
Treatment regiments by line of therapy, including only the eligible lines that were included in the analyses. Experimental category does not include recently accepted treatments (PI3K-δ inhibitors, R^2, and EZHi), even if they were not approved at the time of the study. Radiotherapy alone was not considered 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)	--

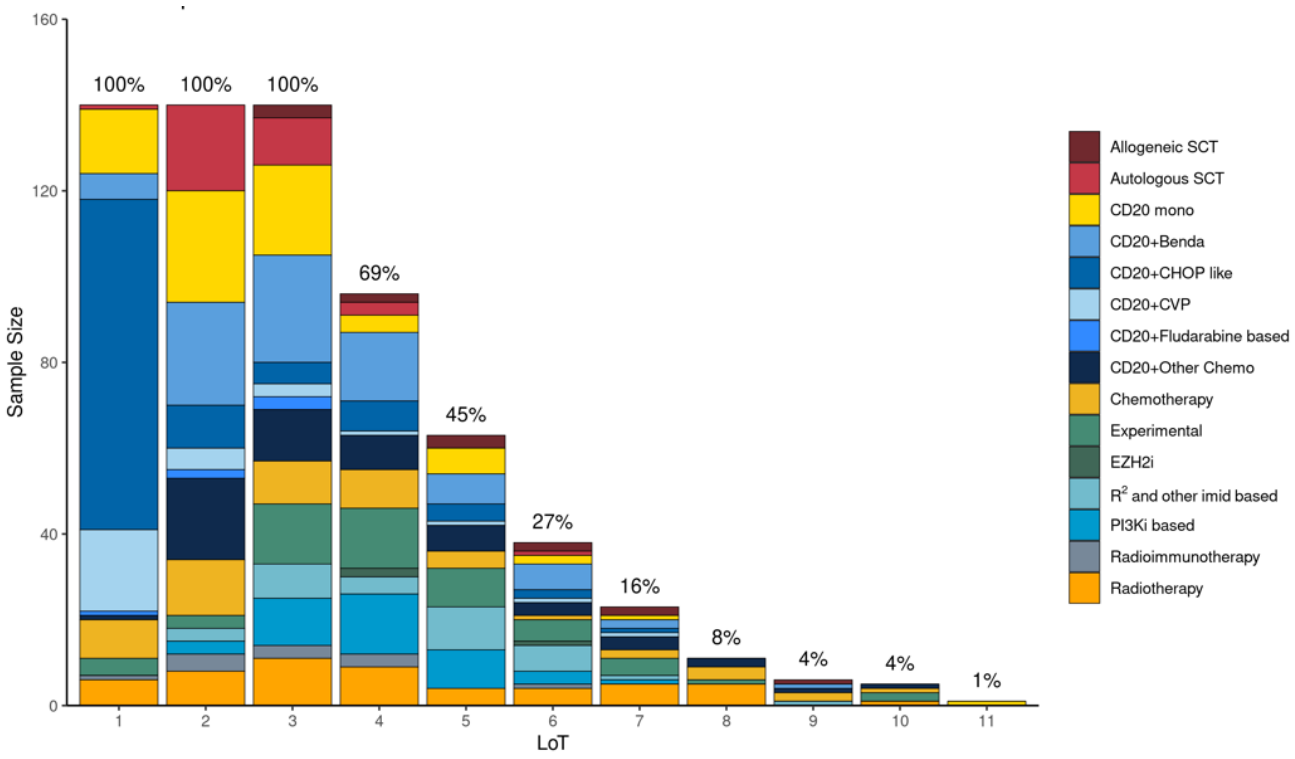
** For ≥5 LoT, multiple LoTs could be included per participant, with the exception of OS which included only the first eligible line per patient. CI: confidence interval; m: months; LoT: Line of therapy; ORR: Overall response rate; CR: Complete response; OS: Overall survival; PFS: Progression-free survival; 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.

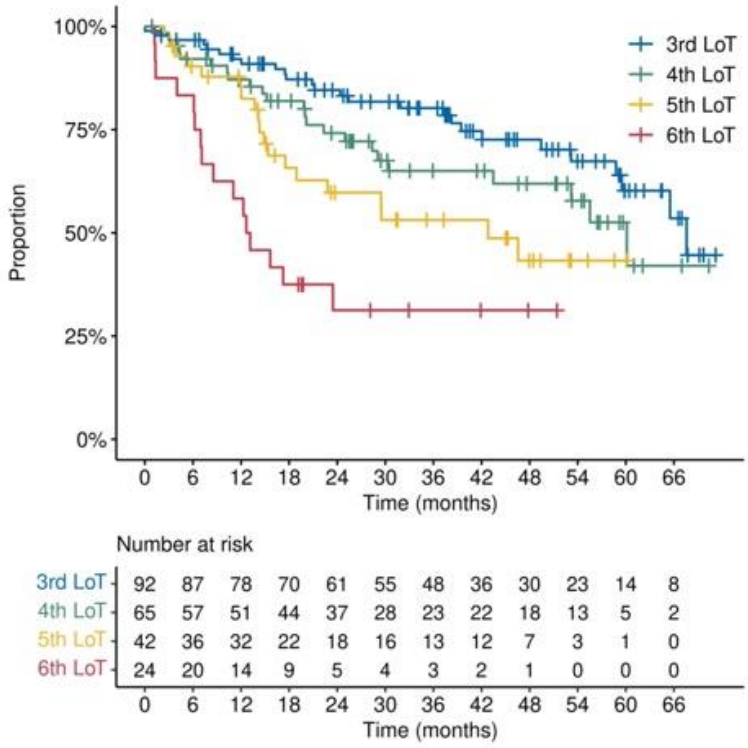
Figure S2 : Treatment patterns across all LoTs when radiotherapy alone is included



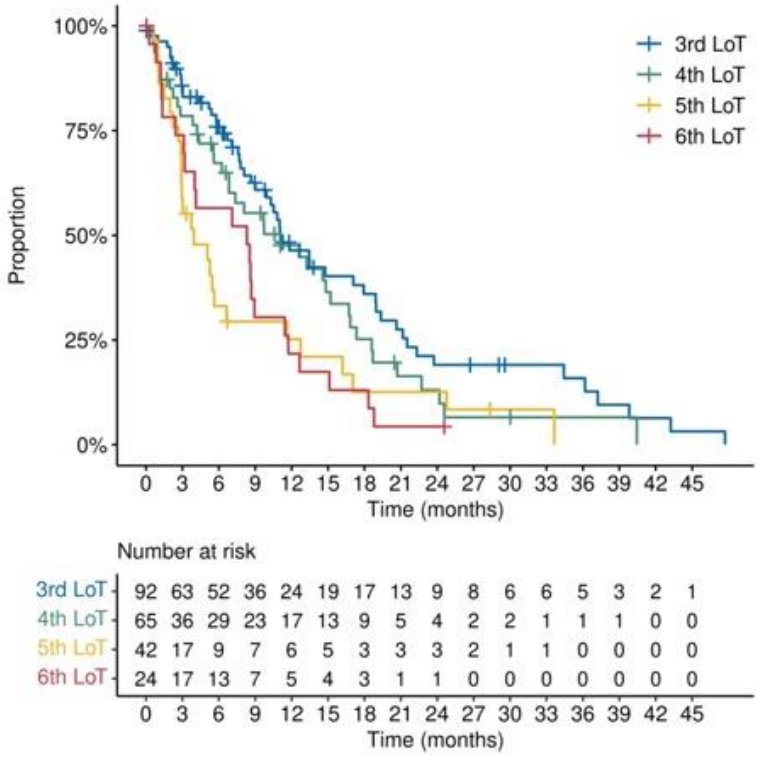
Experimental category does not include recently accepted treatments (PI3K-δ inhibitors, R^2, and EZH2i), even if they were not approved at the time of the study.. The percentage values represent the proportion of patients who contribute to each LoT.

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

a. Overall survival



b. Progression-free survival



c. Time-to-next treatment