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INVITED REVIEW

Personalised therapy in follicular lymphoma – is the dial turning?

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Abstract

Follicular lymphoma is the most common indolent lymphoma accounting for approximately 20%–25% of all new non-Hodgkin lymphoma diagnoses in western countries. Whilst outcomes are mostly favorable, the spectrum of clinical phenotypes includes high-risk groups with significantly inferior outcomes. This review discusses recent updates in risk stratification and treatment approaches from upfront treatment for limited and advanced stage follicular lymphoma to the growing options for relapsed, refractory disease with perspectives on how to approach this from a personalized lens. Notable gaps remain on how one can precisely and prospectively select optimal treatment for patients based on varying risks, with an anticipation that an increased understanding of the biology of these different phenotypes and increasing refinement of imaging- and biomarker-based tools will, in time, allow these gaps to be closed.

KEYWORDS
follicular lymphoma, immunochemotherapy, personalized therapy, POD24, risk factors

1 | INTRODUCTION

Follicular lymphoma (FL) is an indolent B-cell lymphoma with a long natural history and generally favorable outcomes. Current progress is reflected in a median overall survival (OS) exceeding two decades indicating that many patients are more likely to die with rather than from FL, thanks mainly to widespread adoption of immunochemotherapy and a rapidly increasing therapeutic armamentarium. However, important challenges remain. The clinical spectrum is heterogeneous, patients can present with limited or advanced stage disease, low or high tumour burden, with or without symptoms. The disease is characterised by frequent relapses and diminishing response to therapy leading to progressively shorter disease-free periods. Subsets with early progression and histological transformation contribute significantly to morbidity and mortality[1]; groups difficult to identify at diagnosis who remain therapeutically underserved. The availability of numerous therapeutic options, both in upfront and relapsed/refractory settings, is shifting the treatment algorithm and prompts the need to improve the precision of selecting and sequencing therapies. Here, we provide a perspective on the latest updates in FL, from risk assessment to the therapeutic front.

2 | CAN WE ACHIEVE PRECISION THROUGH RISK STRATIFICATION?

Achieving precision strategies in FL requires improved prognostic and predictive tools; gains in understanding pathology and biology are central to this. Despite its wide application in practice, FL grading as a meaningful prognostic tool has recently been challenged due to insufficient reproducibility for distinguishing grades 1–3A, indistinctive underlying genetic alterations and poor correlation with clinical outcomes.[2] Whilst alternative morphological techniques are not yet validated,[3] FL grading has been retained in the International Consensus Criteria,[4] and become optional in the 5th edition of the WHO Classification for Haematolymphoid Tumours.[5]

Major inroads have been made in deciphering the genetic and non-genetic determinants of FL pathogenesis.[6] In addition to the pathognomonic t(14;18) translocation, the standout observation is the high prevalence of mutations targeting epigenetic regulators (including *KMT2D*, *CREBBP* and *EZH2*) with recent data revealing how epigenetic deregulation remodels downstream signaling and reprograms the microenvironment.[7–9] This suggests potential for therapeutic targeting of the deregulated epigenome.[8–10] Notably, t(14;18)-negative FL likely follows a different oncogenesis. The genetic spectrum overlaps with t(14;18)-positive FL, but specifically a high incidence of *CREBBP*, *STAT6* and *TNFRSF14* mutations and deletion of 1p36 in limited-stage disease. Such findings indicate overlapping biology with certain clinical phenotypes (nodal t(14;18)-negative FL; limited-stage inguinal FL with a diffuse growth pattern; nodal stage I FL with a follicular growth pattern), but evidence to delineate clinical or biological groups is inconclusive.[11–13] A pattern differentiating translocation-negative limited-stage FL is also emerging,[14] substantiating the importance of refined molecular diagnosis to improve risk stratification.

A potential roadblock to achieving precision therapeutic targeting is recognised biological heterogeneity, both at spatial and longitudinal levels.[15,16] Attempts to stratify based on biology are ongoing and may represent a strategy for biologically-guided therapy. Recent studies identified genotype-based[17] and T-cell composition-based[18] subgroups, the latter showing inferior failure-free survival for T-cell depleted tumors; however, these studies represent first iterations requiring refinements. Importantly, the biology of high-risk FL remains undefined. Implementation of single cell technologies is providing further insights into the unprecedented heterogeneity of different subpopulations of FL tumours and its microenvironment.[18–21]

Historically, risk stratification at diagnosis (Table 1) was based on clinically defined indices (FLIPI, FLIPI-2). Recent iterations include simpler (PRIMA-PI; using just bone marrow (BM) involvement and beta-2 microglobulin), more granular (FLEX; using 9 parameters), incorporation with biology (m7-FLIPI) or purely biology-based (PRIMA 23-gene expression) prognostic models.[22–26] Interestingly, small studies suggest that the accuracy of these tools is variable and may be influenced by therapy.[27,28] A recent comparative study showed that FLIPI and m7-FLIPI offered the highest accuracy (between 66% and 69%) to identify patients at risk of early progression.[29] These findings require validation and, despite segregating risk groups, offer a suboptimal level of precision to guide therapy decisions.

Minimal or measurable residual disease (MRD) evaluated using PCR detection of BCL2-IGH rearrangements has been studied for years.[30] Although standardised, routine use is limited by variable assay sensitivity and the absence of a molecular marker to track a significant proportion of patients. Two recent studies evaluating circulating tumour DNA (ctDNA) in FL suggest potential to augment risk-stratification strategies, however this remains investigational and requires further analyses in clinical trials.[31,32] Baseline positron emission tomography (PET)-based biomarkers such as maximum standardised uptake value (SUV_{max}), total metabolic tumor volume (TMTV) and baseline total lesion glycolysis are promising emerging predictors of clinical outcomes (Table 2).[36,37,42,43]

Post-induction outcomes have the strongest prognostic utility in FL. In the GALLIUM trial, patients achieving less than complete

TABLE 1 Clinical and biological risk prediction tools in follicular lymphoma (FL).

Parameters	Prognosis	Patient Cohorts	Validation and comments	Prognostic accuracy for predicting POD24	Applied in routine practice
Clinical indices					
FLIPI					
Age >60 Stage III/IV Hb <120 g/L >4 nodal sites Elevated LDH	5-year OS Low: 91% Inter: 78% High: 53%	Non-R treated patients	• Extensively validated in both non-R and R-treated cohorts • Simple to compute apart from nodal sites	Sens: 53%–78% Spec: 56%–62%	Yes, but does not impact treatment selection
FLIPI-2					
Age >60 BM involvement Elevated β2M Hb <120 g/L Mass >6 cm	5-year OS Low: 90% Inter: 75% High: 38%	Heterogeneous including R-treated patients	• Validated • Easy to compute • Needs BM biopsy	Sens: 53% Spec: 59%–76%	No
PRIMA-PI					
BM involvement β2M >3 mg/L	5-year PFS Low: 69% Inter: 55% High: 37%	R-CHOP/R-CVP/ R-FCM, R^2 and R-maintenance-treated patients	• Independently validated across chemo-free and different chemo and anti-CD20 therapies • Simple to compute • Need for bone marrow only if β2M normal	Sens: 69% Spec: 48%	No
FLEX					
Male sex SPD in highest quartile Histologic grade 3A Elevated LDH >2 extranodal sites Hb <120 g/L ECOG PS >1 Elevated β2M NK count >100/μL	3-year PFS Low: 86% High: 68%	R- and O-chemotherapy (CHOP/CVP/ Bendamustine)	• Independently validated • Grading now not routinely recommended • NK cell count not routinely done	Sens: 60% Spec: 68%	No
Biological indices					
M7-FLIPI					
FLIPI high-risk ECOG PS >1	5-year FFS Low: 77% High: 38%	R-CHOP R-CVP	• Prognostic validity not confirmed in rituximab chemo-free or benda- treated patients • Need for NGS assessment (not routinely available)	Sens: 43%–61% Spec: 77%–86%	No
Mutation status: EZH2, FOXO1, EP300, CREBBP, CARD11, MEF2B, ARID1A	5-year OS Low: 90% High: 65%				

(Continues)

TABLE 1 (Continued)

Parameters	Prognosis	Patient Cohorts	Validation and comments	Prognostic accuracy for predicting POD24	Applied in routine practice
PRIMA-23-gene					
Gene expression of 23 defined genes	5-year PFS Low: 73% High: 26%	R-CHOP R-CVP	• Prognostic validity not confirmed in benda-treated patients • Need for gene expression profiling (not routinely available)	Sens: 43% Spec: 79%	No

Abbreviations: BM, bone marrow; CHOP, rituximab, cyclophosphamide, vincristine, prednisolone; CVP, cyclophosphamide, vincristine, prednisolone; FFS, failure-free survival; FLEX, follicular lymphoma evaluation index; FLIPI, follicular lymphoma international prognostic index; LDH; lactate dehydrogenase; NGS; next generation sequencing; O, Obinutuzumab; OS, overall survival; PFS, progression-free survival; PRIMA-PI, PRIMA prognostic index; PS, performance status; R, rituximab; Sens, sensitivity; SPD, sum of the products of lesion diameters; Spec, specificity; β2M – beta-2 microglobulin.

metabolic response (CMR) to end-of-induction (EOI) PET had significantly inferior 2.5 year PFS (54.9% vs. 87.4%) and OS (84% vs. 96.6%),[40] with greater prognostic precision shown for the Deauville 5-point scale than IHP criteria.[40,42] Prognostic utility was further improved when EOI-PET was combined with MRD in GALLIUM,[44] or with TMTV[41] and TLG[42,43] in other studies. Complete response rate at 30 months (CR30) was also shown to be a surrogate endpoint for PFS in a pooled analysis of randomised first-line chemotherapy, immunotherapy, and immunochemotherapy FL trials[45] and may be used as an alternative endpoint in clinical trials. Disease progression within 24 months of diagnosis (POD24), consistently reported in ~20% of FL patients regardless of immunochemotherapy type, was significantly associated with inferior OS in a pivotal analysis, with a hazard ratio of 7.17 compared to those without early POD, independent of FLIPI score.[46] These findings were confirmed using chemotherapy-free and other anti-CD20 therapies.[47–49] Recent evidence found that POD24 is associated with histological transformation, particularly after bendamustine-containing regimens,[50] and that POD24 transformed patients have worse outcomes than relapsed FL, however these observations were limited by a paucity of biopsies at first progression.[51] Nonetheless, survival outcomes remained poor among patients with earliest relapse (POD12), regardless of transformation status and, as for patients achieving <CMR or <CR30, this suggests aggressive disease biology. These patients should be separately assessed in future relapsed FL studies.

Despite great strides in defining prognostic biomarkers in FL, pre-induction tools lack precision and post-induction models cannot guide initial therapy, precluding meaningful selection or implementation of prognostic tools in current practice. Consequently, most clinicians adopt a pragmatic risk-stratification approach using clinical factors such as disease stage and burden, symptoms and need for therapy. In the modern era, limited-stage and asymptomatic advanced-stage low tumour burden (LTB) FL may be regarded as low-risk based on excellent OS at 5 years (87%–94%) irrespective of treatment modality and FLIPI score.[52–54] High-risk features including high-tumour-burden (HTB) and symptoms or signs of rapid progression evaluated against GELF or BNLI criteria[52,55] are widely used to determine the need for systemic therapy but without clear prognostic utility.[56]

3 | PERSONALISED FIRST LINE MANAGEMENT

3.1 | Localised disease

Radiation therapy (RT) is well established and potentially curative for patients with localised stage I or contiguous stage II disease.[57] Due to more precise selection of patients, outcomes have improved for localised disease staged with PET-CT and BM biopsy, with 10-year PFS of ~50%, increasing to ~70% for stage I disease.[57,58] PET-CT is particularly important for stage I/II patients where the therapeutic approach relies on accurate staging, but BM involvement is poorly identified by PET-CT; thus BM biopsies should continue to be performed in this setting.[59,60]

Involved site radiotherapy is the preferred modality in accordance with International Lymphoma Radiation Oncology Group guidelines,[61–63] limiting treatment to the macroscopic lymphoma volume and adjacent lymph nodes to encompass suspected subclinical disease. A standard total dose of 24 Gy[64] was superior to 4 Gy for long-term PFS in an updated analysis of the randomised phase 3 FORT trial, but with no difference in OS.[65] Since FL is exquisitely radiosensitive,[66] de-escalation to 4 Gy achieves excellent local control in most patients[67–70] and remains potentially curative in modern practice (ORR 68%, 2-year local progression 25%).[71,72] During the Covid pandemic an incremental, adaptive strategy was developed involving a single 4 Gy dose in patients needing local control, escalated to 24 Gy at 2–3 months only in patients with insufficient response. Preliminary analyses suggested that most patients required only one treatment.[73]

Adding chemotherapy, rituximab or both to RT was found to improve PFS but not OS.[74,75] The ongoing GAZAI trial is investigating 4 Gy in 2 fractions in combination with obinutuzumab in a response-adapted single-arm design aimed at reducing RT doses in patients

TABLE 2 PET-based risk prediction tools in follicular lymphoma (FL).

First author, year	*N* total	Treatment	HRFL definition	HRFL %	Impact on PFS (high vs. low risk)	*p* value for PFS (vs. low-risk)
Baseline SUV_{Max}						
Strati 2020[33]	*N* = 346	Non anthracycline regimens	SUV_{max} >18	4%	mPFS 77 months versus NR	$p = 0.02$
		R-CHOP		11%	mPFS 114 versus 144 mo	$p = 0.73$
Li 2022[34]	*N* = 126	60% R-CHOP, 7% CHOP 11% BR, 4% R-CVP 7% R^2, 7% Fludarabine 7% observed	SUV_{max} >17.6	17%	NA HR: 3 (1.6–5.6)	$p < 0.001$
Rossi 2022[35]	*N* = 132	83% R-CHOP + RM 6% R-CVP + RM 6% R^2 + RM 5% GA101-Len + OM	SUV_{max} >14.5	14%	2y PFS 54% versus 86%	$p = 0.006$
Baseline TMTV						
Meignan 2016[36]	*N* = 185	82% R-CHOP 14% R-CVP 4% R-FM	>510 ml (41%SUV_{max}*)	29%	5y PFS 33% versus 56%	$p = 0.001$
Liang 2019[37]	*N* = 48	79% R-CHOP 10% observed Radiotherapy No RM	>476 ml (SUV >3.0**)	NA	NA HR: 5.4 (1.3–22.0)	$p = 0.019$
Li 2022[34]	*N* = 126	60% R-CHOP, 7% CHOP 11% BR, 4% R CVP 7% R^2, 7% Fludarabine 7% observed	>408 ml (41%SUV_{max}*)	32%	NA HR: 4.6 (2.4–8.7)	$p < 0.001$
Baseline D_{max}						
Li 2022[34]	*N* = 126	60% R-CHOP, 7% CHOP 11% BR, 4% R-CVP 7% R^2, 7% Fludarabine 7% observed	56.73 cm	62%	5y PFS 39% versus 67%	$p < 0.001$
Interim PET						
Dupuis 2012[38]	*N* = 111	After 4 x R-CHOP	DS 4–5	24%	2y PFS 61% versus 86%	$p = 0$ 0.0046
EOI PET						
Dupuis 2012[38]	*N* = 106	R-CHOP	DS 4–5	22%	2y PFS 51% versus 87%	$p < 0.001$
Trotman 2014[39]	*N* = 246	R-chemo	DS 4–5	23%	4y PFS 23% versus 63%	$p < 0.0001$
Trotman 2018[40]	*N* = 508	R/O-chemo	DS 4–5	29%	2.5y PFS 55% versus 87%	$p < 0.0001$
Combined models						
Meignan 2016[36]	*N* = 177	R-CHOP, R-CVP, R-FM	TMTV + FLIPI-2	14%	mPFS 19 mo 5y PFS: 20% (both high) 46% (either high) 89% (both low)	P 0.001

(Continues)

TABLE 2 (Continued)

First author, year	N total	Treatment	HRFL definition	HRFL %	Impact on PFS (high vs. low risk)	p value for PFS (vs. low-risk)
Jimenez 2023[32]	N = 84	67% R-CHOP, 17% R-Benda, 16% R, radiotherapy	EOI PET + EOI MRD	17%	mPFS 7 months 2y EFS: 0%	$p < 0.001$ Sens 88% Spec 100%
Cottereau 2018[41]	N = 159	82% R CHOP 14% R-CVP 4% R-FM	TMTV + EOI PET (2 risk factors if high TMTV >510 cm^3 and positive EOI PET)	8%	5y PFS: 23% (2 risk factors) 33% (1 risk factor) 67% (0 risk factors)	$p < 0.001$

Abbreviations: D_{max}, lesion dissemination at baseline; EOI, end of induction; HR, hazard ratio; HRFL, high-risk follicular lymphoma; M, maintenance; mo, months; MRD, minimal residual disease; O, obinutuzumab; R, rituximab; R^2, rituximab-lenalidomide; sens, sensitivity; spec, specificity; SUV_{max}, maximum standardised uptake value; TMTV - total metabolic tumour volume (can be calculated with different methods, using 41% of $SUV_{max\ area}$* or area with SUV>3**).

responding to combination therapy.[76] There are no randomised data comparing RT with chemoimmunotherapy or watch-and-wait. However, large database studies consistently show a significant improvement in both PFS and OS for patients treated with RT.[77,78] Notably in the US RT is under-utilised for limited-stage FL in the rituximab-era, despite guideline recommendations.[79] Given the disparities in treatment patterns, opportunities to guide treatment for this indication are warranted.

4 | ASYMPTOMATIC LOW TUMOUR BURDEN FL

For low-risk patients with asymptomatic, LTB FL, a watch-and-wait (W&W) approach is generally recommended until the onset of symptoms or signs of progression as early treatment does not improve OS.[80] The alternative use of rituximab monotherapy in this setting was assessed in a NCRI randomised phase 3 trial comparing W&W; weekly rituximab for 4 doses (RI); and rituximab induction followed by maintenance 2-monthly for 2 years (RM). Three-year[80] and recently updated 10-year results[54] showed that rituximab significantly delays time to next treatment (TTNT) with median not reached, 9.9 and 2.7 years respectively for RM, RI and W&W. In this trial, RM achieved the greatest effect,[54,80] but was not cost effective due to the long duration of maintenance.[81] The US RESORT trial showed that re-treatment with rituximab until disease progression at each relapse was comparable to RM for disease control,[82] but used less rituximab, motivating many clinicians to adopt the more cost effective RI approach.[81] Recently, the LYSA group reported results of a randomised trial showing that maintenance can be shortened to four 2-monthly doses with retained superiority over standard RI for PFS (4-year PFS 58.1% vs. 41.2%). Interestingly, exposure to rituximab during the first 3 months was the only parameter associated with improved outcomes, further validating a role for short course maintenance.[83] Together these studies provide evidence that rituximab monotherapy (RI+/-RM) is an effective option for LTB FL patients seeking to delay immunochemotherapy, achieving long term control that could deliver a functional cure, especially in older patients. That said, the NCRI W&W trial did not show a survival advantage for rituximab over W&W, even with longer follow-up. At 10 years, nearly 30% of patients under W&W had not initiated therapy, indicating a different disease tempo in these patients and supporting an ongoing role for W&W in selected patients.[54] An individualised evaluation of patient factors (such as age, frailty, psychological burden, patient preference) provides the context for discussing options. Ideally, an understanding of the clinical or biological markers differentiating those who require or may never need treatment would refine decision-making in future.

5 | SYMPTOMATIC OR HIGH TUMOUR BURDEN FL

First-line rituximab monotherapy can also significantly delay chemotherapy in FL patients with symptomatic advanced-stage disease, as shown by the Nordic and SAKK groups.[28] However, in most countries, Rituximab (R) or obinutuzumab (O) is offered in combination with chemotherapy (CVP, CHOP, bendamustine)[84,85] as initial treatment for patients with HTB FL. As previously discussed, GELF criteria do not contextualize individual risk, pre-treatment risk assessment tools vary in complexity and prognostic accuracy (Table 1) and biomarkers of response and resistance are lacking. How best to choose an optimal therapy is the subject of much debate; selection remains largely empirical and guided by outcomes from trials evaluating specific therapies against prognostic endpoints, matched to patient age, fitness and preference.

Several randomised controlled studies showed that R-CHOP and R-Bendamustine (BR) achieve durable disease control and OS exceeding 80% at 10 years.[86–90] The GALLIUM trial showed that O-chemotherapy extends PFS, TTNT and reduces POD24 from 17% to 10% compared to R-chemotherapy. A sub-analysis reported consistently high MRD negative rates >90% for obinutuzumab regardless of chemotherapy backbone, offering useful insights to inform decisions in practice.[44] There was a small increase in toxicity driven mainly by infusion-related reactions and slightly more severe neutropenia and infections,[48,84] but this did not impact quality of life.[91] At 7.9 years median follow-up, this trial has not yet demonstrated a

survival advantage for obinutuzumab, lending credence to individualised decisions when choosing the antibody backbone.

When combined with either anti-CD20 antibody, bendamustine was associated with improved PFS and CMR rates over CVP/CHOP in a GALLIUM sub-analysis, but also excess toxicity and mortality, notably in older patients and when followed by maintenance,[92] where the role is less clear especially in CR patients.[93] Most additional deaths unrelated to new anticancer treatments were concentrated in patients with multiple existing medical conditions, aged over 80 years, or with a poor performance status.[93]

Since advanced FL is incurable, strategies to improve PFS and OS are desirable. Based on limited evidence, consolidation involved-field radiotherapy after immunochemotherapy, including to sites of previous bulk, does not change the relapse pattern or clinical course of advanced stage FL,[94] but may be useful for treating symptomatic residual sites. In unselected patients responding to induction therapy, adding antibody maintenance for two years prolongs remission, with sustained benefit after long follow-up, but also excess toxicity and no OS advantage.[87] The findings have driven wide variation in practice and prompted risk-adapted trials such as FOLL12 and PETReA to improve patient selection. In FOLL12, patients were randomised to standard maintenance (reference arm) or PET/MRD-adapted maintenance (experimental arm) in a non-inferiority design. In the reference arm, patients in partial or complete metabolic PET response after R-CHOP/BR received standard rituximab maintenance two monthly for two years, regardless of MRD status. Patients in the experimental arm were observed if PET and MRD-negative; treated with up to four doses of rituximab until MRD-negative if PET-negative and MRD-positive; or treated with (90)Y Ibritumomab Tiuxetan and rituximab maintenance two monthly for two years if PET-positive. Results demonstrated a higher risk of progression for the experimental arm (3-year PFS 72% vs. 86%), despite adjustment by FLIPI2 and type of induction therapy.[95]

Despite FOLL12 being a negative study, the evolution toward precision-based approaches in FL is inspiring and an important example for future development of risk-adapted trials. The ongoing international phase 3 PETReA trial[96] is randomising EOI PET-negative patients to standard maintenance for two years or no further therapy, to quantitate the trade-off between PFS advantage and toxicity of maintenance, and PET-positive patients to standard maintenance or maintenance plus lenalidomide, to test if the addition of lenalidomide improves prognosis for this poor risk group. This more precise evaluation of the magnitude of benefit in PET response groups is expected to inform future individualised risk-benefit maintenance decisions.

Rituximab[28] and rituximab combined with lenalidomide (R^2)[97,98] are effective first-line treatments. The RELEVANCE trial demonstrated comparable safety and efficacy outcomes for R^2 and R-chemotherapy, even after long follow-up,[97] underscoring the value of R^2 as a standard option (where approved) for previously untreated FL, with different side effects on which to base personalised choice. The GALEN trial investigating O-lenalidomide in previously untreated FL also demonstrated high response rates and 3-year PFS of 82%, building on the possibility of shifting away from chemotherapy.[91] Immune-directed bispecific antibodies and chimeric antigen receptor T (CAR-T) approaches demonstrating high and potentially durable responses at relapse are moving to evaluation in first-line trials (Table 3).

6 | PERSONALISED MANAGEMENT AT RELAPSE

Relapsed FL is considered incurable regardless of initial stage at diagnosis. As such, goals of treatment are to alleviate symptoms, treat cytopenias, and improve quality of life; therapy at the time of relapse is not always required. It is imperative to exclude transformation, as this carries an inferior prognosis and requires an immediate but differing therapeutic strategy.

Relapse after primary RT for localised disease almost always occurs outside the previously irradiated volume and, as for relapse after systemic therapy, early relapse after RT (<12 months) was recently shown to be an independent predictor of inferior survival in a multi-centre retrospective series (88.7% vs. 97.6%).[99] Rates of relapse vary from 30% to 50% according to stage (I/II) and staging modality (PET-CT/CT).[58,99]

Radiotherapy is the mainstay of treatment for localised relapse and can provide long disease-free intervals and effective palliation of symptomatic disease at one or few localised sites. Although 24 Gy is superior to 4 Gy for long-term outcomes,[65] 4 Gy achieves local control in most patients, even when delivered to large volumes,[67–70,100] and may be preferred for palliation as treatment is exceptionally well tolerated and the same area can be re-treated several times.

Patients relapsing with asymptomatic advanced-stage LTB disease have historically been managed with a W&W strategy, akin to the first-line setting. A recent small retrospective study confirmed the validity of this approach in patients managed at first progression, showing no negative impact on time to treatment failure, OS or transformation. Within the W&W cohort, risk factors for a shorter TTNT were rituximab-refractory disease, POD24 and FLIPI 3-5 at initial diagnosis.[101]

When systemic therapy is indicated at relapse the current therapeutic armamentarium offers a wide choice. According to multicentre retrospective registries, immunochemotherapy is the most common treatment at each line of therapy but practice varies considerably,[102] indicating a dearth of published outcomes for conventional immunochemotherapy at relapse. Choice is typically based on prior therapies, potential toxicities and patient preference, including consideration of re-treatment with the same therapy (excepting anthracycline-based) when time to relapse is prolonged (generally >5 years) or switching to a non-cross resistant immunochemotherapy or rituximab plus lenalidomide (R^2) for earlier relapse.[103] R^2 was FDA/EMA approved in 2019 based on the pivotal AUGMENT[104] and MAGNIFY[105] trials and has since become a frequent choice from second line across all age and risk groups due to consistently high activity in patients aged over and under 70 years,

TABLE 3 First line trials open to recruitment in previously untreated follicular lymphoma (FL).

Trial identifier	Trial name	Trial phase	FL risk group (criteria)
NCT04883437	Acalabrutinib and obinutuzumab for the treatment of previously untreated follicular lymphoma or other indolent non-Hodgkin lymphomas	2	LTB
NCT03361852	Personalized neoantigen cancer vaccine + pembrolizumab after rituximab for follicular lymphoma	1	LTB planned for rituximab (4 weekly doses)
NCT04669171	A novel Vaccine (EO2463) as monotherapy and in combination, for treatment of patients with indolent non-Hodgkin lymphoma (SIDNEY)	1/2	LTB not requiring therapy
NCT04663347	Safety and efficacy trial of epcoritamab combinations in subjects with B-cell non-Hodgkin lymphoma (B-NHL) (EPCORE™ NHL-2; arm 3 epcoritamab + BR; arm 6 epcoritamab + R^2)	1/2	Any
NCT05410418	Mosunetuzumab and Polatuzumab Vedotin for untreated follicular lymphoma	2	HTB (GELF)
NCT04450173	Obinutuzumab, Ibrutinib, and Venetoclax for the treatment of previously untreated stage II-IV follicular lymphoma	2	HTB (GELF/GITMO)
NCT04404088	Acalabrutinib, lenalidomide, and rituximab for the treatment of CD20 positive stage III-IV, grade 1-3a Follicular lymphoma	2	HTB (GELF)
NCT05169658	Mosunetuzumab with or without Polatuzumab Vedotin and obinutuzumab for the treatment of untreated indolent B-cell non-Hodgkin lymphoma	2	HTB (Any)
NCT04792502	Mosunetuzumab with lenalidomide Augmentation as first-line therapy for follicular and marginal zone lymphoma	2	HTB (GELF)
NCT05073250	IBI376 plus rituximab in patients with untreated indolent lymphoma.	2	HTB (Any)
EudraCT 2016-004010-10	NCRI PETReA trial: a Phase 3 evaluation of PET-guided, response-adapted therapy in patients with previously untreated, advanced -stage, high-tumour-burden follicular lymphoma	3	HTB (GELF)

Abbreviations: HTB, high tumour burden; LTB, low tumour burden.

and those with poor risk features. Updated AUGMENT results confirmed long-term safety and efficacy.[106]

Recent data for R^2 and BR suggest high responses after 2 median prior lines of therapy (R^2 ORR 71%[107] BR ORR 84%[108]). Obinutuzumab-bendamustine followed by obinutuzumab maintenance is effective in rituximab-refractory relapsed disease.[108] There are no published outcome data for R-CVP or R-CHOP in the relapsed/refractory post-rituximab era however data from the LEO CReWE study, which exclusively enrolled patients previously treated with alkylating agent- and anti-CD20-containing therapy, showed a poor median PFS of just 17 months for pooled therapy outcomes from third line onwards.[109]

Multiply relapsed and refractory patients (r/r FL) and those with early disease progression after primary therapy have poor outcomes after standard immunochemotherapy.[46,109,110] Targeted agents with demonstrated activity in r/r FL, including high-risk groups (Table 4), are changing practice and shaping a paradigm shift towards personalised management of these difficult-to-treat groups. We present the most recent updates in licensed therapies, acknowledging that access to these treatments varies considerably.

Phosphoinositide 3-kinase inhibitors (PI3Ki) were among the earliest targeted therapies approved for FL from the third line. These agents, including copanlisib, idelalisib, duvelisib, and umbralisib, deliver modest clinical efficacy in r/r FL with considerable toxicity and an emerging pattern of high mortality leading to withdrawal of most agents in the past year due to unacceptable safety on FDA review.[123] To our knowledge, at present there is restricted access only to copanlisib, and the future of this class of drugs is uncertain.[124]

Tazemetostat is a first-in-class inhibitor of EZH2, an epigenetic regulator mutated in about a quarter of patients. In a pivotal phase 2 trial responses were higher in mutated tumours (ORR 64%–78% $EZH2^{MT}$ vs. 25%–35% $EZHT^{WT}$)[117] leading to licensing in 2020 of the first mutation-targeted therapy in FL. Interestingly, there was no significant difference in PFS between mutated and non-mutated cohorts (median 14 months $EZH2^{MT}$ vs. 11 months $EZHT^{WT}$) suggesting dependence on EZH2 regardless of mutation status. Subset analysis hinted at longer PFS in $EZH2^{MT}$ versus $EZH2^{WT}$ POD24 and refractory subsets which if confirmed in larger series could justify mutation testing prior to therapy. Tazemetostat is licensed after at least two prior lines of therapy only in patients who have no alternative treatment options, reflecting modest activity as a single agent. This drug is however remarkably well tolerated with serious treatment-related adverse events reported in just 4% of trial patients leading to interest in evaluating combination therapies to boost efficacy.[117]

Mosunetuzumab, a first-in-class CD3xCD20 dual targeting bispecific antibody (BsAb), received EMA approval and FDA priority review in 2022 for r/r FL from third line, marking the first licensed BsAb agent in a rapidly expanding class that includes epcoritamab,[125] odronextamab,[119] and glofitamab[126] among the leading agents. In a

TABLE 4 Clinical outcome data for approved and emerging targeted therapies in follicular lymphoma (FL).

Treatment, study	Efficacy patients, treatment line (median, range)	Median follow-up (months)	Clinical outcomes in FL subsets						
						Refractory			
			Outcome	All FL	POD24	Last line	Double	FLIPI ≥3	Bulk >7 cm
Axicabtagene ciloleucel ZUMA-5[111]	*n* = 86 3 (2–4)	23	*N*	79%	55%	68%		44%	
			ORR	94%	93%	93%		95%	
			CR	79%	72%	75%			
			1.5y PFS	69%	55%	62%			
			1.5y OS	88%					
Tisagenlecleucel ELARA trial[112,113]	*n* = 94 4 (2–13)	29	*N*	100%	63%	78%	67%	59%	64%
			ORR	86%	82%		85%	81%	86%
			CR	68%	59%		66%	61%	65%
			2y PFS	57%					
			2y OS	88%					
Mosunetuzumab pivotal phase 2[114,115]	*n* = 90 3 (2–4)	18	*N*	100%	52%	69%	53%		
			ORR	80%	85%	77%	71%		
			CR	60%	57%	52%	50%		
			2y PFS	48%					
			2y OS	87%					
Epcoritamab-R^2, EPCORE NHL-2[116]	*n* = 66 1 (1–9)	6	*N*	100%	42%	38%	39%	51%	
			ORR	95%	92%	92%	88%		
			CR	80%	75%	75%	67%		
Rituximab lenalidomide (R^2) MAGNIFY[107]	*n* = 318 2	41	*N*	81%	34%		22%		
			ORR	72%	65%		51%		
			CR	42%	32%		25%		
			mPFS	51 mo	27 mo		18 mo		
Tazemetostat Pivotal phase 2[117]	*N* = 99 2^{mut} 3^{WT}	22^{MT} 36^{WT}	*N*	$45\%^{MT}$ $55\%^{WT}$	$19\%^{MT}$ $32\%^{WT}$	$33\%^{MT}$ $42\%^{WT}$	$9\%^{MT}$ $15\%^{WT}$		
			ORR	$69\%^{MT}$ $35\%^{WT}$	$63\%^{MT}$ $25\%^{WT}$	$64\%^{MT}$ $29\%^{WT}$	$78\%^{MT}$ $27\%^{WT}$		
			CR	$12\%^{MT}$ $4\%^{WT}$	$11\%^{MT}$ $3\%^{WT}$		$22\%^{MT}$ $0\%^{WT}$		
			mPFS	14^{MT} 11^{WT}	14 mo^{MT} 6 mo^{WT}	11 mo^{MT} 8 mo^{WT}	8 mos^{MT} 4 mos^{WT}		
Tazemetostat + R^2 Symphony-1[118]	*N* = 41	7^{MT} 32^{WT}	*N*	100% $18\%^{MT}$ $82\%^{WT}$	27%				
			ORR CR	98% $100\%^{MT}$ $97\%^{WT}$ 51%	100%				
			mPFS	NR @ 11 mo					

(Continues)

TABLE 4 (Continued)

Treatment, study	Efficacy patients, treatment line (median, range)	Median follow-up (months)	Clinical outcomes in FL subsets						
						Refractory			
			Outcome	All FL	POD24	Last line	Double	FLIPI ≥3	Bulk >7 cm
Odronextamab ELM-2[119]	*n* = 121 3 (2–13)	22	*N*	100%	50%	73%	45%	57%	
			ORR	82%	83%	81%	76%	81%	
			CR	75%					
			1.5y PFS	55%					
			1.5y OS	76%					
Rituximab + lenalidomide (R^2) AUGMENT[106]	*n* = 178 1 (1–12)	66	*N*	83%		17%			
			ORR	79%					
			CR	32%					
			mPFS	28 mo					
			5y OS	83%					
Obinutuzumab + lenalidomide GALEN[120]	*N* = 86 2 (1–7)	31	*N*	100%	28%	27%		42%	13%
			ORR	79%	75%	74%			82%
			CR	38%					
			PFS 2y	65%	63%	52%			81%
			OS 2y	87%	83%	68%			91%
Obinutuzumab + lenalidomide + atezolizumab[121]	*N* = 32 1 (≥2)	30	*N*	100%	37%	29%	38%	26%	16%
			ORR	78%					
			CR	72%	50%		67%		
			3y PFS	68%					
			3y OS	90%					
Pembrolizumab + rituximab[122]	*N* = 30 1 (1–4)	35	*N*	100%	37%			20%	50%
			ORR	67%	36%				
			CR	50%					
			mPFS	13 mo					
			3y OS	97%					

Abbreviations: CR, complete response; Double refractory, refractory to alkylator agent chemotherapy and anti-CD20 antibody therapy; FLIPI, follicular lymphoma international prognostic index; m, median; mo, months; MT, EZH2 mutated; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; POD24, progression of disease within 24 months of diagnosis; WT, EZH2 wild type; y, years.

pivotal phase 2 trial,[114] mosunetuzumab produced high responses across high-risk subgroups (ORR 71%–80%, CR 50%–60%), including POD24 (ORR 85%, CR 57%). Median PFS was 17.8 months for the study population, the majority of whom (52%–69%) had high-risk features.

Two autologous anti-CD19 CAR-T cell therapies, axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) were FDA/EMA approved in 2021/22 for r/r FL from third line onwards based on single arm trials (ZUMA-5 and ELARA) enriched for poor prognostic risk groups. Remarkably high response rates (ORR 81%–95%, CR 59%–75%) were achieved across all risk groups and responses were durable, especially for complete responders with 73% and 78% of axi-cel and tisa-cel CR patients, respectively, in ongoing response at a median follow-up of 23–24 months[111–113] CAR-T therapy outperformed standard third and later line therapies in historic controls[127,128] and this is being further investigated in randomised trials such as ZUMA-22. Notably, whilst successive lines of standard immunochemotherapy typically produce shortening remissions due to increasing treatment resistance,[110] CAR-T therapy remains active at later lines, highlighting the value of immunotherapy to eradicate chemo-resistant disease. Indeed, axi-cel delivered the most robust PFS hazard ratio reduction compared to standard therapies for patients treated at ≥ fourth line.[127] Whether this trend will translate into a cure is a question of considerable interest with encouraging data (43% PFS at 5 years) reported from an early study of tisa-cel.[129] Longer follow-up of pivotal trials is needed to confirm this.

Although CAR-T therapy delivers high response rates across all prognostic groups, a shorter duration of response was observed for some groups in a ZUMA-5 subset analysis, namely ECOG 1 versus 0; ≥3 prior therapy lines; high tumour bulk by GELF criteria; and POD24.[111] In the ELARA trial, HTB measured by TMTV ≥510 mm^3 and ≥4 nodal areas were also associated with lower efficacy, as was POD24 and an exhausted tumour microenvironment marked by high numbers of LAG3+CD3+ tumour infiltrating T cells prior to CAR-T delivery.[113]

Choosing between BsAb and CAR-T therapy and their optimal sequencing is not yet known as very few patients previously treated with either agent were enrolled into trials, and no trials directly compared therapies or delivered biological insights to guide patient selection. In terms of sequencing, there is some evidence that prior lenalidomide and auto-SCT do not impact the efficacy of axi-cel[111] but lower CR rates were reported for mosunetuzumab in lenalidomide-exposed patients.[114] These data should be interpreted with caution due to small numbers in sub-analyses. A recent LYSA study in r/r B-cell non-Hodgkin lymphoma reported preserved efficacy for CAR-T therapy after BsAb failure, but only two patients with FL were included in the analysis.[130] Consequently, at present choice of BsAb versus CAR-T therapy is based on ease of administration, toxicity, treatment cost and availability. This equation currently favours BsAb ahead of CAR-T in the treatment pathway, but this may change if longer follow-up confirms curative potential for CAR-T products.

The advent of BsAb and CAR-T immunotherapies has seen a practice drift away from haematopoietic stem cell transplant (SCT), which historically had an important role in managing r/r FL. Despite this, the relative value of these agents against SCT is largely unknown as there are no prospective comparative studies and long-term outcomes for immunotherapy trials are pending. Considering this uncertainly, and when these agents are not available, transplantation remains a valid treatment strategy in the relapsed setting and knowledge of outcomes in high-risk FL is useful. A large retrospective SCT study in FL with POD24 reported 5-year OS of 70% after autologous SCT (auto-SCT) and 73% after matched sibling donor allogeneic stem cell transplant (allo-SCT).[131] Patients with chemosensitive disease, especially by PET-CT,[132] and those transplanted in earlier lines of therapy achieved longest survival, specifically auto-SCT at second line[133] and allo-SCT at early lines in young patients with good performance.[134] In patients with primary treatment failure, auto-SCT improved survival only if performed within a year of failure.[135] Outcomes from these retrospective series may have been biased by inadvertent inclusion of patients with high grade transformation as routine practice varies for biopsy at relapse. Nevertheless, these data support consideration of early ASCT in chemosensitive POD24 patients, especially at second line where there are currently no licensed targeted agents apart from R^2. The choice between alloSCT and targeted therapies from third line onwards is a challenging and more nuanced decision which longer follow-up of targeted therapy trials may help to resolve.

Many targeted agents are now being investigated in combination trials. Due to its widespread use and favourable features, R^2 is the most common comparator and backbone for such combinations with several ongoing randomised phase 3 trials including Symphony-1 (NCT04224493) and InMIND (NCT04680052) evaluating R^2 plus tazemetostat/placebo and tafasitamab/placebo, respectively; Celestimo (NCT04712097), Epcore FL-1 (NCT05409066) and MAHOGANY (NCT05100862) comparing R^2 with mosunetuzumab-lenalidomide, R^2-epcoritamab and obinutuzumab-zanubrutinib, respectively. Results of these studies will inform the value of R^2 combinations in the r/r setting, but their value compared to standard immunochemotherapy at relapse will remain poorly understood as very few prospective studies are examining this question. This will become an increasingly important consideration if R^2 usage increases at first line.

7 | CONCLUSION

With the evolving treatment landscape, the clinical course of FL is prolonged with potential to achieve a normal life expectancy for many patients. Given its clinical heterogeneity and ever-expanding treatment landscape, there is a great unmet need for predictive biomarkers and enhanced precision strategies to inform treatment selection. Follicular lymphoma is rare, therefore it is imperative to approach these challenges as a global community. Herein, this group of international experts outlines the roadmap of progress made over the past two decades and future directions. Many effective treatment options exist with great enthusiasm among clinicians for immunotherapy combinations. As technologies evolve, our understanding of lymphomagenesis will be refined, and this knowledge will need to be incorporated into comprehensive risk stratification tools to inform unmet need and patient selection for efficient and high impact studies. Future directions should be aimed at minimising toxicity exposure for low-risk patients, personalising treatment selection for high-risk patients, and identifying optimal sequencing strategies.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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PEER REVIEW

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