The Oncologist®

Hematologic Malignancies

Follicular Lymphoma: Recent and Emerging Therapies, Treatment Strategies, and Remaining Unmet Needs

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Follicular lymphoma • Non-Hodgkin lymphoma • Antineoplastic agents • Neoplasms

Abstract

Follicular lymphoma (FL) is a heterogeneous disease with varying prognosis owing to differences in clinical, laboratory, and disease parameters. Although generally considered incurable, prognosis for early- and advanced-stage disease has improved because of therapeutic advances, several of which have resulted from elucidation of the biologic and molecular basis of the disease. The choice of treatment for FL is highly dependent on patient and disease characteristics. Several tools are available for risk stratification, although limitations in their routine clinical use exist. For limited disease, treatment options include radiotherapy, rituximab monotherapy or combination regimens, and surveillance. Treatment of advanced disease is often determined by tumor burden, with surveillance or rituximab considered for low tumor burden and chemoimmunotherapy for high tumor burden disease. Treatment for relapsed or refractory disease is influenced by initial first-line therapy and the duration and quality of the response. Presently, there is no consensus for treatment of patients with early or multiply relapsed disease; however, numerous agents, combination regimens, and transplant options have demonstrated efficacy. Although the number of therapies available to treat FL has increased together with an improved understanding of the underlying biologic basis of disease, the best approach to select the most appropriate treatment strategy for an individual patient at a particular time continues to be elucidated. This review considers prognostication and the evolving treatment landscape of FL, including recent and emergent therapies as well as remaining unmet needs. ***The Oncologist*** 2019;24:e1236–e1250

Implications for Practice: In follicular lymphoma, a personalized approach to management based on disease biology, patient characteristics, and other factors continues to emerge. However, application of current management requires an understanding of the available therapeutic options for first-line treatment and knowledge of current development in therapies for previously untreated and for relapsed or refractory disease. Thus, this work reviews for clinicians the contemporary data in follicular lymphoma, from advances in characterizing disease biology to current treatments and emerging novel therapies.

Introduction

Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma (NHL) in Western countries, with an annual incidence of 3.4–5 per 100,000 in Europe and the U.S. [1, 2]. Median age of diagnosis is 65 years [3], but a large proportion of cases also occurs in younger adults [4]. Although incurable, prognosis has improved for early- and advanced-stage disease, largely attributed to therapeutic advances.

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FL is a heterogeneous disease with varying prognosis, influenced by differences in clinical, laboratory, and disease parameters between patients. Spontaneous regressions might occur in about 5%–10% of patients [5]. Although many patients can be initially observed, most require therapy after a median of 3–4 years after diagnosis [6]. Approximately 20% of patients will have early relapse within 2 years following current first-line therapy [7]. Thus, FL has a typically protracted course, with multiple remissions and relapses.

Although continued elucidation of the biologic and molecular basis of FL is leading to identification of new potential therapeutic avenues, the heterogeneity of FL presents challenges, including selection of appropriate management for individual patients. This review considers prognostic approaches and the FL treatment landscape, including recent and emergent therapies and remaining unmet needs.

Pathobiological Heterogeneity

The World Health Organization (WHO) FL grading system is formed on the basis of differing proportions of centroblasts per high-powered field, with a greater proportion indicative of a more aggressive phenotype [8]. Grades 1–2 and 3A are considered histologically low-grade and indolent disease [9], whereas grade 3B is considered biologically distinct from grades 1–3A [10, 11] and typically treated as an aggressive lymphoma [2, 12]. However, it is important to note that centers largely group grades 1–3A as low-grade lymphoma given inter- and even intraobserver variability in scoring grade, whereas grade 3B remains a routinely distinguishable pathologic entity characterized by sheets of immunoblasts. Further highlighting the histologic heterogeneity, the 2016 WHO classification update includes entities (e.g., duodenal-type disease) [13] that are distinguished from nodal FL by different immune-microenvironment profiles [14].

FL transformation from an indolent to more aggressive disease is a well-recognized complication during the natural disease history. Transformation is defined by histologic evidence of diffuse large B-cell lymphoma (DLBCL) or other high-grade morphology, usually accompanied by rapid progression of lymphadenopathy, extranodal disease outside the marrow, B symptoms, elevated serum lactate dehydrogenase, and, less commonly, hypercalcemia [15]. Histologic-transformation risk has historically been reported in 3% of patients annually [16, 17] but is believed to be lower in the rituximab era [18–20].

An extensive catalog of genetic changes occurring in FL is available. An unexpected revelation was the high prevalence of mutations in genes encoding proteins regulating the epigenome through specific histone post-translational modifications (*KMT2D*, *CREBBP*, *EP300*, *EZH2*) [21–24]. Mutations in genes involved in cellular processes such as JAK-STAT, BCR-NFkB, mTOR signal transduction, cell-cycle regulation, immune modulation, and cellular differentiation are also frequent [23–27], several of which are potential therapeutic targets and some of which are prognostically relevant [25, 28]. Furthermore, genetic profiles of FL tumors can evolve longitudinally over the disease course [23, 24, 29–31] and spatially within tumors at different sites of involvement [32].

In addition to genetic alterations, tumor cells exist within a milieu of nonmalignant cells making up the microenvironment, which is pivotal in contributing to disease development, maintenance, and progression. A seminal study identified that gene expression signatures derived from nonmalignant immune cells (T cells vs. macrophages) independently predicted clinical outcome in FL, underpinning the critical role of the tumor microenvironment [33]. It is envisaged that building a more in-depth understanding of the biological basis of FL will inform newer approaches to targeting these tumors.

Risk Stratification

Recent data suggest the strongest predictor of long-term FL outcomes is length of first remission after front-line therapy. Patients with progression of disease within 24 months of completing induction chemoimmunotherapy (POD24), which made up 19% of patients in this data set, had poorer outcomes compared with those with longer remission durations (5-year overall survival [OS]: 50% vs. 90%, respectively) even after adjustment for Follicular Lymphoma International Prognostic Index (FLIPI) score (discussed below) [7]. These results were validated in the University of Iowa and Mayo Clinic Molecular Epidemiology Resource data sets [7], and in the GALLIUM study and using the FLASH data set [34, 35]. Additionally, a longer duration from diagnosis to progression (i.e., event-free survival of >12 months after diagnosis) did not result in excess mortality compared with the age- and sex-matched general population [36].

Based on retrospective survival data from patients diagnosed in the preimmunotherapy era, the FLIPI consists of five clinical parameters and categorizes patients into one of three risk groups (Table 1) [37]. The FLIPI has been validated in clinical trials of chemoimmunotherapy and in the National LymphoCare study observational cohort and was validated using OS and progression-free survival (PFS) in the prechemoimmunotherapy era [38, 39]. FLIPI-2 was subsequently developed as a more contemporary prognostic model using data reflective of treatment in the chemoimmunotherapy era [40]. It includes bone marrow involvement, nodal diameter, and β2-microglobulin levels and was built on PFS in chemoimmunotherapy-treated patients. A streamlined index has been proposed, the PRIMA-PI, which uses a simplified algorithm of bone marrow involvement and β2-microglobulin level to predict PFS [41]. Other tools to predict outcome in FL have been proposed, including total metabolic tumor volume (TMTV) as determined from baseline positron emission tomography (PET) [42], combining FLIPI-2 with TMTV [43], and assessment of the presence of circulating peripheral blood lymphoma cells [44].

The m7-FLIPI, a clinicogenetic risk score derived from a combination of the mutation status of seven candidate genes (*EZH2*, *ARID1A*, *MEF2B*, *EP300*, *FOXO1*, *CREBBP*, *CARD11*) together with clinical parameters (FLIPI score and Eastern Cooperative Oncology Group performance status) stratifies patients into a low-risk group (78% of patients) with a 5-year failure-free survival of 68% versus 25% in a high-risk group (22% of patients) [45]. m7-FLIPI was used to identify patients at risk of early relapse (POD24) using data from the German Low-Grade Lymphoma Study Group trial and the British Columbia Cancer Agency population-based

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Table 1. Currently used clinical prognostic models for follicular lymphoma

Model	Criteria	Risk stratification	Prognosis
FLIPI [37, 39]	1. Age: >60 years 2. Ann Arbor Stage: III–IV 3. Hb concentration: <12 g/dL 4. Number of nodal sites: >4 5. Serum LDH concentration: >normal	Low: 0–1 risk factors	2-year OS: 98%; 2-year PFS: 84%
		Intermediate: 2 risk factors	2-year OS: 94%; 2-year PFS: 72%
		High: 3–5 risk factors	2-year OS: 87%; 2-year PFS: 65%
FLIPI-2 [40]	1. Age: >60 years 2. Bone marrow involvement: yes 3. Hb concentration: <12 g/dL 4. Greatest diameter of largest involved node: >6 cm 5. Serum β2 microglobulin concentration: >ULN	Low: 0–1 risk factors	3-year PFS: 91%
		Intermediate: 2 risk factors	3-year PFS: 69%
		High: 3–5 risk factors	3-year PFS: 51%
GELF [60]	1. Tumor size: any site >7 cm or ≥ 3 sites >3 cm 2. B symptoms: yes 3. Spleen: below umbilical line 4. Compressive symptoms: yes 5. Pleural or peritoneal effusion: yes 6. Leukemic phase >5 × 10^9/L 7. Neutropenia (<1 × 10^9/L) or thrombocytopenia (<100 × 10^9/L) due to disease	High tumor burden: ≥1 risk factors	

Abbreviations: FLIPI, Follicular Lymphoma International Prognostic Index; GELF, Groupe d'Etude des Lymphomes Folliculaires; Hb, hemoglobin; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; ULN, upper limit of normal.

registry [46]. They confirmed that 5-year OS of patients with POD24 was significantly worse than that of patients without POD24 (26%–41% vs. 86%–91%, respectively; $p < .0001$) and that the m7-FLIPI had a higher accuracy in predicting POD24 compared with FLIPI. Recently, a 23-gene expression-based prognostic tool was developed that again segregates patients into a low-risk (5-year PFS 73%) and high-risk group (5-year PFS 26%) [47]. Both of these tools were established and validated in retrospective cohorts of patients with FL with symptomatic, advanced stage, grade 1–3A disease requiring systemic first-line therapy (commonly chemotherapy plus rituximab) [45, 47].

Metabolic responses to therapy have also been considered as a means of predicting subsequent outcomes in FL [7, 34, 48–53]. For instance, end-of-induction PET was shown to be prognostic after first-line FL therapy, correlating with outcome in prospective trials, retrospective analyses of prospective trials, and pooled analyses [49–51].

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Choice of FL treatment is highly individualized, dependent on extent, burden, and progression of disease and associated symptoms; treatment decisions currently cannot be driven by available prognostic models, and work in this field is currently active. Although the current risk stratification models are predictive of outcomes, they do not have sufficient sensitivity or specificity to guide decision making and remain primarily research tools that are being examined in prospective clinical trials

FL Treatment

Newly Diagnosed Disease

Assessment of a patient newly diagnosed with FL includes consideration of disease burden, lymphoma-related symptoms, presence of comorbidities, patient preference, and age. Newly diagnosed FL can be broadly classified as limited or advanced-stage disease and further classified according to degree of tumor burden; choice of management varies accordingly (Fig. 1).

Localized/Limited-Stage Disease

Approximately 10%–15% of patients with FL have limited, nonbulky disease at diagnosis, which includes Ann Arbor stage I–II disease [2]. For Ann Arbor stage I or II (possibly confirmed by fluorodeoxyglucose-PET) disease, use of 24-Gy involved-field radiotherapy (IFRT) administered in 12 fractions is potentially curative and is often the preferred treatment option for disease encompassed in a single appropriate radiation port, with no additional apparent efficacy benefit of higher doses [2, 12, 54]. By restricting the radiation field size to smaller volumes, IFRT limits radiation exposure to adjacent uninvolved tissue, thereby reducing risk of long-term adverse effects [12]. A recent assessment of outcomes of definitive IFRT found that local relapses in or near irradiated fields are rare, and the vast majority of failures are distant [55]. Additionally, only about 25% of patients experience grade 1/2 and <1% have grade 3 toxicities. For palliation and local control alone, two fractions of 2 Gy may be sufficient [2, 56].

Based on experience in advanced disease, patients with mildly symptomatic, localized disease have been treated with rituximab monotherapy [2, 12], but this strategy should only be used if radiotherapy cannot be safely administered. Different rituximab treatment strategies (alone, in combination with chemotherapy, or together with radiation therapy) and comparison with radiotherapy alone in limited disease have been reported [57, 58]. Although combined modality approaches improved PFS compared with radiotherapy alone, no OS difference between treatment approaches was seen. Additionally, extrapolation from the experience in advanced-stage disease,

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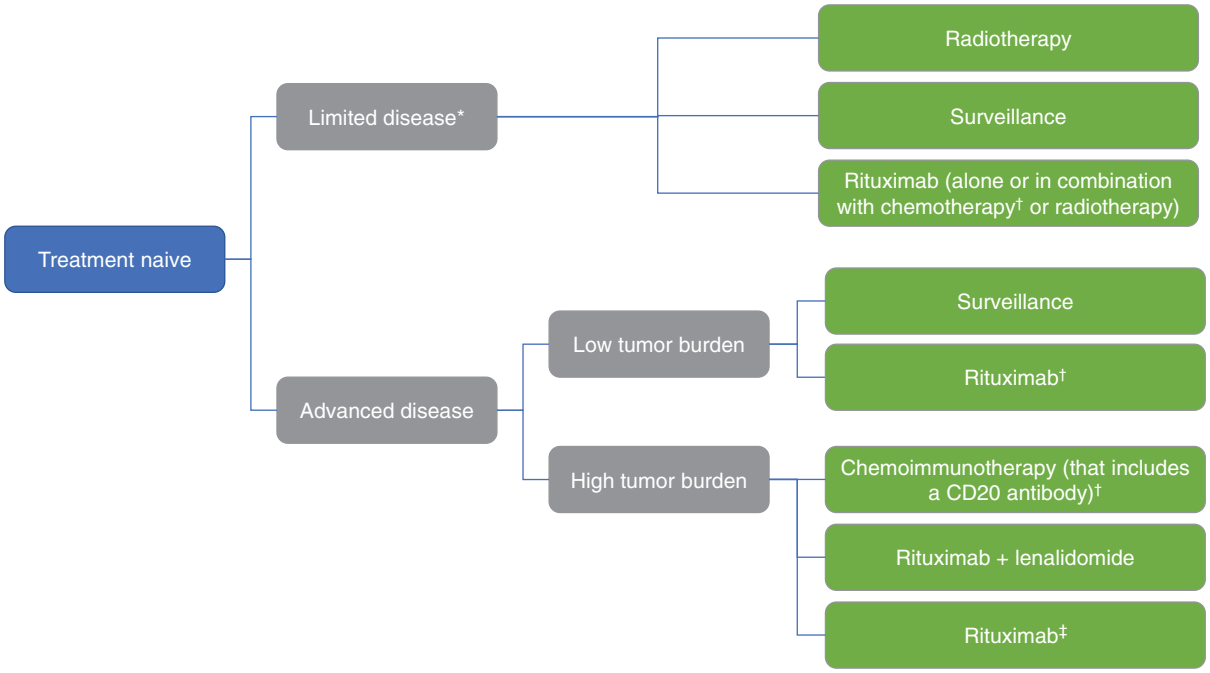

Figure 1. Treatment options in newly diagnosed follicular lymphoma. *Patients with limited disease but high tumor burden should be treated as per patients with advanced disease and high tumor burden. †With or without anti-CD20 maintenance therapy. ‡For frail patients.

in which surveillance is standard, has been used as a rationale to support use of surveillance for management of limited-stage disease in selected patients [59].

Advanced Disease

Patients with advanced disease may be symptomatic or asymptomatic at diagnosis, and not all require immediate therapy. The Groupe d'Etude des Lymphomes Folliculaires criteria, which include tumor burden and clinical parameters, offer guidance for when treatment should be initiated (Table 1) [60].

Surveillance is routinely favored for advanced disease, with therapy typically reserved for patients with symptoms from or significant burden or rapid pace of disease [2]. For advanced disease but low tumor burden and no disease-related symptoms, surveillance or rituximab monotherapy may be considered front-line therapy [2, 12]. Rituximab monotherapy is a relevant consideration for such patients, particularly those who are frail and unsuitable for chemoimmunotherapy, as a notable proportion of patients (30%) with symptomatic, advanced disease treated with rituximab alone may not need further therapy for >10 years [20].

Studies have assessed the benefit of immediate rituximab treatment versus surveillance in asymptomatic, advanced-stage disease [5, 20]. The largest showed a predictable PFS benefit of immediate rituximab therapy versus observation but no OS difference [5]. Additionally, the RESORT trial compared an extended rituximab schedule (four weekly doses followed by a single dose every 3 months until treatment failure) with a retreatment schedule (four weekly doses followed by retreatment at each disease progression) in stage III/IV and low tumor burden FL [61]. The retreatment strategy provided comparable disease control and delay of need for cytotoxic chemotherapy comparable to the extended schedule (median time to treatment failure: 3.9 vs. 4.3 years) and required cumulatively fewer rituximab doses, the latter of which is anticipated to result in benefits to the patient and health care system in terms of decreased direct and indirect costs. Importantly, this approach should only be used for patients with advanced stage but low tumor burden and not for patients who are candidates for chemoimmunotherapy.

Current standard of care (SOC) for advanced FL with high disease burden is chemoimmunotherapy regimens that include a CD20 antibody (e.g., rituximab, obinutuzumab) [2]. The addition of rituximab to combination chemotherapy regimens has resulted in improvement in clinical outcomes including objective response rates (ORR), complete responses (CR), time-to-progression, and OS in untreated, advanced-stage FL compared with chemotherapy alone [62–69]. Additionally, the 10-year follow-up of the PRIMA study showed that 2 years of rituximab maintenance therapy after first-line chemoimmunotherapy significantly improved PFS and >50% of patients did not require second-line treatment 10 years after chemoimmunotherapy [70, 71]. However, there continues to be no difference in OS with maintenance rituximab in this setting. Although these regimens remain SOC for first-line FL therapy, no randomized studies have shown OS superiority of a particular chemotherapy backbone among the available options; however, the safety profiles differ between regimens [67, 72–74]. For instance, the StiL and BRIGHT trials showed that a bendamustine backbone is as effective as rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) and has a better-tolerated side-effect profile especially with regard to hematological toxicities and infection rates [72, 73]. However, although bendamustine is favored as the chemotherapy backbone by many, there continues to be some variability in clinical practice [75, 76].

Obinutuzumab is a glycoengineered anti-CD20 monoclonal antibody that has greater antibody-dependent cellular toxicity and direct B-cell killing compared with rituximab [77]. First-line obinuzutuzumab in combination with chemotherapy was reported in the phase III GALLIUM study in indolent FL or

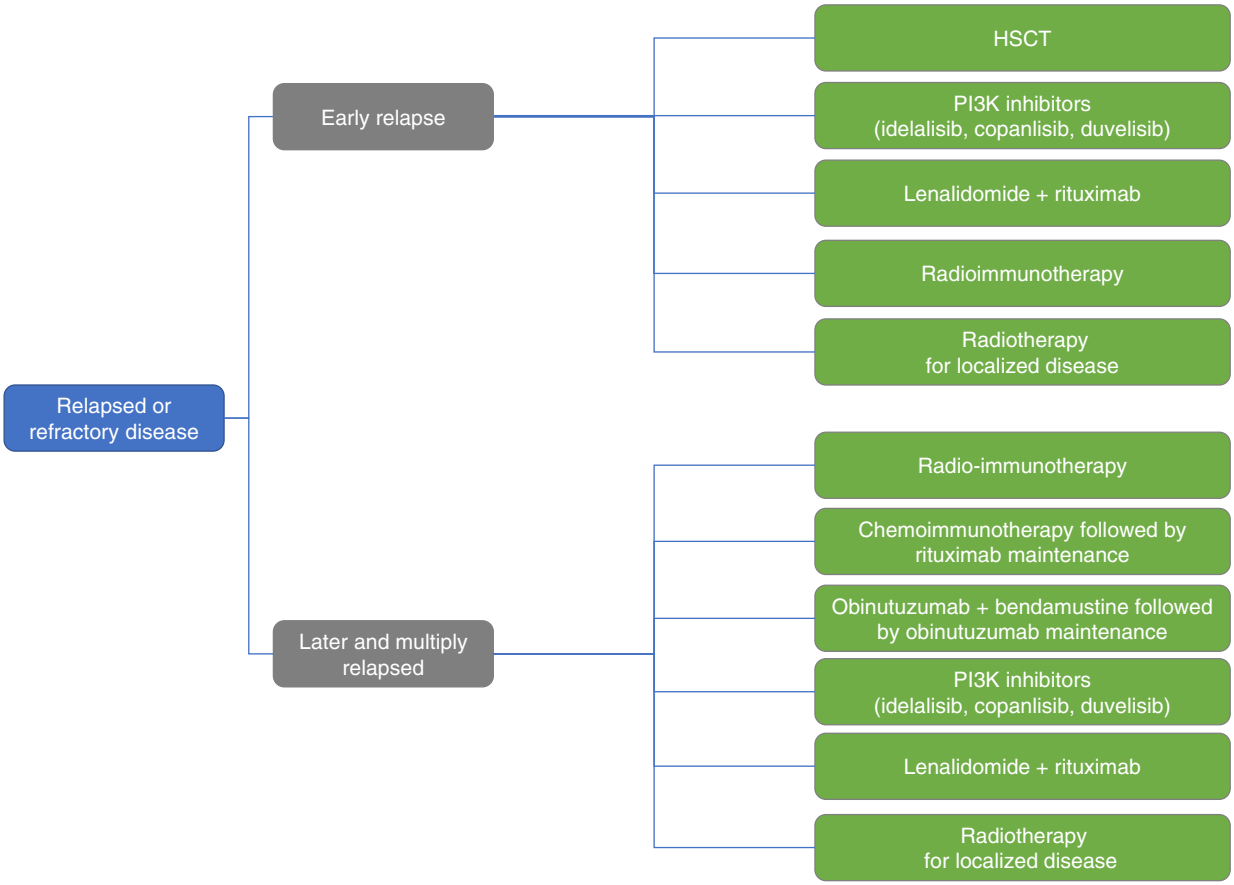

Figure 2. Treatment options in relapsed or refractory follicular lymphoma.
Abbreviation: HSCT, hematopoietic stem cell transplant.

marginal zone lymphoma [78]. Patients were randomized to induction treatment with obinutuzumab-based or rituximab-based chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP], cyclophosphamide, vincristine, prednisone [CVP], or bendamustine), and responding patients received ≤2 years of maintenance treatment with the same anti-CD20 antibody received during induction. An improvement in 3-year PFS was observed with obtinuzumab-based therapy (80% vs. 73%; p = .001), with no difference in 3-year OS. Post hoc analysis suggested that greater PFS benefit was seen in intermediate or high versus low FLIPI disease. ORR at the end of induction was similar in the two groups (89% vs. 87%), with PFS curves separating during maintenance therapy. Notably, obinutuzumab was associated with higher rates of infusion reactions (59% vs. 49%). Additionally, the side-effect profile varied by chemotherapy regimen and treatment phase; bendamustine was associated with higher grade 3–5 infection and second neoplasm rates during maintenance treatment, and CHOP with higher grade 3–5 neutropenia rates during induction.

Recently, results of the RELEVANCE trial in advanced, untreated FL indicated similar efficacy with rituximab plus lenalidomide (an immunomodulatory agent) compared with rituximab plus chemotherapy [79]. As a primary objective of this study, superiority of lenalidomide in combination with rituximab versus rituximab-based chemoimmunotherapy was not demonstrated (interim 3-year PFS: 77% vs. 78%). Moreover, higher rates of grade 3/4 neutropenia (50% vs. 32%) and cutaneous reactions (7% vs. 1%) were observed in the lenalidomide-containing arms. However, these results support consideration of rituximab and lenalidomide as a relevant first-line therapeutic option for select patients.

Relapsed/Refractory Disease

Even with therapeutic advances, FL remains largely characterized by multiple recurrences. Successive treatment lines will often be required in the disease course, and the choice of each treatment (Fig. 2) should aim to achieve disease control, promote quality of life (QoL), and minimize treatment-related toxicity.

Later and Multiply Relapsed Disease

Treatment of FL relapse or progression depends in part upon duration of remission with previous treatments [2, 12]. For patients with relapse or progression on first-line treatment who have a longer duration of remission, options can include chemoimmunotherapy followed by rituximab maintenance.

Obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance is also available for patients with rituximab-refractory FL [80, 81]. Approval in this setting is based on the phase III GADOLIN trial of obinutuzumab plus bendamustine versus bendamustine alone in patients with CD20 + indolent NHL refractory to rituximab [82]. PFS was significantly longer with combination therapy than with bendamustine monotherapy (25.8 vs. 14.1 months; hazard ratio [HR] = 0.57; p < .001), as was OS (HR = 0.67; p = .027) [83]. Obinutuzumab in combination with bendamustine represents a validated strategy for rituximab-refractory patients not previously treated with

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either agent; however, given the increased use of bendamustine as first-line therapy, this option may be relevant to only a small patient subset.

The oral PI3K-δ inhibitor idelalisib is included in treatment guidelines as a second-line treatment option in relapsed/refractory FL [12, 84], although U.S. approval is for relapsed FL in patients who have received ≥2 prior systemic therapies [84]. Importantly, idelalisib in combination regimens has been associated with increased risk of serious and potentially fatal adverse events (AEs) such as colitis or pneumonitis. This led to early halting of several phase III clinical trials and a low clinical uptake of idelalisib [85].

Copanlisib is an intravenously administered pan-class I PI3K inhibitor with higher potency against all class I isoforms than other clinically investigated PI3K inhibitors and specifically with heightened activity against the α and δ isoforms [86]. Copanlisib was licensed in the U.S. for patients with relapsed FL who have received ≥2 prior systemic therapies [87]. Accelerated approval was based on the phase II CHRONOS-1 trial in patients with indolent BCL (73% had FL) relapsing after or refractory to ≥2 prior therapies and who had received prior treatment with rituximab and an alkylating agent [88]. After a median treatment duration of 6 months, ORR was 60.6% in the full population and 58.7% in patients with FL; overall median duration of response was 14.1 months, and median PFS was 12.5 months [89]. The safety profile differs from that of daily oral PI3K inhibitors, with low rates of liver toxicity, colitis, pneumonitis, and opportunistic infections [88, 89]. Unique toxicities associated with copanlisib included transient hypertension and hyperglyemia. Phase III trials of copanlisib in relapsed FL are ongoing, including in combination with rituximab in patients relapsing after their last rituximab-containing therapy (NCT02367040), and in combination with chemoimmunotherapy (R-CHOP or bendamustine, rituximab [BR]; NCT02626455) [90].

Duvelisib, an oral PI3K inhibitor targeting both the δ and γ catalytic subunits, recently gained U.S. approval for relapsed/refractory indolent BCL including FL after ≥2 prior lines of therapy based on results of the phase II DYNAMO trial [91, 92]. ORR was 46% and median PFS and OS were 8.4 and 18.4 months, respectively, among patients refractory to both rituximab and alkylating chemotherapy [92]. Grade ≥ 3 AEs were seen, including neutropenia (28%), diarrhea (15%), and infection (20%); 5% of patients had a fatal AE.

Early encouraging reports are emerging from the phase III AUGMENT trial (NCT01938001), comparing rituximab and lenalidomide ("R^2") with rituximab monotherapy in patients with indolent NHL who were previously treated and had rituximab-sensitve relapsed disease [93]. R^2 was recently reported to achieve improved PFS (39.4 vs. 14.1 months) and ORR (78% vs. 53%; both $p < .0001$) compared with rituximab alone, although no significant OS benefit is yet seen at a median follow-up of 28.3 months.

Radioimmunotherapy (RIT) regimens, in which radioisotopes are conjugated to antibodies (commonly, anti-CD20 agents), have been used for the treatment of relapsed/refractory FL [2, 94]. Response rates of approximately 60% and median PFS and OS of >4 years have been reported with RIT in patients who have received ≥1 prior therapy, with best responders those with minimal bone marrow involvement and low tumor burden [95, 96]. RIT provides a valuable less toxic alternative for a select group of patients, although complexities in delivery of this treatment and availability of numerous competing agents have limited its widespread adoption; currently, ibirtumomab tiuxetan is the only RIT remaining on the market for FL treatment [97].

Early Relapse

Patients with FL experiencing early relapse after initial therapy are at high risk of poor outcomes. Currently, no single SOC exists for patients with POD24, and therapeutic approaches are generally intensification with standard agents or use of agents with novel mechanisms of action compared with front-line therapy.

High-dose chemotherapy with autologous hematopoietic stem cell transplantation (auto-HSCT) can prolong PFS and OS and should be considered as consolidative therapy in early relapse [2, 12, 98]. Few prospective data are available regarding HSCT in the era of modern therapies, and its role continues to be elucidated [2, 12]. Retrospective data suggest that patients with POD24 benefit from auto-HSCT (i.e., increased PFS and OS compared with those not receiving transplant) [98–101]. A recent study compared auto-HSCT with either matched-sibling donor (MSD) or unrelated matched donor (UMD) allogeneic HSCT (allo-HSCT) in patients with POD24 [102]. Findings suggest that outcomes are similar with either autologous or allogeneic transplant with MSD, whereas outcomes with UMD transplant were inferior, largely because of higher transplant-related mortality. Currently, allo-HSCT is largely restricted to fit patients who cannot achieve complete remission or have multiply relapsed disease.

In high-risk FL and early relapse after initial chemoimmunotherapy, idelalisib was studied in a retrospective analysis of patients with POD24, with 59% of patients achieving lymph-node response with idelalisib. The ORR was 57% and did not differ significantly whether patients had refractory or early relapsing disease (within 12 vs. 12–24 months) after initial therapy.

Data in early relapse are emerging for other agents and are particularly important for transplant-ineligible patients. In high-risk FL and early relapse after initial chemoimmunotherapy, idelalisib was studied in a retrospective analysis of patients with POD24, with 59% of patients achieving lymph-node response with idelalisib [103]. The ORR was 57% and did not differ significantly whether patients had refractory or early relapsing disease (within 12 vs. 12–24 months) after initial therapy. Lenalidomide is being investigated in the phase III MAGNIFY trial in combination with rituximab in relapsed/refractory NHL, including FL [104]. In patients with POD24, the ORR was 48% compared with an ORR of 67% in all patients with FL included in the study; 1-year PFS was 45% and 66%, respectively. Recently, exploratory assessments from the CHRONOS-1 trial of copanlisib in patients with relapsed/refractory NHL who had received ≥2 prior therapies suggested that ORR was similar between patients with FL with and without POD24 (60.3% vs. 58.8%) [105]. Additionally, the ongoing phase II SWOG 1608 study is evaluating obinutuzumab-based therapeutic combinations in early-relapsing/refractory FL.

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Table 2. Select clinical trials of investigational therapies in follicular lymphoma

Agent	Type	Phase	Trial registration	Design	Status (primary completion date)	Findings
BCL-2 inhibitors						
Venetoclax	BCL-2 inhibitor	2	NCT02187861	In combination with rituximab ± bendamustine in relapsed or refractory FL (n = 164)	Completed	ORR favored the triplet combination (68% vs. 33%) [133]
			NCT02877550	In combination with obinutuzumab in previously untreated FL (n = 25)	Recruiting (June 2021)	—
Histone-modifying enzyme inhibitors						
Tazemetostat	EZH2 inhibitor	1/2	NCT01897571	As a single agent in advanced solid tumors or B-cell lymphomas (n = 420)[a]	Recruiting (November 2019)	—
CPI-1205	EZH2 inhibitor	1	NCT02395601	As a single agent in B-cell lymphomas (n = 41); includes expansion cohort of patients ± *EZH2* mutation	Active (October 2018)	CPI-1205 found to be well tolerated with manageable toxicities and with evidence of antitumor activity [109]
Abexinostat	HDAC inhibitor	2	NCT03600441	In relapsed or refractory FL (n = 51)	Recruiting (September 2019)	—
		2	EudraCT-2009-013691-47	In relapsed or refractory NHL or CLL (n = 100)	Completed	ORR was 28% in the entire study population with the highest responses observed in the follicular lymphoma cohort (56%) Owing to hematologic toxicities, less dose-dense schedule recommended [113]
Mocetinostat	HDAC inhibitor	1/2	NCT02282358	In FL or DLBCL harboring *CREBBP* or *EP300* mutations (n = 72); FL cohort discontinued after 31 patients treated owing to sponsor decision	Active (October 2019)	ORR was 11.5% (95% CI 1.7%–20.7%) and TTR was 3.7–7.9 months in patients with FL [110]
Panobinostat	HDAC inhibitor	2	NCT01261247	In relapsed or refactory NHL (n = 41)	Active (May 2016)	21% (95% CI 7%–38%) had a confirmed ORR, and median OS was 14.9 (95% CI 8.8–46.4) months [90]
Vorinostat	HDAC inhibitor	2	NCT00875056	In previously treated FL or other indolent B-cell NHL or MCL (n = 56)	Active (February 2011)	ORR was 49% and median PFS was 20 months in patients with FL [111]
		2	NCT00253630	In relapsed or refractory FL, MZL, or MCL (n = 35)	Completed	ORR was 47% and median PFS was 15.6 months in patients with FL [112]
Immune checkpoint inhibitors						
Atezolizumab	PD-L1 inhibitor	2	NCT03465891	Atezolizumab ± low-dose radiotherapy in relapsed or refractory FL (n = 50)	Recruiting (March 2021)	—
			NCT02631577	Atezolizumab + obinutuzumab + lenalidomide in relapsed or refractory FL (n = 38)	Active (October 2018)	—
			NCT02596971	Atezolizumab with obinutuzumab + bendamustine or obinutuzumab + CHOP in relapsed or refarctory FL (n = 91)	Active (April 2018)	—
			NCT02729896	Atezolizumab + obinutuzumab + polatuzumab vedotin in relapsed or refractory FL (n = 36)	Active (September 2018)	—

(continued)

Table 2. (continued)

Agent	Type	Phase	Trial registration	Design	Status (primary completion date)	Findings
			NCT03276468	Atezolizumab + obinutuzumab + venetoclax in relapsed or refractory lymphomas including FL (n = 138)	Recruiting (November 2019)	—
Nivolumab	PD-1 inhibitor	2	NCT02038946	In relapsed or refractory FL (n = 116)	Active (May 2017)	ORR was 4.3% in 92 evaluable patients [90]
Pembrolizumab	PD-1 inhibitor	2	NCT02677155	Pembrolizumab + sequental intranodal therapy in untreated and relapsed FL (n = 20)	Recruiting (January 2020)	—
			NCT02446457	Pembrolizumab + rituximab in relapsed FL (n = 32)	Active (July 2019)	ORR was 64% in evaluable patients [121]
			NCT02501473	Intratumoral G100 ± pembrolizumab in treatement-naïve or relapsed or refractory FL (n = 117)	Active (December 2020)	—
			NCT03401853	Pembrolizumab + rituximab in relapsed or refractory FL (n = 37)	Recruiting (February 2021)	—
			NCT02650999	Pembrolizumab in patients not responding to or relapsing after CART for relapsed or refractory CD19+ lymphomas, including FL (n = 12)	Recruiting (January 2019)	—
			NCT03498612	In treatment-naïve NHLs, including FL (n = 33)	Recruiting (March 2020)	—
			NCT02332980	Pembrolizumab ± idelalisib or ibrutinib in relapsed or refractory CLL or low-grade NHLs, including FL (n = 68)	Recruiting (January 2020)	—
			NCT03035331	Pembrolizumab + dendritic cell therapy + cryosurgery in NHL, including FL (n = 44)	Recruiting (February 2021)	—
B-cell receptor pathway inhibitors						
Umbralisib	PI3K inhibitor	2	NCT03269669	Obinutuzumab ± umbralisib, lenalidomide or combination chemotherapy in patietns with relapsed or refractory grade I–IIIa FL (n = 150)	Recruiting (December 2022)	—
ME-401	PI3K inhibitor	1	NCT02914938	In relapsed or refractory FL or CLL/SLL and ME-401 + rituximab in elapsed or refractory B-cell NHL or CLL/SLL (n = 133)	Recruiting (March 2020)	Found to be well tolerated with no dose-limiting toxicities [115] ORR of 75% observed in the FL cohort [115]
Cerdulatinib	Syk/Jak inhibitor	1/2	NCT01994382	Cerdulatinib in patients with relapsed or refractory NHL or CLL (n = 283)	Recruiting (December 2019)	—
Ibrutinib	BTK inhibitor	3	NCT01974440	Ibrutinib + bendamustine vs. rituximab + R-CHOP in previously treated NHLs, including FL (n = 403)	Active (July 2020)	—
			NCT02947347	Ibrutinib + rituximab vs. rituximab alone in older adults with treatment-naïve FL (n = 440)	Recruiting (January 2022)	—

(continued)

Table 2. (continued)

Agent	Type	Phase	Trial registration	Design	Status (primary completion date)	Findings
Antibody–drug conjugates						
Polatuzumab vedotin	Anti-CD79 mAb conjugated to a microtubule toxin	1/2	NCT02729896	Obinutuzumab + atezolizumab + polatuzumab vedotin in relapsed or refractory FL (n = 36)[b]	Active (September 2018)	—
			NCT01691898(ROMULUS)	Pinatuzumab vedotin or polatuzumab vedotin in combination with rituximab or polatuzumab vedotin + obinutuzumab in relapsed or refractory FL or DLBCL (n = 230)	Active (March 2017)	In patients with FL receiving polatuzumab vedotin plus rituximab, the ORR was 75% [90] In patients with FL receiving polatuzumab vedotin plus obinutuzumab, the ORR was 78% [130]
			NCT02257567	Polatuzumab vedotin + bendamustine + rituximab or obinutuzumab in relapsed or refractory FL or DLBCL (n = 314)	Recruiting (January 2020)	In the FL cohort, 67% of patients had grade 3/4 AEs (most commonly neutropenia and thrombocytopenia) and 25% had serious AEs [129] All six patients with FL had a CR or PR regardless of treatment regimen [129]
Bispecific antibodies						
Mosunetuzumab	Bispecific CD3 and CD20 inhibitor	1	NCT02500407	Single agent and combined with atezolizumab in patients with relapsed or refractory NHL or CLL (n = 665)	Recruiting (September 2019)	—
Anti-CD47 therapies						
Hu5F9-G4	CD47 antigen inhibitor	1/2	NCT02953509	Hu5F9-G4 + rituximab in relapsed or refractory NHLs, including follicular lymphoma (n = 72)	Recruiting (March 2020)	—
CAR-T						
Tisagenlecleucel		3	NCT03570892 (BELINDA)	Tisagenlecleucel vs. SOC in relapsed or refractory B-cell NHLs, including FL (n = 318)	Not yet recruiting (May 2025)	—
Axicabtagene ciloleucel		2	NCT03105336 (ZUMA-5)	Axicabtagene ciloleucel following conditioning fludarabine plus cyclophosphamide conditioning regimen in relapsed or refractory indolent NHLs (n = 80)	Recruiting (March 2020)	—
JCAR017		1	NCT02631044 (TRANSCEND-NHL-001)	Single- or 2-dose JCAR017 schedule in relapsed or refractory B-cell NHL, including FL (n = 274)	Recruiting (December 2020)	—

Data from ClinicalTrials.gov are current as of January 31, 2019. The database was searched for clinical trials using the search term "follicular lymphoma" and limited to clinical trials that are "not yet recruiting," "recruiting," "active, not recruiting," or "completed." The resulting entries were reviewed to identify clinical trials of nonlicensed agents. Listed are the latest phase clinical trial (i.e., phase I, II, or III) for each individual nonlicensed agent.

[a]Combination therapy with prednisolone in patients with DLBCL is also being assessed.

[b]Includes assessment of rituximab + atezolizumab + polatuzumab vedotin in relapsed or refractory DLBCL.

Abbreviations: BCL-2, B-cell leukemia/lymphoma-2; CAR-T, chimeric antigen receptor T-cell therapy; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HDAC, histone deacetylasetransferase; JAK, Janus kinase; mAB, monoclonal antibody; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; ORR, objective response rate; OS, overall survival; PD-L1, programmed death–ligand 1; PFS, progression-free survival; SLL, small lymphocytic lymphoma; SOC, standard of care; Syk, spleen tyrosine kinase.

Table 3. Unmet needs in follicular lymphoma

Unmet need	Current practice	Areas of research and potential solutions
Selecting the most appropriate treatment for an individual patient at a particular time	Identifying patients with limited disease who are candidates for radiation therapy versus rituximab monotherapy or chemoimmunotherapy regimens as front-line management is not always clear; it is not known whether surveillance should be a management option for these patients in the context of the availability of active and minimally toxic therapies. Identifying therapies to manage disease that is refractory to anti-CD20 regimens is difficult, as the activity and safety of investigational agents in this setting has been limited.	Consensus is needed regarding how to manage patients with high-risk disease. Development of novel therapies in the coming years should consider how to tailor and optimize the benefit-risk ratio of therapies and regimens. Determining predictive biomarkers of progression, response, and resistance to specific therapies will improve patient selection for observation and intervention. Therapeutic strategies should be developed to reduce the risk for histologic transformation.
Availability of a clinically useful tool to identify patients with high-risk disease	Most prognostic tools do not guide therapy; they are measured at diagnoses and never measured again during the disease course, as they have not been validated in these later settings.	Prospective validation, head-to-head comparisons, and international consensus for clinically useful tools to identify patients with high-risk disease. Potential integration of molecular, clinical, and imaging parameters may be required to define with improved prognostic accuracy.
Specific genetic and epigenetic aberrations in an individual patient are not currently accounted for in their management	Therapies targeting molecular alterations do not feature in the current SOC.	A better understanding of disease biology may reveal new therapeutic avenues. Targeted therapies, presently available and in development, need to be matched to individual disease biology.

Abbreviation: SOC, standard of care.

Investigational Therapies

The armamentarium of treatment options is continually expanding, with numerous novel therapies attempting to exploit specific biological vulnerabilities of FL. Enrollment in clinical trials evaluating emerging therapies remains a high priority for patients with relapsed/refractory FL requiring treatment, especially those who are refractory to both rituximab and alkylating agents (double refractory). The following section summarizes some of these emerging therapies (Table 2).

Drugs Targeting Epigenetic Modification

A genetic hallmark of FL is the presence of mutations in histone-modifying enzymes [106]. The gene for one such enzyme, EZH2, is mutated in about 25% of cases [107]. Oral inhibitors of EZH2 (e.g., tazemetostat, CPI-1205) are being examined in phase II studies in FL, with early analyses suggesting high response rates in *EZH2*-mutated disease (ORR 82% for tazemetostat) [108, 109]. Several histone deacetylase inhibitors are also undergoing clinical investigation in FL to address loss of histone acetylation associated with *CREBBP* and *EP300* mutations, including phase II trials with panobinostat [90], mocetinostat [110], vorinostat [110–112], and abexinostat [113].

Drugs Targeting Signaling Pathways

Chronic activation of B-cell receptor (BCR) signaling is critical in FL progression, leading to activation of several signal transduction pathways (e.g., NF-kB, PI3K-AKT) promoting proliferation and survival of malignant B cells [106]. Mutations in genes encoding proteins in BCR pathways are also common [23, 24, 29–31]. In addition to PI3K already described, new PI3K inhibitors are under development in FL, including umbralisib (which also targets casein kinase-1ε) [114] and ME-401 [115].

Mutations in the BCR and NF-κB signaling pathway can occur in patients with FL, affecting the caspase recruitment domain-containing protein 11 (CARD11) commonly and Bruton tyrosine kinase (BTK) infrequently [116]. Ibrutinib is a small-molecule BTK inhibitor with effects on apoptosis, cellular adhesion, migration, and the tumor microenvironment [117]. In the phase II DAWN trial in relapsed/refractory FL, single-agent ibrutinib did not meet the lower bound ORR threshold for the primary endpoint (ORR 20.9%) [118]. Similar low ORR was reported in another phase II trial of ibrutinib in recurrent FL (37.5%), although interestingly, *CARD11* mutations predicted resistance to ibrutinib [119]. Given limited monotherapy activity, combination ibrutinib regimens in FL are being investigated [90].

Drugs Targeting the Immune System

The programmed cell death-1 (PD-1) protein is widely expressed and found on activated T cells, B cells, and natural killer (NK) cells [120]. PD-1 binding to programmed death ligand-1 and ligand-2 produces inhibitory signals leading to T-cell apoptosis. Additionally, PD-1 inhibits antitumor cytotoxicity through decreased NK cell-mediated killing. Inhibitors of the PD-1 pathway (i.e., immune checkpoint inhibitors) are undergoing clinical investigation in FL, including pembrolizumab [121], nivolumab [90], and atezolizumab [122]. Although single-agent

CME

activity appears limited in FL [123], there may be synergy with other agents, including CD20 antibodies [124].

CD47 is a ubiquitously expressed penta-transmembrane domain immunoglobulin-like protein that associates with integrins and is a receptor for thrombospondin, an extracellular matrix protein [125]. CD47 is also involved in the macrophage interaction that inhibits phagocytosis, and is involved in several biologic processes (e.g., motility, adhesion, and migration of leukocytes, phagocytosis, recognition of "self"). Hu5F9-G4 is a humanized antibody targeting CD47 that stimulates tumor phagocytosis and antitumor responses [126], and results in a phase I/IIb trial in relapsed/refactory FL have recently been reported (ORR and CR of 71% and 43%, respectively, in the seven patients in the FL cohort) [127].

Antibody-drug conjugates, designed to provide targeted delivery of cytotoxic agents to antigen-expressing tumor cells, are also being investigated in FL [128]. Phase I/II trials suggest polatuzumab vedotin is active in FL in combination with rituximab (ORR 75.0%) [90], in combination with rituximab and bendamustine (ORR 100%) [129], and in combination with obinutuzumab (ORR 78%) [130].

Another strategy for immune-based therapy is development of biphenotypic antibodies that are able to bind to malignant lymphocytes as well as engage and activate cytotoxic T cells [90, 129]. Mosunetuzumab is one such biphenotypic antibody, with binding domains for both CD20 and CD3, and evaluation of the agent in FL is ongoing [131]. Additionally, tisagenlecleucel, an anti-CD19 chimeric antigen receptor (CAR) T-cell therapy in which autologous T cells are gene-modified to carry antigen specificity for CD19, is licensed for the treatment of relapsed/refractory high-grade B-cell lymphoma and DLBCL arising from FL based on results from a single-arm clinical trial [132]. Tisagenlecleucel is under investigation in a phase III trial in relapsed/refractory FL [90, 117]. Other CAR-T therapies undergoing clinical investigation in FL include axicabtagene ciloleucel and JCAR017.

Remaining Unmet Needs

- The protracted multiply relapsing clinical course of FL presents a fundamental challenge for how clinicians should best balance treatment efficacy, minimizing toxicity and preserving QoL.
- Although the armamentarium of FL therapies has expanded, the optimal approach to selecting and sequencing treatments for an individual patient continues to be elucidated (Table 3).
- Although several risk stratification tools exist with new models being developed, we continue to lack a clinically useful tool that can accurately identify patients with high-risk disease who may benefit from individualized management to achieve longer remission, prevent transformation or resistance, and thereby further improve clinical outcomes.

Conclusion

Significant strides have been made in outcomes for patients with FL. Our next priorities must tackle the subsets of patients that are early progressors or multiply relapsed by defining optimum strategies to improve survival. Successfully achieving this will require improved prognostication, understanding and integration of the disease biology, and delineating molecular determinants of response and resistance to existing and emergent therapies. Most notably, POD24 has been shown to be a powerful predictor of poor outcome, although it is not clear if it can become a standard surrogate endpoint to evaluate efficacy of investigational treatments. Finally, current FL treatment strategies are based on a "one size fits all" approach; specific genetic and epigenetic aberrations in an individual patient are not currently accounted for in their management. No genomic studies can be recommended currently with sufficient validation, although this is an area of ongoing investigation if we can identify biomarkers correlated with predictive or prognostic value. In the future, a personalized approach to treatment could help determine the most appropriate treatment for an individual patient based on specific patient, clinical, genetic, and epigenetic factors with our improved ability to marry disease biology to therapy.

Acknowledgments

This review article was written on behalf of LYMPHOMA CONNECT; for more information, please visit www.lymphomaconnect.info. LYMPHOMA CONNECT is supported by an Independent Educational Grant from Bayer. Bayer did not have a critical role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review and approval of the manuscript; or decision to submit the manuscript for publication. We thank Dr. Georg Lenz for his helpful comments in the preparation of this review. Medical writing assistance was provided by Tricia Newell, Ph.D., and Mark English, Ph.D., of COR2ED, Basel, Switzerland.

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CME

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(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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