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

Paola Ghione,[1,2*] Maria Lia Palomba,[2*] Hervé Ghesquieres,[3] Sabela Bobillo,[4] Anik R Patel,[5] Myrna Nahas,[5] Steve Kanters,[6] Kevin Deighton,[7] Anthony Hatswell,[7] Long Ma,[5] Eve H. Limbrick-Oldfield,[6] Julia Thornton Snider,[5] Sally W. Wade,[8] Maria Teresa Riberio,[9] John Radford,[10] Sara Beygi[5] and John Gribben[11]

[1]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]Centre Hospitalier Lyon Sud, Lyon, France; [4]Vall D'Hebron Insitute of Oncology, Barcelona, Spain; [5]Kite, A Gilead Company, Santa Monica, CA, USA; [6]RainCity Analytics, Vancouver, British Columbia, Canada; [7]Delta Hat, Nottingham, UK; [8]Wade Outcomes Research and Consulting, Salt Lake City, UT, USA; [9]Portuguese Oncology Institute of Porto, Porto, Portugal; [10]The Christie NHS Foundation Trust and University of Manchester, Manchester, UK and [11]Barts Cancer Institute, Queen Mary University of London, London, UK

**PG and MLP contributed equally as co-first authors*

Correspondence: M.L. Palomba
palombam@mskcc.org

Received: June 1, 2022.
Accepted: October 7, 2022.
Early view: October 20, 2022.

https://doi.org/10.3324/haematol.2022.281421

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 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 LoT. 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 CR 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 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 and European Society for Medical Oncology 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 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 LoT. 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, multicenter, 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 *Online Supplementary Appendix S1.1*.

Study population and follow-up

In order 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 the *Online Supplementary Appendix S1.2 and S1.3* 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 LoT. 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 1,100 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 predefined 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 two prior LoT after re-alignment with the study LoT definition. Sixteen patients did not have an eligible ≥ 3rd 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 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 *Online Supplementary 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 LoT, (panel A), and then separated by geography for 3rd and 4th LoT (panels B and C). The majority

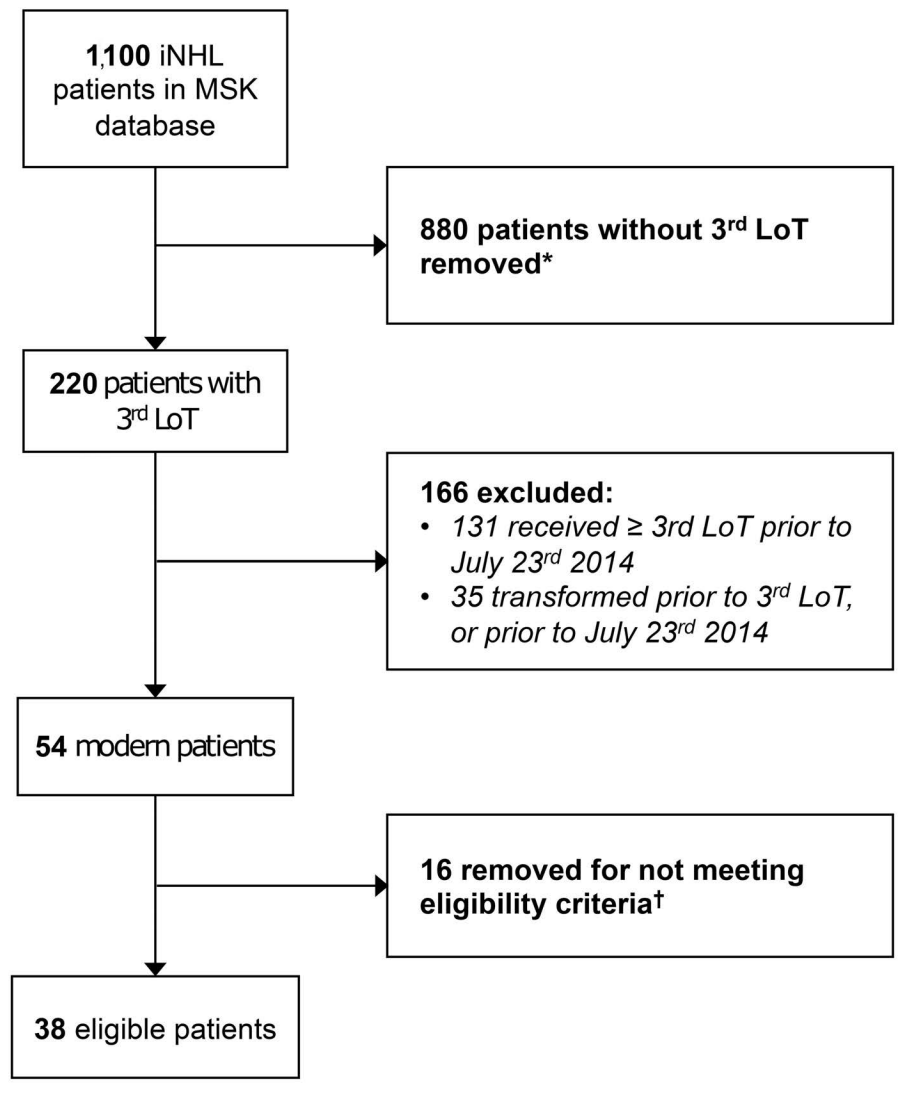


Figure 1. Flowchart of patient selection at Memorial Sloan Kettering Cancer Center. †Eligibility criteria were patients aged ≥18 years; with histologically confirmed diagnosis of indolent non-Hodgkin lymphoma (iNHL), with histological subtype limited to follicular lymphoma (FL) grade 1, grade 2, or grade 3a based on criteria established by the World Health Organization 2016 classification; with relapsed/refractory (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.

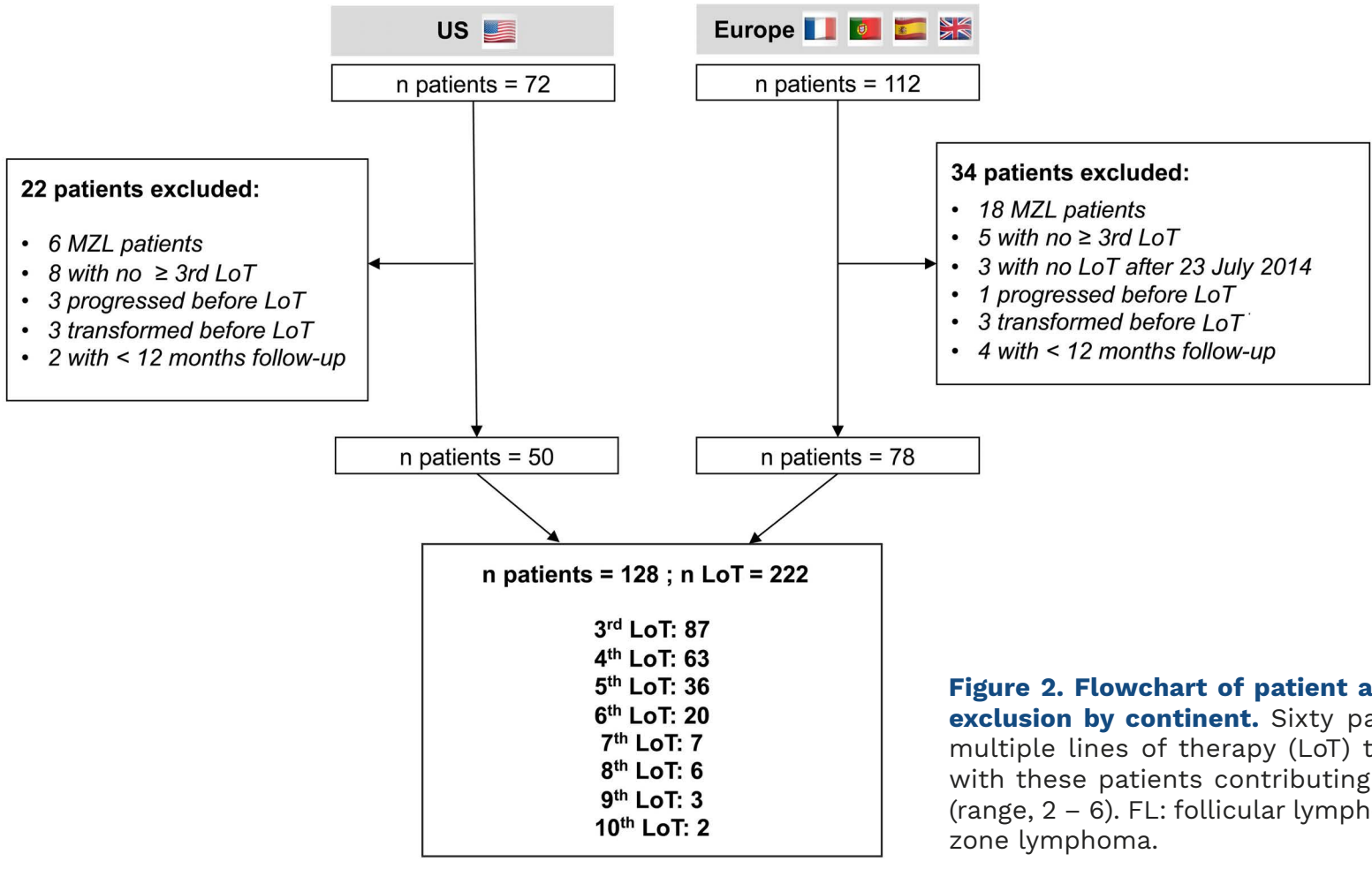


Figure 2. Flowchart of patient and line-of-therapy exclusion by continent. Sixty patients contributed multiple lines of therapy (LoT) to the analysis set, with these patients contributing a median of 2 LoT (range, 2 – 6). FL: follicular lymphoma. MZL: marginal zone lymphoma.

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 *Online Supplementary 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 line of treatment

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 time point 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 LoT 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 (*Online Supplementary 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

Table 1. Baseline characteristics at first eligible line of therapy.

	Europe	US	Overall
Sample size	**78**	**50**	**128**
Age in 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, N (%)	41 (52.6)	32 (64.0)	73 (57.0)
Follicular lymphoma subtype, N (%)			
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, N (%)			
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, N (%)			
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†, N (%)			
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, N (%)	24 (30.8)	10 (20.0)	34 (26.6)
Bone marrow involvement at index date, N (%)	16 (38.1)	3 (18.2)	18 (34.0)
*Missing**	*36*	*34*	*70*
Prior SCT, N (%)			
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, N(%)			
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, N (%)			
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, N (%)			
≥ 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 complete response, partial response or stable disease >6 months after completion of the most recent prior treatment. All characteristics are at or within 6 months of the initiation of 1st eligible line of treatment in analysis, with the exception of disease stage and FLIPI, which are at diagnosis. POD24: having progressed within 24 months of 1st line anti-CD20 monoclonal antibody and chemotherapy combination; FLIPI: Follicular Lymphoma International Prognostic Index.

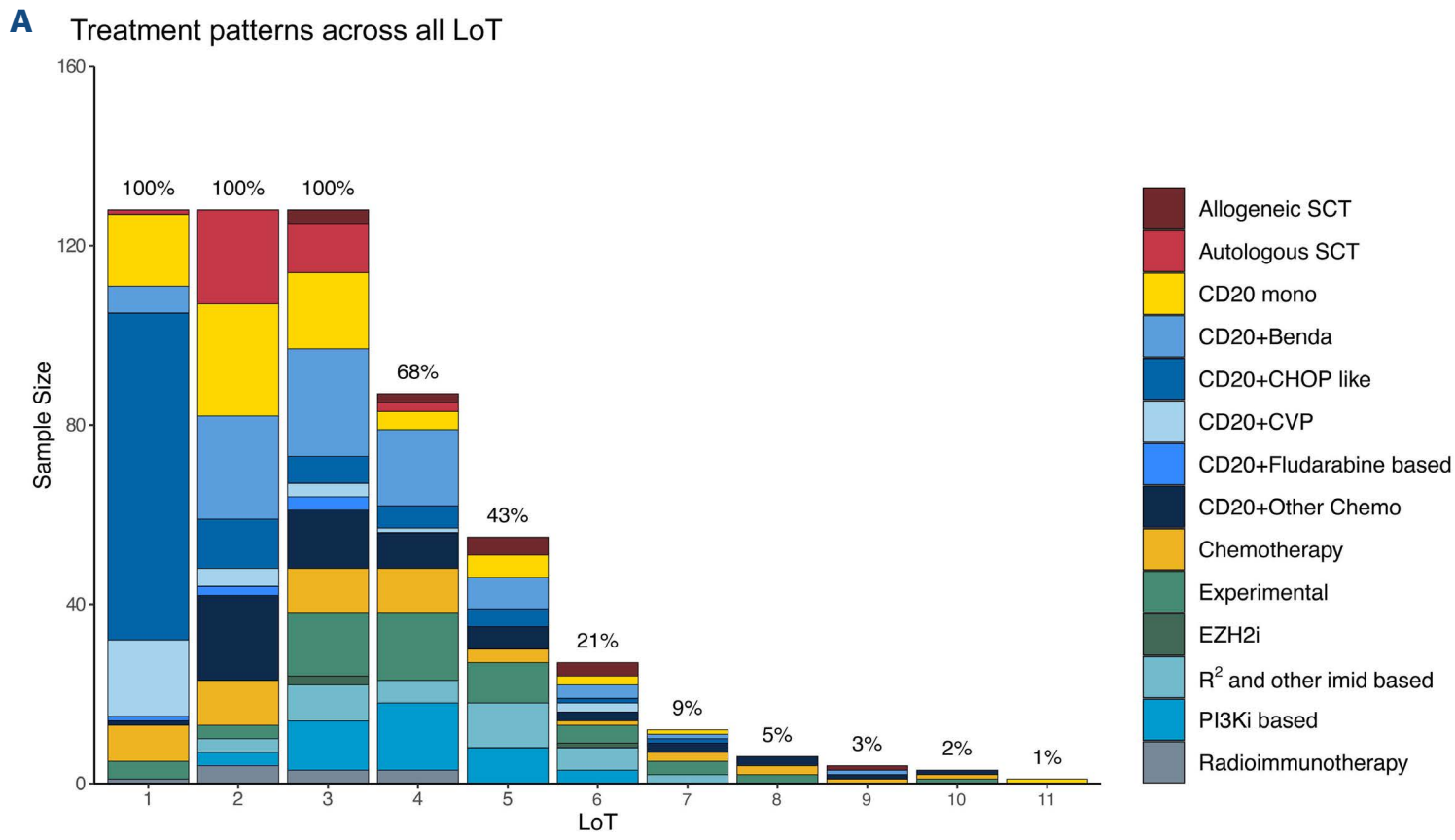


Figure 3. Treatment patterns. Experimental category does not include recently accepted treatments (PI3K-δ inhibitors, R^2, and EZH2i), even if they were not approved at the time of the study. (A) Treatments received by eligible patients, by line of therapy (LoT). The percentage values represent the proportion of patients who contribute to each LoT. (B) Eligible 3rd LoT by continent. (C) Eligible 4th LoT by continent. Note that (A) includes treatments received prior to the approval of idelalisib, whereas (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, ImiDs: immunomodulatory drugs; R^2: rituximab and lenalidomide; SCT: stem cell transplant; PI3Ki: phosphoinositide 3-kinase inhibitor.

Table 2. Clinical outcomes by line of therapy.

		3rd LoT	4th LoT	≥ 5th LoT
Response outcomes (best)				
ORR	N responders	56/82	37/59	24/65
	% (95% CI)	68.3 (57.1-78.1)	62.7 (49.1-74.9)	37.2(25.2-51.1)
CR	N responders	36/82	16/59	14/65
	% (95% CI)	43.9 (33.0- 55.3)	27.1 (16.4-40.3)	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 line of therapy (LoT), 72 eligible lines from 47 patients were included in the analysis, with the exception of overall survival (OS) which included only the 1st eligible line per patient. CI: confidence interval; ORR: overall response rate; CR: complete response; 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 time point. ne: not estimable; nr: not reached.

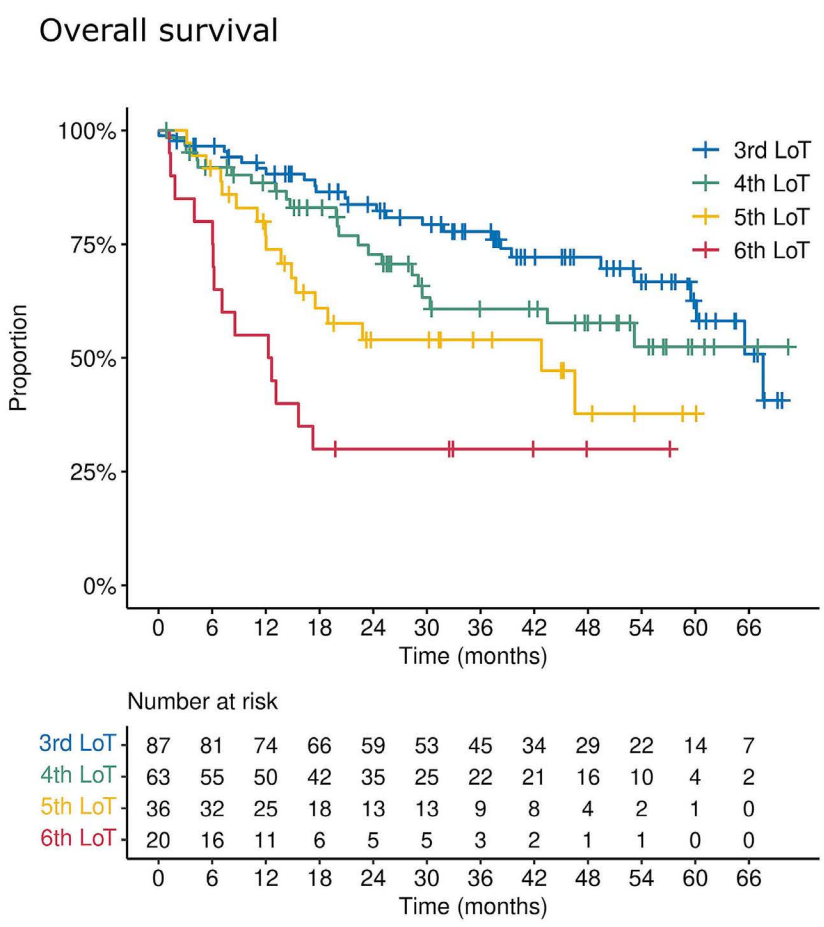
the lower LoT, PFS at 24 months was 16.8% for 3rd LoT, 10.4% for 4th LoT, and 7.9% at ≥5th LoT (Figure 4B). There were no clear trends for PFS and OS when examining the 5th and 6th LoT separately. This is partially a reflection of the much sharper decline in the proportion of progression-free patients relative to the decline in OS. 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.

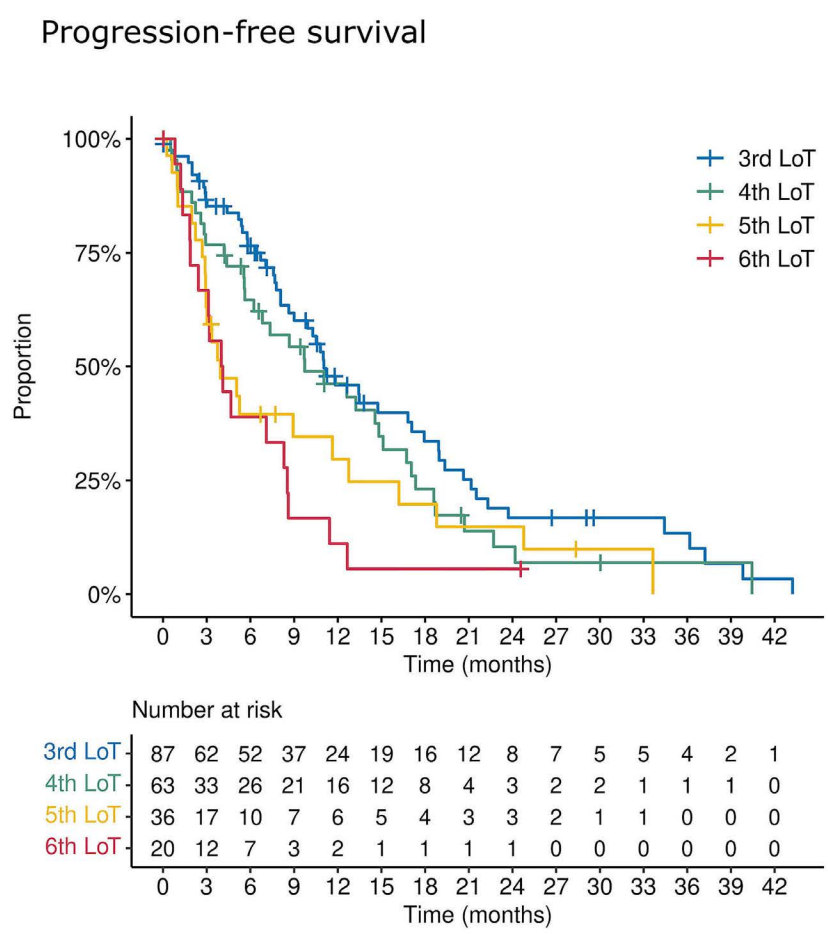
Discussion

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.*) and Japan (Fuji *et al.*) and a large multicenter cohort from the US (Link *et al.*).[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 LoT (i.e., shorter survival at higher LoT) in SCHOLAR-5 is consistent with the trends docu-





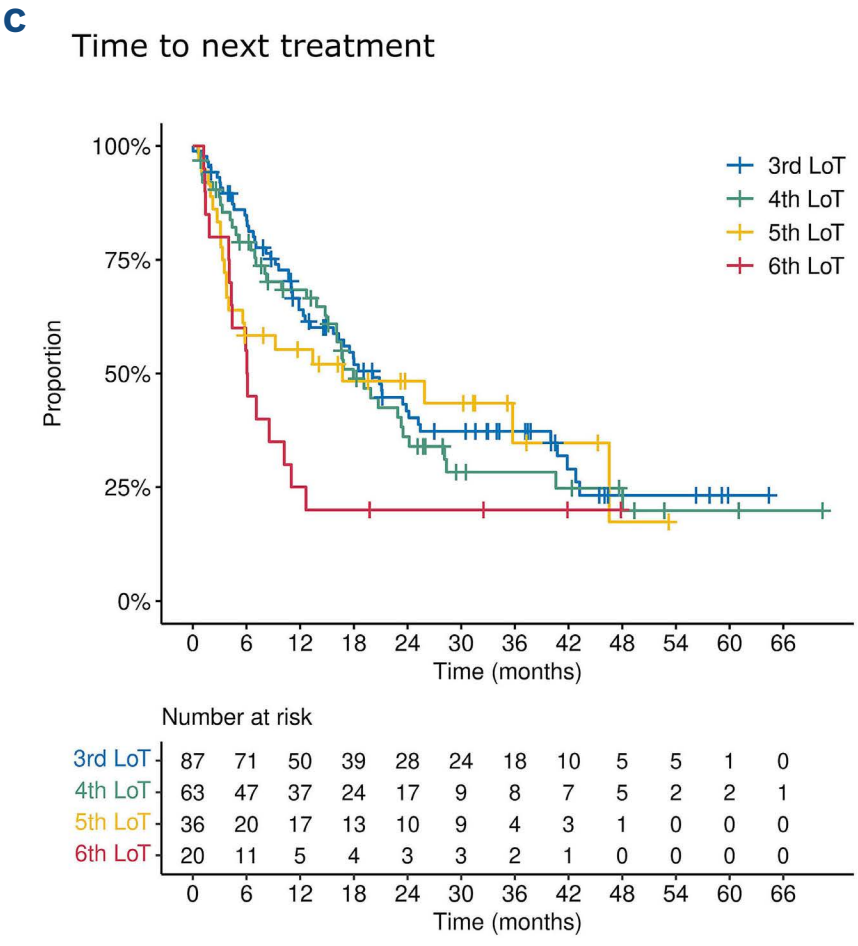


Figure 4. Survival curves by line of therapy. (A) Overall survival and (B) progression-free survival by line of therapy (LoT). Blue: 3rd LoT; green: 4th LoT; yellow: 5th LoT; red: 6th LoT. (C) Time to next treatment.

mented 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, ASCT may improve PFS 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 Food and Drug Administration 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. In order 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 LoT 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 5th 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.

Disclosures

PG is a consultant or advisory board member of AstraZeneca and Daiichi Sankyo. MLP is a consultant of or has advisory role at Novartis, Kite, PCYC and BeiGene; has stock ownership of Seres and Notch; has received research funding from Seres; as well as other remunerations including patents, royalties, other IP from Juno, Seres and Wolters Kluwer. HG is a consultant or advisory role member of Gilead Sciences, Celgene and Roche; has received honoraria from Gilead, Janssen and Celgene; has received travel grants from Roche, Gilead Sciences, Celgene and Takeda. SBo is a consultant or has an advisory role at Jansen, Celgene and Roche. AP is employed by or has a leadership position at Kite, a Gilead company; has stock ownership of Kite, a Gilead company. MN is employed by or has a leadership position at Kite, a Gilead company; has stock ownership of Kite, a Gilead company. SK is employed by or has a leadership position at RainCity Analytics; has received research funding from RainCity Analytics; has received funds from for profit healthcare companies for research. KD and AH are employed by or have a leadership position at Delta Hat. LM is employed by or has a leadership position at Kite, a Gilead company. EHLO is employed by or has a leadership position at RainCity Analytics. JTS is employed by or has a leadership position at Kite, a Gilead company; has stock ownership of Gilead Sciences. SWW is a consultant for or has an advisory role at Kite Pharma, Amgen and Allergan. MTR has no conflicts of interests to be declare. JR is a consultant for or has an advisory role at Takeda, ADCT, BMS, Novartis and KitePharma; has stock ownership of ADCT & AZ (spouse); has received honoraria from Takeda, ADCT, BMS, Novartis and KitePharma; has received other remunerations i.e., speaker's bureau and expert testimony at Takeda and ADCT. SBe is employed by or has a leadership position at Kite, a Gilead company; has stock ownership of Kite, a Gilead company. JG is a consultant or has an advisory role at AZ; has received research funding from Janssen and AZ.

Contributions

The study design and analysis were conducted in a collaboration between Kite, a Gilead Company (study sponsor), and the authors. PG, LP, HG, MTR, SB, SK, AP, JR and JG contributed to data collection and verification. SK, EHLO and KD contributed to data verification and data analysis. All authors contributed to results interpretation, writing of the manuscript and approved the final submitted version. The corresponding author had final responsibility for the decision to submit for publication.

Acknowledgments

We thank patients, family, friends and caregivers as well as the study staff. In addition to the listed authors, support for ethics, data collection and management was provided by Anna Purdum of Kite, a Gilead Company; Victoria Tse, Herve Besson, Nikita Jeswani, and Domitilla Masi, of IQVIA, with funding from Kite, a Gilead Company; Janet Matthews and Sarah Mueller of Cancer Research UK Barts Center; Clare Day and Emma Armstrong of the Christie NHS Foundation; Marion Choquet and Maryam Idlhaj of Centre Hospitalier Lyon Sud; Michelle Okwali of Memorial Sloan Kettering Cancer Center; Yasmina Bernabe of Vall d'Hebron Institute of Oncology; Marina Borges and Maria José Bento of Instituto Português de Oncologia do Porto Francisco Gentil.

Funding

This study was supported by Kite, a Gilead Company.

Data-sharing statement

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

References

1. Gribben JG. How I treat indolent lymphoma. Blood. 2007;109(11):4617-4626.
2. Al-Hamadani M, Habermann TM, Cerhan JR, Macon WR, Maurer MJ, Go RS. Non-Hodgkin lymphoma subtype distribution, geodemographic patterns, and survival in the US: a longitudinal analysis of the National Cancer Data Base from 1998 to 2011. Am J Hematol. 2015;90(9):790-795.
3. Flinn IW, van der Jagt R, Kahl BS, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood. 2014;123(19):2944-2952.
4. Wang TP, Scott JH, Barta SK. The evolving role of targeted biological agents in the management of indolent B-cell lymphomas. Ther Adv Hematol. 2017;8(12):329-344.
5. Batlevi CL, Sha F, Alperovich A, et al. Follicular lymphoma in the modern era: survival, treatment outcomes, and identification of

high-risk subgroups. Blood Cancer J. 2020;10(7):74.
6. Link BK, Day BM, Zhou X, et al. Second-line and subsequent therapy and outcomes for follicular lymphoma in the United States: data from the observational National LymphoCare Study. Br J Haematol. 2019;184(4):660-663.
7. National Institute for Health and Care Excellence. Single technology appraisal - Idelalisib for treating follicular lymphoma refractory to 2 treatments [ID1379]. 2018 Available from: https://www.nice.org.uk/guidance/ta604/evidence/appraisal-consultation-committee-papers-pdf-6906724813.
8. Dreyling M, Ghielmini M, Rule S, et al. Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021;32(3):298-308.
9. Zelenetz AD, Gordon LI, Chang JE, et al. NCCN Guidelines® Insights: B-cell lymphomas, Version 5.2021. J Natl Compr Canc Netw. 2021;19(11):1218-1230.
10. Al Khabori M, de Almeida JR, Guyatt GH, Kuruvilla J, Crump M. Autologous stem cell transplantation in follicular lymphoma: a systematic review and meta-analysis. J Natl Cancer Inst. 2012;104(1):18-28.
11. Leonard JP, Jung SH, Johnson J, et al. Randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma: CALGB 50401 (Alliance). J Clin Oncol. 2015;33(31):3635-3640.
12. Robinson KS, Williams ME, van der Jagt RH, et al. Phase II multicenter study of bendamustine plus rituximab in patients with relapsed indolent B-cell and mantle cell non-Hodgkin's lymphoma. J Clin Oncol. 2008;26(27):4473-4479.
13. Dreyling M, Santoro A, Mollica L, et al. Phosphatidylinositol 3-kinase inhibition by copanlisib in relapsed or refractory indolent lymphoma. J Clin Oncol. 2017;35(35):3898-3905.
14. Gopal AK, Kahl BS, de Vos S, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med. 2014;370(11):1008-1018.
15. Morschhauser F, Tilly H, Chaidos A, et al. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. Lancet Oncol. 2020;21(11):1433-1442.
16. Jacobson C, Chavez JC, Sehgal AR, et al. Primary analysis of Zuma-5: a phase 2 study of Axicabtagene Ciloleucel (Axi-Cel) in patients with relapsed/refractory (R/R) indolent non-Hodgkin lymphoma (iNHL). Blood. 2020;136(Suppl 1):S40-41.
17. Kanters S, Kahl BS, Wiesinger A, et al. Clinical outcomes in patients relapsed/refractory after ≥ 2 prior lines of therapy for follicular lymphoma: a systematic literature review and meta-analysis. J Clin Oncol. 2021;39(15 Suppl):e19548.
18. Fowler NH, Chen G, Lim S, Manson S, Ma Q, Li FY. Treatment patterns and health care costs in commercially insured patients with follicular lymphoma. J Health Econ Outcomes Res. 2020;7(2):148-157.
19. Ta JT, Itani T, Shapouri S, et al. Real-world treatment patterns and outcomes in patients with follicular lymphoma in the United States. J Clin Oncol. 2021;39(15 Suppl):e19534.
20. Ghione P, Ghesquieres H, Bobillo S, et al. Outcomes in later-lines of therapy for relapsed/refractory follicular lymphoma: results from the international SCHOLAR-5 study. Hematol Oncol. 2021;39(S2):851-860.
21. Fuji S, Tada Y, Nozaki K, et al. A multi-center retrospective analysis of patients with relapsed/refractory follicular lymphoma after third-line chemotherapy. Ann Hematol. 2020;99(9):2133-2139.
22. Casulo C, Larson MC, Lunde JJ, et al. Treatment patterns and outcomes of patients with relapsed or refractory follicular lymphoma receiving three or more lines of systemic therapy (LEO CReWE): a multicentre cohort study. Lancet Haematol. 2022;9(4):e289-e300.
23. Salles G, Schuster SJ, Fischer L, et al. A retrospective cohort study of treatment outcomes of adult patients with relapsed or refractory follicular lymphoma (ReCORD-FL). Hemasphere. 2022;6(7):e745.