Ther Adv Hematol
2019, Vol. 10: 1–20
DOI: 10.1177/2040620718820510

Novel treatment approaches and future perspectives in follicular lymphoma

Grerk Sutamtewagul and Brian K. Link

Abstract: Follicular lymphoma (FL) is a common B-cell malignancy characterized by relatively indolent growth and incurability with an expected lifetime course of serial intermittent treatment courses. Many patients with FL have lives shortened by the disease and despite a relatively favorable prognosis relative to other incurable systemic malignancies, optimal management of FL has not been achieved. This review focuses on identifying both patients for whom novel therapies might be most beneficial as well as systematically reviewing novel strategies at various levels of investigation. Prognostic markers incorporating clinical measurements and tumor genetics are discussed, yet at the time of diagnosis do not yet powerfully discriminate patients for whom specific strategies are beneficial. Reassessment of prognosis after evaluating the response to initial therapy is the most powerful identifier of those in need of novel management strategies. For initial therapy of high burden systemic disease, anti-CD20 antibody along with chemotherapy or immunomodulators all offer relatively similar effects on overall survival with subtly different effects on progression-free survival and quality of life. Several new agents currently under investigation in the upfront setting are discussed. Perhaps the best testing ground for novel therapies is in patients with early relapse following initial immunochemotherapy. Ongoing research in multiple therapy classes including, novel monoclonal antibodies, antibody drug conjugates, immunomodulatory agents, intracellular pathway inhibitors, immune checkpoint inhibitors, and epigenetic regulators are discussed herein.

Keywords: antibody–drug conjugate, anti-CD20 antibody, BCL2 inhibitor, BTK inhibitor, EZH2 inhibitor, follicular lymphoma, immune checkpoint inhibitor, PI3K inhibitor, radioimmunotherapy, SYK inhibitor

Received: 31 August 2018; revised manuscript accepted: 30 November 2018.

Introduction

Follicular lymphoma (FL) is the third most common lymphoid malignancy, after diffuse large B-cell lymphoma (DLBCL) and chronic lymphocytic leukemia/small lymphocytic lymphoma, with 13,960 estimated new cases in the United States (US) in 2016. The incidence rate of FL has been stable in the past decade.[1] The economic impact of FL is substantial, reflected in the healthcare cost approximate of DLBCL (US$10,460 per patient, per month).[2] Despite generally being considered as an incurable disease, the outlook in most patients is good with a 5-year overall survival (OS) around 75%,[3] and median OS of more than 18 years in the most recently available data.[4] However, FL is a heterogeneous disease, clinically and biologically, with a prognosis varied among individuals and varying within an individual over time. The strongest predictor of a poor outcome is the progression of the disease within 2 years after diagnosis following treatment with chemoimmunotherapy which predicts a 5-year OS of approximately only 50%.[5,6] Conversely, patients whose disease does not progress within 2 years have a subsequent expected 10-year survival indistinguishable from age and sex-matched peers.[6] Histologic transformation to a high-grade lymphoma is uncommon and not very predictable but has substantial impact on a few patients affected. The high

Correspondence to:
Grerk Sutamtewagul
Division of Hematology, Oncology, and Blood & Marrow Transplantation, Department of Internal Medicine, University of Iowa Carver College of Medicine, 200 Hawkins Dr., C305 GH, Iowa City, IA 52242, USA
grerk-sutamtewagul@uiowa.edu

Brian K. Link
Division of Hematology, Oncology, and Blood & Marrow Transplantation, Department of Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, IA, USA

incidence, relapsing natural history, and clinical heterogeneity of FL make it a fertile environment for testing novel anti-lymphoma therapies occasionally leading to challenges in retaining focus on truly unmet patient needs and identifying genuinely impactful advances in patient care.

This review focuses primarily on the management of advanced-stage, high-tumor burden FL. Following a brief discussion of standard treatment in the treatment-naïve and relapsed and refractory settings, we identify areas of unmet need and review clinical experience of novel therapeutic agents and ongoing clinical studies.

Novel treatment approach in treatment-naïve follicular lymphoma

Prognosis evaluation: moving toward a risk-adapted and response-adapted approach

Even though the prognosis of FL has been improving in the past decades, this improvement does not apply to all patients. There are many measurable outcomes of interests in FL including OS, progression-free survival (PFS), progression of disease at 24 months after diagnosis (POD24), and histologic transformation. Harder to measure, but no less important are measures of quality of life among surviving FL patients. Several prognostic indices have been developed to predict the measurable clinical course of patients (Table 1). The best known and most widely used prognostic index is the Follicular Lymphoma International Prognostic Index (FLIPI)[7] which was built from the analysis of 4167 patients, mostly in the pre-rituximab era. FLIPI performs well in identifying three balanced risk groups with a different 10-year OS. FLIPI-2 was developed to counter the problem of counting nodal sites in FLIPI, determine PFS, and identify prognosis in the rituximab era. However, FLIPI-2 has not gained popularity, likely due to the lack of clear superiority in prognostication or guidance in therapeutic strategy.[8–10]

Since tumor burden is a major component of these prognostic models, yet relatively hard to precisely quantify, radiographic data were also exploited to better determine FL risk. Baseline total metabolic tumor volume (TMTV) from positron-emission tomography (PET) greater than 510 cm^3 predicts inferior OS and PFS independent of the FLIPI score.[14] Moreover, combination of TMTV and FLIPI-2 also identifies patients at high risk of early progression. Integrating positive end-of-treatment PET imaging with baseline TMTV seems to enhance its prognostic value.[15] Besides clinical, genetic, and radiographic data, many measures of tumor burden were tested in determining prognosis including circulating tumor cells, cell-free DNA, mutational burden, and minimal residual disease.[16–18] If these findings are externally validated, it will add other aspects in building a more comprehensive prognostic model.

Just as the above early measures of response to treatment are prognostically important, other opportunities to reassess prognosis beyond initial diagnosis add value for the patient with FL. One of the most important events that determine prognosis in patients with FL treating with chemoimmunotherapy is POD24. Despite being most predictive of poor OS, we are still not able to identify this very high-risk group at the time of diagnosis or before initiation of the first therapy. Novel prognosis scoring systems have addressed this issue and tried to predict POD24 at the time of diagnosis. This includes a simple clinical scoring system, PRIMA-PI,[13] and a clinicogenetic scoring system, m7-FLIPI,[12] both of which seem to correlate better with POD24 than the FLIPI score but neither of which identifies with adequate sensitivity or specificity those patients destined for early relapse.

Despite the prognostic capability for populations of patients with FL, today's models still have a minimal role in clinical decision making for individual patients such as when to initiate treatment or how frequent the follow up should be. GELF (Groupe d'Etude des Lymphomes Folliculaires) criteria were developed to standardize patients enrolled in clinical trials of initial treatment with immunochemotherapy,[19] and are often adapted as guidelines for the initiation of treatment. Focusing on absolute OS may misguide the care of patients of different age groups who do not have the same life expectancy or who have relatively high competing mortality risks; and so, looking at relative survival is an appropriate alternative. The ideal prognostic model should be able to predict which patients will soon be symptomatic and may need treatment sooner. Ultimately, the ideal model needs to identify those who are at risk of dying from FL, or its surrogates such as POD24, with good discriminatory power and subsequent randomized clinical

Table 1. Summary of selected prognostic indices in follicular lymphoma.

Prognostic index	Patient population	Components	Risk groups	Survival
FLIPI[7]	Multinational retrospective cohort, pre-rituximab era	Number of nodal sites >4 Elevated LDH Age > 60 years Stage III or IV disease Hemoglobin < 12 g/dl	Low risk (0–1 factor) Intermediate risk (2 factors) High risk (⩾3 factors)	10-y OS Low risk 71% Intermediate risk 51% High risk 36%
FLIPI-2[11]	Prospective multicenter study	Age > 60 years Elevated β2-microglobulin Hemoglobin < 12 g/dl Bone marrow involvement Lymph node dimension >6 cm	Low risk (0 factor) Intermediate risk (1–2 factors) High risk (3–5 factors)	5-y PFS Low risk 80% Intermediate risk 51% High risk 19%
m7-FLIPI[12]	Prospective study and population-based registry of patients receiving chemoimmunotherapy	High-risk FLIPI ECOG performance status >2 Mutation status of 7 genes (*EZH2, ARID1A, MEF2B, EP300, FOXO1, CREBBP, CARD11*)	Weighed summation Low risk (<0.8) High risk (>0.8)	5-y FFS Low risk 77% High risk 38% 5-y OS Low risk 90% High risk 65% Predictive of POD24
PRIMA-PI[13]	Prospective study and population-based registry of patients receiving chemoimmunotherapy	β2-microglobulin > 3 mg/l Bone marrow involvement	Low risk (0 factors) Intermediate risk High risk (β2-m > 3 mg/l)	5-y PFS Low risk 69% Intermediate risk 55% High risk 37% Predictive of EFS24

ECOG, Eastern Cooperative Oncology Group; EFS, event-free survival; FFS, failure-free survival; FLIPI, Follicular Lymphoma International Prognostic Index; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; POD24, progression of disease at 24 months.

trials should be developed, assigning different strategies for this particularly high-risk group.

There is currently no established risk-adapted approach to assign different treatments to patients of different risk groups. Examples of risk-adapted approach studies based on the FLIPI score include a study of consolidation with 90-yttrium-ibritumomab tiuxetan after fludarabine, mitoxantrone, and rituximab for intermediate-high risk FL[20] and a study of bendamustine-rituximab with or without bortezomib followed by rituximab with or without lenalidomide in patient with high-risk FLIPI (ClinicalTrials.gov identifier: NCT01216683).[21]

Histologic transformation (HT) occurs in patients with FL at the rate of approximately 2% per year. There is currently no prognostic model to predict HT; however, several risk factors have been identified such as advanced age, high FLIPI score, elevated lactate dehydrogenase (LDH) and certain genetic markers.[22,23] Risk factors and preventive strategies were previously reviewed and discussed.[24]

Standard frontline treatments of follicular lymphoma: what have we learned from them?

Treatment of FL is mainly motivated by stage, and disease burden. Patients with advanced-stage, asymptomatic disease with low tumor burden can be observed[25] or treated with single-agent rituximab.[26] In patients with advanced-stage, high-tumor burden disease, treatment with chemoimmunotherapy plus consideration of maintenance rituximab is the standard of care. Bendamustine-rituximab (BR) has demonstrated superior efficacy to other available regimens in two phase III trials. The StiL study compared BR with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in indolent non-Hodgkin's lymphoma (NHL) and mantle cell lymphoma. BR was shown to result in longer PFS (69.5 *versus* 31.2 months overall, and not reached *versus* 40.9 months in the FL subgroup) and a higher complete response rate (CRR; 40% *versus* 30%) with no difference in overall response rate (ORR) or OS.[27] BR also caused less hematologic toxicity, alopecia, peripheral neuropathy, infection and mucositis. A 9-year

updated result confirms a PFS benefit without an apparent difference in OS and the rate of secondary malignancy.[28] The BRIGHT study, which is similar in patient population to the StiL study, showed noninferiority of BR to R-CHOP or rituximab plus cyclophosphamide, vincristine and prednisone (R-CVP) with similar CRRs, which was the primary endpoint.[29] Side-effect profiles were different, with more vomiting and drug hypersensitivity in the BR group and more neuropathy and alopecia in the R-CHOP/R-CVP group. A 5-year update of the BRIGHT study confirmed the findings of StiL study, with a better 5-year PFS (65.5% *versus* 55.8%) and a similar 5-year OS (81.7 *versus* 85.0%) in BR *versus* R-CHOP/R-CVP groups, respectively.[30] There are several limitations of StiL and BRIGHT studies. Both have included mantle cell lymphoma which seems to benefit the most from bendamustine. However, in the StiL study, a PFS benefit in the FL subgroup was demonstrated and the interaction test for histology subtypes was not statistically significant, but the subgroup analysis and interaction test were not prespecified. Using CRR as its primary endpoint and the noninferiority design of the BRIGHT study limit the claim for superiority of a PFS benefit for bendamustine. Exploratory analysis of the GALLIUM study raises the concern for safety of a full course of bendamustine-anti-CD20 antibody followed by antibody maintenance.[31,32] The nonrelapsed death rate was higher in bendamustine-treated patients than in patients who received CHOP or the CVP chemotherapy backbone (5.2% *versus* 1.8%). Of note, the assignment of chemotherapy was not randomized, and this finding is subjected to several confounders.

There are several situations where R-CHOP may be selected preferentially to BR in the frontline treatment of FL despite the lack of strong evidence. This includes FL with high SUVmax on a PET scan,[33] grade 3 FL,[34] aggressive behavior such as solid organ invasion, destructive bony lesion, or other markers of aggressive biology.

The role of maintenance rituximab after treatment with chemoimmunotherapy was clarified in the PRIMA trial.[35] Chemoimmunotherapy regimens in this study include R-CVP, R-CHOP, and R-fludarabine, cyclophosphamide, and mitoxantrone. PFS was improved with maintenance rituximab (MR; 74.9% *versus* 57.6% at 3 years). OS did not differ significantly. Patients in the MR group developed more grade 2–4 infections (39% *versus* 24%). This was confirmed in the 10-year update of the PRIMA study with median PFS of 10.49 years in the MR arm *versus* 4.06 years in the control arm. Again, there was no OS difference between the arms with 10-year OS of 80% in both groups.[36] The benefit of MR after BR is less well defined. A retrospective analysis of the BRIGHT study, in which the use of MR was at investigator discretion, showed a PFS benefit in the BR subgroup [hazard ratio (HR) 0.50, $p = 0.0295$].[37] BR-treated patients who achieved complete response (CR) after induction treatment were less likely to receive MR (40% *versus* 22%). A retrospective analysis of real-world data showed that MR improved PFS in patients who achieved PR (HR 0.36, $p = 0.003$) but not in patients who already achieved CR.[38]

StiL, BRIGHT, and PRIMA studies did not only establish efficacy of chemoimmunotherapy and MR in frontline setting but also gave us insight to the current upfront FL management. Regimens with better PFS do not dependably translate to difference in OS, at least within the time frame of the studies. Moreover, most patients in this setting will do well; and so, clinical trials for this setting should test for regimens that have less short and long-term toxicity, are easy to administer, and give acceptable, noninferior PFS compared with the current standard. Potentially curable therapies may be achieved using agents with novel mechanisms of action but the anti-lymphoma activity of candidate agents is best identified in the relapsed setting.[39]

Because the addition of rituximab to chemotherapy significantly improved the response, PFS, and OS,[40,41] new generations of anti-CD20 monoclonal antibodies (mAbs) were developed. Obinutuzumab is a glycoengineered type II mAb with greater antibody-dependent cellular cytotoxicity (ADCC) and phagocytosis and direct caspase-dependent programmed cell death, but less complement-dependent cytotoxicity (CDC) than rituximab. In the GALLIUM study utilizing a large prospective randomized phase III study design, obinutuzumab was combined with CHOP, CVP or bendamustine (O-chemotherapy) and followed by a 2-year obinutuzumab maintenance, compared with rituximab-chemotherapy followed by MR as a control group.[31] PFS at 3 years was statistically longer with O-chemotherapy than rituximab-chemotherapy (80.0% *versus* 73.3%). There was no OS difference during 34.5 months median follow up.

ORR and CRR were also similar. Patients in the O-chemotherapy group developed more neutropenia especially during the maintenance phase (16.4% *versus* 10.7%) and more infusion-related reaction (59.3% *versus* 48.9%). Whether the improved PFS was due to the inherent properties of obinutuzumab or just because it was used at higher dose (approximately two-fold higher cumulative dose) remains unknown. This 7% PFS difference at 3 years at the expense of an increase in toxicity makes it marginally appealing to change practice from using rituximab to obinutuzumab in the frontline setting for all patients. Based on the result of the GALLIUM trial, the United States Food and Drug Administration (US FDA) has approved obinutuzumab in combination of chemotherapy for previously untreated FL.

Novel therapeutics in treatment-naïve follicular lymphoma

New-generation anti-CD20 monoclonal antibodies. Currently there are no other anti-CD20 mAbs that have been or are being tested in the first-line treatment of FL. Many are being tested in the relapsed and refractory setting and will likely move toward treatment in the upfront setting if they show good activity.

Immunomodulatory agents. Attempts to treat malignant disease without conventional cytotoxic/DNA-damaging chemotherapy have been made in FL as well as in other cancers with the hope to reduce adverse reaction and second malignancy. The combination of rituximab and lenalidomide (R^2) has given promising results. In the SAKK 35/10 study, rituximab with or without lenalidomide is tested in previously untreated symptomatic FL, demonstrating higher CRR in the combination arm (36% *versus* 25%) along with longer PFS (not reached *versus* 2.3 years).[42] In the RELEVANCE study (ClinicalTrials.gov identifier: NCT01650701), rituximab weekly for 4 weeks followed by every 4 weeks was combined with lenalidomide 20 mg daily for 3 weeks in each 4-week cycle for 6–12 cycles. This was compared with R-CHOP, R-CVP or BR as the control arm. Both arms had similar CRR, 2-year and 3-year PFS, and also OS. However, because of its superiority trial design, the RELEVANCE study did not meet their primary endpoints. In term of adverse reactions, the R^2 regimen caused less neutropenia, febrile neutropenia (2% *versus* 6%), and nonhematologic toxicity but resulted in more dermatologic toxicity (7% *versus* 1%). This similar efficacy and favorable tolerability to R-chemotherapy in the interim analysis makes this R^2 regimen a potential new approach to treat FL in the first-line setting for some patients, especially those wishing to avoid hematologic toxicity. Moreover, different approaches to conventional chemoimmunotherapy may pave the way to cross the barrier of PFS-OS correlation. Long-term follow-up data are eagerly awaited.[43]

A study of obinutuzumab and lenalidomide for the frontline treatment of FL is ongoing (ClinicalTrials.gov identifier: NCT02871219).

Intracellular pathway inhibitors

Bruton tyrosine kinase inhibitors. Bruton tyrosine kinase (BTK) is one of the upstream components in the B-cell receptor pathway, among others, which is essential in B-cell homeostasis and survival.[44] With activity across various B-cell lymphomas, it is also tested in FL. In a phase II study, frontline treatment with ibrutinib plus rituximab resulted in ORR of 75–85% and CRR of 35–40%. The 1-year PFS rates were 77–87% in this preliminary report.[45] Randomized phase III studies of ibrutinib plus rituximab in elderly patients (ClinicalTrials.gov identifier: NCT02947347) and in all-comers (ClinicalTrials.gov identifier: NCT02451111) are ongoing. Also, a study of ibrutinib and obinutuzumab is underway (ClinicalTrials.gov identifier: NCT02689869).

A phase I trial of ibrutinib, lenalidomide and rituximab combination was reported to have ORR of 95% and 1-year PFS of 80%; however, it led to significant toxicity including rash (all grades 82% with 36% grade 3). Half of the patients required dose reduction due to toxicity. With toxicity and lack of significant additional benefit to R^2 regimen, further investigation of this combination in the upfront setting is unlikely.[46]

Phosphatidylinositol 3-kinase inhibitor. Signaling of the B-cell receptor pathway is also mediated by phosphatidylinositol 3-kinase (PI3K), AKT, the mechanistic target of the rapamycin (mTOR) pathway. There are four catalytic isoforms of PI3K that differ in their tissue expression; and the γ and δ isoforms are quite specific to hematopoietic cells. The first-in-class PI3Kδ inhibitor, idelalisib, has shown good activity in chronic lymphocytic leukemia (CLL).[47] Although it is approved for use in relapsed FL, it has not paved the way to the frontline setting at this point,

likely due to concerns of toxicity. A study of idelalisib in combination with rituximab in untreated FL patients was terminated early due to high rate of severe hepatotoxicity (ClinicalTrials.gov identifier: NCT02258529).

Duvelisib, a dual PI3Kδ/γ inhibitor, is combined with rituximab (DR) or obinutuzumab (DO) in the first-line treatment of FL (ClinicalTrials.gov identifier: NCT02391545). Preliminary analysis showed ORR of 87% and 91% in DR and DO, respectively, with CRR of approximately 20% in both arms. Elevated liver enzymes and rash are common side effects. Of note, many patients need dose modification (63–64%) or discontinuation (7–14%) due to adverse events.[48] Hepatotoxicity seems to be the major barrier for the development of this class of medication.

BCL2 inhibitor. Translocation of chromosomes 14 and 18 is found in 90% of FL patients.[49] This translocation results in deregulated expression of the antiapoptotic protooncogene *BCL2*. BH3-mimetic drugs, which mimic the activity of physiologic antagonist of BCL2 and other antiapoptotic proteins, have demonstrated good activity in relapsed/refractory CLL.[50] The response rate of BCL2 inhibitor alone in relapsed or refractory FL is not as high as expected given the overexpression of BCL2 as the hallmark of the disease. This could be due to the ability to use other anti-apoptotic signaling molecules or just simply an inadequate dosing.[51] Ongoing studies in the first-line setting include venetoclax and obinutuzumab, (ClinicalTrials.gov identifier: NCT02877550) and venetoclax, obinutuzumab and bendamustine in high-tumor burden FL (ClinicalTrials.gov identifier: NCT03113422).

Immune checkpoint inhibitors. FL cells also exploit their immunosuppressive microenvironment to evade antitumoral immunity.[52] While gene expression profile enriched in monocytes and dendritic cells seem to confer to poor prognosis, indicating the importance of FL microenvironment,[53] impact of PD-1 expression in FL remains controversial.[54–56] Inhibition of immune checkpoints PD1 and CTLA4 was shown to rescue inactivated anergic T-cell in several malignancies and was tested in relapsed and refractory FL. Nivolumab produced an ORR of 40% in FL patients enrolled among other hematologic malignancies.[57] Example of ongoing clinical studies in untreated FL include nivolumab plus rituximab (ClinicalTrials.gov identifier: NCT03245021), single-agent pembrolizumab (ClinicalTrials.gov identifier: NCT03498612), and atezolizumab in combination with chemoimmunotherapy (ClinicalTrials.gov identifier: NCT02596971).

Consolidation and maintenance therapy

The fundamental principle of maintenance therapy is to provide ongoing treatment beyond remission induction with minimal toxicity over an extended period of time with a goal of prolonged disease control. As previously discussed, the PRIMA study has established the PFS benefit from using rituximab maintenance. RELEVANCE study continues R^2 as their maintenance therapy in the R^2 arm. Similar studies in relapsed FL randomize patients to rituximab alone or R^2 after induction treatment with R^2 (MAGNIFY trial, ClinicalTrials.gov identifier: NCT0196865) or after chemoimmunotherapy (ClinicalTrials.gov identifier: NCT02390869). Comparison between these maintenance arms has not yet been reported.

Consolidation therapy is a relatively intensive short-course treatment given after completion of standard treatment. Consolidation studies are usually limited to high-risk population such as patients with high FLIPI score or patients who have residual disease after completion of treatment. Radioimmunotherapy with isotope-labeled anti-CD20 mAbs represent a short-course treatment, more potent than unlabeled antibodies, and therefore is a good candidate for testing as a consolidation therapy. ^{90}Yttrium ibritumomab tiuxetan is a beta-emitting radioisotope–mAb conjugate targeting CD20. A phase III study of ^{90}Y-ibritumomab tiuxetan consolidation after having a response to initial therapy (FIT study) showed an improvement of median PFS (4.1 *versus* 1.1 years).[58] However, less than a third of the patients received rituximab as their induction and *post hoc* analysis of this small subgroup did not show statistically significant difference in median PFS. Moreover, most of the patients enrolled have a low-risk FLIPI score; and for these reasons, the applicability of this study is unknown in the present practice of treating FL. The GOTEL study reported ORR of 93.3% and CRR of 76.6% using ^{90}Y-ibritumomab tiuxetan after four cycles of R-CHOP and two cycles of CHOP in FL patients with untreated intermediate-to-high risk FLIPI.[59] PFS at 5 years was recently reported to be 70%.[60] Despite its efficacy, radioimmunotherapy consolidation remains underutilized, likely due to perceived concern for toxicity especially in

patients with bone marrow involvement, cost and logistics, and the availability of other options such as MR.[61] Manufacture and sale of another radioimmunotherapy, ^{131}iodine-tositumomab, were discontinued in 2014.

Relapsed and refractory follicular lymphoma

Identification of high-risk relapsed follicular lymphoma: toward response-adapted approach

In 2015, the National LymphoCare Study (NLCS) published an insightful finding of the different biology of FL that progressed early. Approximately 20% of FL patients progressed within 2 years after treatment with immunochemotherapy across different regimens and despite adding a MR. NLCS data was validated with prospectively collected patient data from University of Iowa and Mayo Clinic Molecular Epidemiology Resource. Patients who developed early disease progression within 24 months (POD24) after diagnosis have a 2-year OS of only 68% and a 5-year OS of 50%, compared with 97% and 90%, respectively, in patients without POD24.[5] This finding is also confirmed by several later prospective dataset such as the recent GALLIUM study.[62] Moreover, it also shows that patients with earlier disease progression (before 6 months, 12 months or 18 months) seem to have even higher risk of death. Substituting obinutuzumab for rituximab in frontline setting does not seem to reduce the risk of POD24. With these data, different treatment at the time of relapse seems to be necessary.

Management of patients with POD24 after treatment with chemoimmunotherapy remains elusive. Treatment with salvage chemotherapy followed by autologous hematopoietic cell transplant (HCT) in second or third remission and allogeneic HCT in later relapse have been suggested.[63] Clinical trial participation is highly encouraged. The ongoing US Intergroup study, S1608 (ClinicalTrials.gov identifier: NCT03269669)[64] was designed to answer this question. Patients who are refractory to a first-line bendamustine-anti-CD20-based regimen or have relapsed within 2 years after completion of treatment are eligible and randomized to a PI3K inhibitor, umbralisib plus obinutuzumab, lenalidomide plus obinutuzumab, or CHOP plus obinutuzumab. This study is also trying to identify set of biomarkers in prediction of POD24. Another study in this setting is a randomized phase II FRESCO trial. Patients who progressed within 24 months after alkylator-based chemotherapy are randomized to duvelisib plus rituximab or R-CHOP (ClinicalTrials.gov identifier: NCT02605694).[65] Results of these studies are eagerly awaited.

Besides POD24, there are other groups of FL patients that may have an increased risk of dying from FL, for example, patients who have positive PET scan after chemoimmunotherapy,[66, 67] patients who relapse multiple times,[68] and patients who are diagnosed at the very young age.[69] It is reasonable to suspect that patients who quickly progress after or refractory to single-agent anti-CD20 mAb treatment may also have shorter survival as well. There are studies that addressed the heterogeneity of FL and try to improve outcomes in these high-risk patients. For example, Fondazione Italiana Linfomi designed a response-adapted treatment based on an end-of-treatment PET scan by adding consolidation therapy with ^{90}Y-ibritumomab tiuxetan in the PET-positive group and, at the same time, study the effect of minimal residual disease in the PET-negative group (ClinicalTrials.gov identifier: NCT02063685). A clinical trial from the Memorial Sloan Kettering Cancer Center was designed to study the effect of 2 years of ibrutinib in patients with a positive end-of-treatment PET scan after completion of chemoimmunotherapy and follow the rate of conversion to PET-negative status (ClinicalTrials.gov identifier: NCT02966730).

Novel therapeutics for relapsed and refractory follicular lymphoma

Several new drugs of various targets have been tested in patients relapsed and refractory FL. These are summarized in Table 2.

Anti-CD20 and other cell surface targets monoclonal antibody-based agents. The second generation of anti-CD20 mAb was engineered to become humanized or fully human to reduce immunogenicity. Ofatumumab is a fully human type I anti-CD20 IgG1 mAb that recognizes a distinct epitope of CD20 from rituximab and has been shown to have a stronger CDC and seemed to work in both rituximab-sensitive and resistant cell lines. A phase I/II trial in FL with various doses showed an ORR from 20 to 63% and a median duration of response of 29.9 months.[87] However, only 38% of these patients were previously treated with rituximab and a subsequent studies in rituximab-refractory patients failed to show meaningful benefit using ofatumumab alone (ORR 22%,

Table 2. Summary of selected novel therapeutics for treatment of FL.

Drug	Phase/year published, presented	Study population	*n*	Treatment regimen	Response (experiment *versus* control arms)	Survival (experiment *versus* control arms)	Adverse reactions
Treatment-naïve FL							
Anti-CD20 monoclonal antibody							
Obinutuzumab[31]	Phase III 2017	Stage III, IV, and bulky stage II PS 0–2 GELF criteria met	1202	Experiment: Obinutuzumab 1000 mg d 1, 8, 15 on cycle 1, d 1 thereafter plus CHOP, CVP or bendamustine Control: Rituximab plus CHOP, CVP or bendamustine Both followed by maintenance q2month for 2 years	ORR 88.5% *versus* 86.9% CRR 19.5% *versus* 23.8%	3y-PFS 80.0% *versus* 73.3%* 3y-OS 94.0% *versus* 92.1%	Infusion reaction Neutropenia
Immunomodulatory agent							
Lenalidomide[42]	Phase II 2016	Stage III, IV Stage II not suitable to radiotherapy PS 0–2 Symptomatic, bulky or significant progression	154	Rituximab 375 mg/m^2 at weeks 1–4, 12–15 with or without Lenalidomide 15 mg daily from 14 days before the first until 14 days after the last rituximab	CRR 42% *versus* 19% CR duration NR *versus* 2.3 years	mPFS NR *versus* 2.3 years* 3y-OS 93% *versus* 92%	Neutropenia, fatigue, thrombocytopenia, maculopapular rash
Lenalidomide	Phase III 2018	Stage II, III, and IV PS 0–2 GELF criteria met	1030	Experiment: Lenalidomide 20 mg/day d2–22 in 28-day cycle, 6–12 cycles Rituximab 375 mg/m^2 weekly in cycle 1, day 1 cycles 2–6 then q8weeks for 12 cycles Control: R-CHOP, R-CVP, or BR followed by maintenance R	CRR 48% *versus* 53%	2-y PFS 84% *versus* 87% 3-y PFS 77% *versus* 78% 3-y OS 94% *versus* 94%	Rash
Cellular pathway-targeted agents							
Ibrutinib[45]	Phase II 2016	Stage II, III, and IV PS 0–2 GELF criteria met	80	Ibrutinib 560 mg/d Rituximab 375 mg/m^2 weekly × 4 doses Arm 1: concurrent therapy Arm 2: Ibrutinib lead-in for 8 weeks then concurrent therapy	Arm 1: ORR 85% CRR 35% Arm 2: ORR 75% CRR 40%	1-y PFS Arm 1: 87% Arm 2: 77% 1-y OS Arm 1: 98% Arm 2: 100%	Maculopapular rash Fatigue Fever Diarrhea Bleeding (only grade 1–2, 33%)
Duvelisib[48]	Phase II 2016	Stage III, IV, and bulky stage II PS 0–2 GELF criteria met	28	Duvelisib 25 mg bid plus either Arm 1: rituximab 375 mg/m^2 weekly × 4 then every 8 weeks or Arm 2: obinutuzumab 1000 mg weekly × 4 then every 8 weeks	Arm 1: ORR 87% CRR 22% Arm 2: ORR 91% CRR 18%	Not reported	Elevated ALT Rash Neutropenia (obinutuzumab arm) PJP infection
Relapsed and refractory FL							
Cell surface targets monoclonal antibody-based agents							
Obinutuzumab[70,71]	Phase III 2016, 2018	CD20+ indolent NHL refractory to rituximab-containing regimen or progressed within 6 months	413 [FL 335]	Obinutuzumab 1000 mg d1, 8, 15 of cycle 1, d1 of cycle 2–6 bendamustine 90 mg/m^2/d d1 and 2 followed by obinutuzumab 1000 mg q2months maintenance until progression or bendamustine 120 mg/m^2 d1 and 2 up to 6 cycles	All patients ORR 69% *versus* 63% CRR 11% *versus* 12% FL patients ORR 68% *versus* 65%	FL patients mPFS 25.3 *versus* 14.0 months* mOS NE *versus* 53.9 months*	Neutropenia, nausea, fatigue, infection

Table 2. (Continued)

Drug	Phase/year published, presented	Study population	*n*	Treatment regimen	Response (experiment *versus* control arms)	Survival (experiment *versus* control arms)	Adverse reactions
Ublituximab[72]	Phase I/II 2017	NHL and CLL	35 [FL 12]	Ublituximab dose escalation from 450, 600, 900, and 1200 mg (no MTD identified) IV weekly × 4 doses then monthly × 3 doses then q3months for maximum of 2 years	FL patients ORR 5/12 (42%) CRR 2/12 (17%) DoR 9.2 months (all patients)	mPFS 7.7 months (all patients) mPFS 4.7 months (rituximab-refractory patients)	Fatigue, fever, diarrhea, neutropenia
Inotuzumab ozogamicin[73]	Phase II 2016	CD22 + indolent NHL Progressed after ⩾2 prior systemic therapies, refractory to rituximab or radioimmunotherapy	119 [FL 72]	Inotuzumab 1.8 mg/m^2 IV q4weeks maximum of 8 cycles	FL patients ORR 71% CRR 35%	mPFS 14.7 months mOS NR	Thrombocytopenia, neutropenia, nausea, fatigue, elevated liver enzymes
Inotuzumab ozogamicin[74]	Phase I 2016	Relapsed/refractory CD22+ B-cell NHL	48 [FL 26]	R-CVP: rituximab 375 mg/m^2, cyclophosphamide 375 to 750 mg/m^2, and vincristine 1.4 mg/m^2 d1; prednisone 40 mg/m^2 d1-5 Inotuzumab 0.8 or 1.3 mg/m^2 d2 of 21-day cycle, maximum of 6 cycles	Indolent NHL (26 FL, 1 SLL) ORR 27/27 (100%) CRR 11/27 (41%)	2-y PFS 50% 2-y OS 89%	Thrombocytopenia, neutropenia, nausea, constipation, fatigue, elevated liver enzymes
Polatuzumab vedotin[75]	Phase II 2018	Relapsed/refractory transplant-ineligible FL and DLBCL	160 [FL 80]	Bendamustine 90 mg/m^2 d1, 2 rituximab 375 mg/m^2 ± polatuzumab 1.8 mg/kg For 6 times of 28-day cycles	FL patients CRR 69% *versus* 63%	FL patients mPFS 17 *versus* 17.3 months mOS NR *versus* NR	Febrile neutropenia, infection
Blinatumomab[76]	Phase I 2016	Relapsed/refractory NHL	76 [FL 28]	Blinatumomab IV infusion dose escalation from 0.5 to 90 µg/m^2/d (MTD 60 µg/m^2/d)	15 FL patients at MTD ORR 12/15 (80%) CRR 6/15 (40%) DoR 404 days (entire cohort)	Not reported	Lymphopenia, fever, fatigue, headache, hyperglycemia, encephalopathy
^{90}Y-Ibritumomab[77]	Phase I 2013	Relapsed or transformed FL	9	^{90}Y-ibritumomab 0.4 m CI/kg d15 of induction cycle Bortezomib 1.0, 1.3, or 1.6 mg/m^2 d1, 8, 15, 22 followed by consolidation bortezomib (MTD 1.3 mg/m^2)	ORR 8/9 (89%) CRR 2/9 (22%)	mPFS 6.5 months	Hematologic toxicity
Immunomodulatory agents							
Lenalidomide[78]	Phase IIIb 2016	Grade 1–3b FL, transformed FL, MZL, or MCL with ⩾1 prior therapy	135 [FL 91]	12 cycles of R2 induction: lenalidomide 20 mg/d d1-21 in 28-day cycle rituximab 375 mg/m^2 weekly in cycle 1 then d1 in odd-number cycles SD or better receive R2 or rituximab maintenance: lenalidomide 10 mg/d d1–21 cycles 13–30 and rituximab q8weeks	FL patients ORR 64% CRR 20%	Not reported	Neutropenia, thrombocytopenia, fatigue

Table 2. (Continued)

Drug	Phase/year published, presented	Study population	*n*	Treatment regimen	Response (experiment *versus* control arms)	Survival (experiment *versus* control arms)	Adverse reactions
Cellular pathway-targeted agents							
Ibrutinib[79]	Phase II 2018	Grade 1–3a FL with ⩾1 prior therapy	40	Ibrutinib 560 mg/d until progression or unacceptable toxicity	ORR 37.5% CRR 12.5% mDoR 13.9 months	mPFS 14.0 months 2-y PFS 20.4% 2-y OS 79.0%	Infection, fatigue, thrombocytopenia, diarrhea
Duvelisib[80]	Phase II 2017	FL, SLL or MZL Double refractory to rituximab and to chemotherapy or radioimmunotherapy	129 [FL 83]	Duvelisib 25 mg bid until progression or unacceptable toxicity	FL patients ORR 43% CRR 1% DoR 7.9 months	mPFS 8.3 months mOS 27.8 months	Neutropenia, diarrhea, nausea, cough, fatigue, rash
Venetoclax[81]	Phase II 2016	R/R FL, bendamustine-naïve or response >1 year	164	Arm A: venetoclax 800 mg daily × 1 year + rituximab cycles 1, 4, 6, 8, 10, 12 Arm B: venetoclax 800 mg daily + 6 cycles of BR Arm C: 6 cycles of BR	ORR Arm A: 33% Arm B: 68% Arm C 64% CRR Arm A 14% Arm B 50% Arm C 14%	Not reported	Tumor lysis syndrome in 3 patients (manageable), neutropenia, thrombocytopenia, nausea/vomiting, diarrhea
Immune checkpoint inhibitors							
Nivolumab[57]	Phase Ib 2016	R/R B-cell malignancies T-cell lymphoma Multiple myeloma	81 [FL 10]	Nivolumab 1 or 3 mg/kg q2weeks	FL cohort ORR 4/10 CRR 1/10	FL cohort mPFS NR (95% CI 7 weeks NR)	Rash, pneumonitis, diarrhea, fatigue
Pidilizumab[82]	Phase II 2014	Rituximab-sensitive relapsed FL	32	Pidilizumab 3 mg/kg IV q4weeks plus rituximab 375 mg/m^2 IV weekly for 4 weeks If response is SD or better, pidilizumab was continued for 1 year.	ORR 66% CRR 52% DoR 20.2 months	mPFS 18.8 months	Respiratory infection, anemia, fatigue
Atezolizumab[83]	Phase Ib 2017	R/R FL and DLBCL	49 [FL 26]	Cycle 1: obinutuzumab d1 (100 mg), d2 (900 mg), d8, 15 (1000 mg) Cycles 2-8: atezolizumab 1200 mg and obinutuzumab 1000 mg q3weeks Maintenance: atezolizumab 1200 mg IV q3weeks for 6 months	FL patients ORR 57%	Not reported	Pain, anemia, neutropenia
Pembrolizumab[84]	Phase II 2017	Rituximab-sensitive relapsed FL	27	Rituximab 375 mg/m^2 d1, 8, 15, 22 of cycle 1 pembrolizumab 200 mg q3weeks up to 16 cycles	ORR 80% CR 60% DoR: NR	Median follow up 7 months mPFS: NR	Nausea, infusion reaction

Table 2. (Continued)

Drug	Phase/year published, presented	Study population	*n*	Treatment regimen	Response (experiment *versus* control arms)	Survival (experiment *versus* control arms)	Adverse reactions
Epigenetic modifier-targeted agents							
Tazemetostat[85]	Phase II 2018	R/R DLBCL or FL (grade 1–3b)	76 FL	Tazematostat 800 mg twice daily	*EZH2* mutant ($n = 22$) ORR 18/22 (82%) CRR 1/22 (5%) DoR > 32 weeks *EZH2* wild-type ($n = 54$) ORR 19/54 (35%) CRR 3/54 (6%) DoR >56 weeks	*EZH2* mutant mPFS > 48 weeks *EZH2* wild-type mPFS > 30 weeks	Nausea, anemia, fatigue, diarrhea
Vorinostat[86]	Phase II 2014	R/R indolent B-NHL	56 [FL 39]	Vorinostat 200 mg bid 2 weeks on, 1 week off	FL patients ORR 49% CRR 18%	FL patients mPFS 20 months	Thrombocytopenia, neutropenia, diarrhea, nausea

* statistically significant.
ALT, alanine transaminase; BR, bendamustine, rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CI, confidence interval; CLL, chronic lymphocytic leukemia; CRR, complete response rate; CVP, cyclophosphamide, vincristine, prednisone; DLBCL, diffuse large B-cell lymphoma; DoR, duration of response; FL, follicular lymphoma; GELF, Groupe d'Etude des Lymphomes Folliculaires; IV, intravenous; MCL, mantle cell lymphoma; mDoR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; NE, not estimated; NHL, non-Hodgkin's lymphoma; NR, not reached; ORR, overall response rate; OS, overall survival; PJP, *Pneumocystis jirovecii* pneumonia; PS, performance status; R/R, relapsed/refractory; R, rituximab; SD, stable disease; SLL, small lymphocytic lymphoma.

mPFS 5.8 months)[88] or ofatumumab in combination with bendamustine (ClinicalTrials.gov identifier: NCT01077518, press release).[89] Ocrelizumab and veltuzumab, both second-generation anti-CD20 mAbs, were not pursued further in clinical study for lymphoma.

The third generation of anti-CD20 mAbs is humanized or fully human and has a protein- or glyco-engineered Fc region to enhance its binding affinity to FcγRIIIa. Obinutuzumab has demonstrated its efficacy in an open-label phase III GADOLIN study.[70] A total of 413 patients with rituximab-refractory indolent NHL, including 335 FL patients, were randomized to receive bendamustine with or without obinutuzumab followed by obinutuzumab maintenance. Median PFS (mPFS) is significantly longer in obinutuzumab arm (not reached *versus* 14.9 months) in its initial published report and was also confirmed in their subsequent presentation to confer mPFS benefit (25.3 *versus* 14.0 months) along with median OS (mOS) benefit (not estimated *versus* 53.9 months) in the FL subgroup.[71]

Ocaratuzumab (AME-133) is another third-generation type I anti-CD20 IgG1 with enhanced ADCC. It has shown some activity in previously treated FL patients who are known to have low-affinity FcγRIIIa with ORR of 30% and CRR of 8% in a phase I/II study.[90] There is currently no ongoing trial of this agent. Ublituximab (TG-1101), a type I glycoengineered anti-CD20 IgG1 with enhanced ADCC, was tested in NHL. In 12 patients with FL, 2 patients had CR and 3 had a partial response. Clinical trials to further assess the clinical efficacy of ublituximab, alone and in combination, are ongoing (ClinicalTrials.gov identifiers: NCT02793583, NCT01647971, NCT02006485).

Several mAbs were developed to target other B-cells surface targets including CD22 (epratuzumab, galiximab), CD37 (otlertuzumab), HLA-DR (IMMU-114). The latter two are being tested in early-phase clinical trials.

Antibody–drug conjugates. Antibody–drug conjugates have a potential of providing specific delivery of potent microtubule inhibitors or DNA-damaging agents to FL cells while minimizing the systemic toxicities. Inotuzumab ozogamicin is an anti-CD22 IgG4 linked to calicheamicin, a DNA-damaging agent. A study in indolent lymphoma refractory to rituximab or radioimmunotherapy revealed ORR of 71% and CRR of 35% in FL subgroup with better response in nonbulky disease.[73] Median PFS was 14.7 months and mOS was not reached. Another study investigated inotuzumab ozogamicin in combination with R-CVP in this setting, including 26 FL patients. ORR was 100% with 41% CR. Within a median follow up of 24.1 months, the 2-year PFS was 50% and the 2-year OS was 89%.[74] This agent is also actively investigated in B-lymphoblastic leukemia.

Polatuzumab vedotin is an anti-CD79b IgG conjugated to monomethyl auristatin E, a microtubule inhibitor. Its phase I study enrolled 95 patients including 30 patients with indolent NHL (unreported number of patients with FL). Within indolent NHL subgroup, polatuzumab vedotin resulted in three CRs and four PRs in the 2.4 mg/kg group ($n = 16$) but no response in the lower dose (1.8 mg/kg) group.[91] Preliminary reports from a randomized phase II trial, comparing bendamustine and rituximab with or without polatuzumab vedotin in relapsed/refractory FL and DLBCL, showed that the addition of polatuzumab vedotin did not improve CRR or PFS in the FL subgroup but increased the rate of febrile neutropenia.[75] The study is still ongoing (ClinicalTrials.gov identifier: NCT02257567). Varieties of combinations are also being tested in relapsed and refractory FL, including with lenalidomide (ClinicalTrials.gov identifier: NCT02600897), obinutuzumab and venetoclax (ClinicalTrials.gov identifier: NCT02611323), and obinutuzumab and atezolizumab (ClinicalTrials.gov identifier: NCT02729896).

Various antibody–drug conjugates are in development, targeting several B-cell surface molecules such as CD19, CD22, CD25, CD37, CD74, CD79b, CD205, and CD269 (BCMA).

Radioimmunotherapy. As a single agent, ^{90}Y-ibritumomab showed 74% ORR and 15% CRR in rituximab-refractory FL patients with the median time to progression of 6.8 months and only 8.7 months in responders.[92] A phase II study of ^{90}Y-ibritumomab plus bortezomib is underway (ClinicalTrials.gov identifier: NCT00372905). In its phase I trial, eight out of nine patients had a response, two with CR, and a mPFS of 6.5 months.[77]

Bispecific T-cell engager. Blinatumomab is the only bispecific T-cell engaging antibody currently available. It transiently joins CD19-positive B-cells to CD3ε-positive T-cells, resulting in T-cell-mediated B-cell lysis along with

T-cell activation. In a phase I dose-escalation study in 76 relapsed NHL patients, including 28 patients with FL, the ORR was 80% in the FL subgroup who received blinatumomab at the target dose of 60 μg/m²/day, and 40% achieved CR.[76] Dose-limiting toxicity was encephalopathy. The major limitation of blinatumomab is its short half-life which necessitates an initial 4 weeks of continuous infusion. Another phase I study combining blinatumomab and lenalidomide is underway (ClinicalTrials.gov identifier: NCT02568553). A regular-half-life anti-CD20/CD3 T-cell-dependent bispecific antibody which will allow weekly or monthly dosing is currently in its early clinical trials (ClinicalTrials.gov identifiers: NCT02651662, NCT02290951).

Immunomodulatory agents. Lenalidomide is an oral immune modulator that exerts its antineoplastic effects through inhibition of tumor cell proliferation, inhibition of angiogenesis, and T-cell and natural killer (NK)-cell-mediated cytotoxicity. Recently, the intracellular target of lenalidomide was identified as cereblon, an E3 ubiquitin ligase. Upon binding to lenalidomide, cerebron activity was increased and resulted in degradation of Aiolos and Ikaros which may be central to the mechanisms of action of lenalidomide. Preclinical studies have identified mechanistically synergistic effects of several lenalidomide combinations, for example, with rituximab, bortezomib, ibrutinib, and anti-programmed cell death protein (PD1) or anti-programmed death ligand (PD-L1).[93] A phase IIIb study of rituximab and lenalidomide (R^2) induction followed by rituximab *versus* R^2 maintenance in relapsed indolent NHL and mantle cell lymphoma (MAGNIFY study) was presented, revealing an ORR of 64% and a 20% CR (ClinicalTrials.gov identifier: NCT01996865).[78] Phase III AUGMENT trial compares rituximab plus lenalidomide or placebo in similar setting. As of this writing, the full result has not yet released except a press announcement stating that its PFS endpoint was met (ClinicalTrials.gov identifier: NCT01938001).[94] A preliminary result of the phase I/II trial for lenalidomide and obinutuzumab combination in relapsed FL was presented, showing an ORR of 100% with a 78% CR. The estimated 2-year PFS was 61%. All rituximab-refractory patients had a response. This trial is still ongoing (ClinicalTrials.gov identifier: NCT01995669).[95]

CC-122 is another cereblon-targeted agent which has shown good activity in relapsed/refractory indolent NHL in a phase I study in combination with obinutuzumab.[96]

Cellular pathway-targeted agents

Phosphatidylinositol 3-kinase inhibitors. Currently, two PI3K inhibitors are approved for relapsed FL, the oral PI3Kδ inhibitor idelalisib and the intravenous PI3Kα/δ inhibitor copanlisib. Duvelisib is a dual PI3Kδ/γ inhibitor that is being studied in the DYNAMO trial for relapsed/refractory FL. The preliminary results showed an ORR of 43%, with 1% achieving a CR. The duration of response was 7.9 months and mPFS was 8.3 months. Diarrhea is common (47%; 16% ⩾ grade 3).[80] The US FDA has accepted duvelisib for filing with a priority review in order to get accelerated approval for the treatment of relapsed/refractory FL.

Bruton tyrosine kinase inhibitors. Response to single-agent ibrutinib in recurrent FL was not encouraging. In a phase II study, ibrutinib resulted in an ORR of 37.5% with a CRR of 12.5%, mPFS of 14 months and a 2-year PFS of 20.4%. Less response was observed in patients who were rituximab resistant and no response was observed in *CARD11*-mutated patients.[79] In another phase II DAWN study, ibrutinib showed ORR of 20.9% with a CRR of 11% and mPFS of 4.6 months. The median duration of response (DoR) was 19.4 months which seems to indicate a durable response in a small subset of patients who achieve an initial response. Unfortunately, no biomarkers predictive of response were identified.[97] A more-selective BTK inhibitor, acalabrutinib, showed an ORR of 33–39% in relapsed/refractory FL with 2 CRs out of 25 patients.[98] This study is still underway (ClinicalTrials.gov identifier: NCT02180711).

BCL2 inhibitors. The first-in-human study of venetoclax in relapsed/refractory NHL, which included 29 patients with FL, showed an ORR of 38% and a mPFS of 11 months in the FL subgroup.[51] Since *BCL2* overexpression is the hallmark of FL, this response to a BCL2 inhibitor is unimpressive and a combination with other agents may be required. In a phase I study, venetoclax in combination with BR for relapsed/refractory NHL, including 32 patients with FL, showed very good signal of response and was quite well tolerated.[99] The target dose of 800 mg is used in the ongoing randomized phase II CONTRALTO study which only enrolled patients with relapsed/refractory FL. Its preliminary results showed an

ORR of 68% in the venetoclax plus BR arm and 64% in BR alone. Venetoclax plus BR also resulted in more toxicity and more treatment discontinuation but may improve PFS.[81] We will need to wait for the data to mature to see if adding venetoclax to chemoimmunotherapy has any benefit at all.

Spleen tyrosine kinase inhibitors. Spleen tyrosine kinase (SYK) is a key regulator of B-cell receptor signaling, upstream of BTK and PI3K, and is also involved in signal transduction in other classical immunoreceptors.[100] Fostamatinib, an early SYK inhibitor currently approved for treatment of relapsed immune thrombocytopenia, was studied in NHL but showed only a 2/21 ORR in the FL subgroup.[101] Cerdulatinib, a dual SYK/JAK inhibitor, is being tested in a wide-range of lymphoma subtypes (ClinicalTrials.gov identifier: NCT01994382) and early results showed good response in FL (ORR 50%).[102]

Immune checkpoint inhibitors

Anti-PD1 and anti-PD-L1. A preliminary result of nivolumab, an anti-PD1, for the treatment of various lymphomas, has shown an ORR of 4/10 in the FL subgroup with 1 CR. Overall, three out of four patients continued to respond over the median observation time of 91.4 weeks.[57] A study of nivolumab in relapsed or refractory FL (Checkmate 140) has completed the accrual total of 92 patients. Only three patients had a PR and one had a CR, with a DoR of 10.9 months and a mPFS of 2.2 months in a preliminary report.[103] Formal presentation or publication is expected to follow. Pidilizumab, also an anti-PD1, has shown an ORR of 66% and a 52% CR with a median DoR of 20.2 months and a mPFS of 18.8 months.[82] Pembrolizumab and atezolizumab in combination with anti-CD20 mAbs also showed very good response rates in their preliminary results.[83,84]

Other immune checkpoint inhibitors. CD47 is exploited by different types of tumor cells to evade phagocytosis by macrophage. Hu5F9-G4 is a humanized mAb targeting CD47. In a phase Ib/II in combination with rituximab, Hu5F9-G4 resulted in an ORR of 71% and a CRR of 43% in follicular lymphoma subgroup. Most of the patients continued to respond during a median 8.1 months of follow up. The phase II study of this agent is in progress (ClinicalTrials.gov identifier: NCT02953509).[104] Agents targeting a costimulatory molecule, CD137 (4-1BB), and an NK-cell receptor, killer Ig-like receptor, are also being studied.

Epigenetic regulator-targeted agents. The relapsing clinical course and HT of FL are in part driven by the presence of a population of common precursor cells. These cells carry several mutations involved in immune surveillance, B-cell development, B-cell receptor signaling pathway and a plethora of mutations in epigenetic modifiers such as *KMT2D* (previously *MLL2*), *CREBBP, EZH2, EP300, MEF2B*, and *ARID1A*. Almost all FL patients have at least one mutation in epigenetic modifier genes,[105,106] and many of these mutations are associated with high-risk FL.[107]

EZH2 mutation is found in around 25% of FL and several agents were developed to target *EZH2*. For example, tazemetostat as a single agent resulted in an ORR of 82% in *EZH2*-mutated and 35% in wild-type *EZH2* relapsed or refractory FL and seemed to be well tolerated. All patients with *EZH2* mutation had evidence of tumor reduction but only 1 in 22 patients achieved a CR.[85] CPI-1205 is being studied in various B-cell lymphomas in its phase I trial (ClinicalTrials.gov identifier: NCT02395601). The study of GSK2816126 was terminated due to a lack of clinical efficacy.

Vorinostat, a histone deacetylase (HDAC) inhibitor, was demonstrated to have some activity in relapsed and refractory FL with an ORR of 49% and a PFS of 20 months as a single agent.[86] Other HDAC inhibitors, including panobinostat and mocetinostat, are being tested in their phase II clinical trials (ClinicalTrials.gov identifiers: NCT 01261247 and NCT02282358, respectively).

Chimeric antigen receptor T-cell therapy. Chimeric antigen receptor (CAR) T-cells are autologous T-lymphocytes, with receptors that are engineered to include both antigen-recognition moieties and T-cell signaling domains.[108] Anti-CD19 CAR T-cells have demonstrated clinical efficacy in relapsed and refractory B-lymphoblastic leukemia and DLBCL.[109,110] This concept of treatment is also appealing in the treatment of FL that is refractory to several lines of treatment. The ELARA study is a phase II trial in its development to study the efficacy and safety of tisagenlecleucel in this setting (ClinicalTrials.gov identifier: NCT03568461).

Conclusion

In a disease such as FL with a relatively high prevalence and no established cure, the environment is ripe for developing novel approaches. Patient advocacy groups, physicians, and the pharmaceutical

industry will all embrace the search for novel management options to replace current options with toxicity and transient benefits. The information reviewed above confirms that many new classes of therapies are being actively investigated. At the moment there is no clear choice for a new mechanism of action that will have transformative impacts on the morbidity and mortality of FL, but the next big discovery may be just around the corner. Those in the clinical research field will need to stay focused on testing the most logically exciting new agents while addressing questions of truly unmet need for patients. Patients and their advocacy groups will be invaluable in helping prioritize the importance of endpoints such as OS or relative survival, PFS, and quality of life.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

Grerk Sutamtewagul declares that he has no conflict of interest. Brian K Link is a consultant for Genentech/Roche and serves on the Data and Safety Monitoring Board for AbbVie.

ORCID iDs

Grerk Sutamtewagul https://orcid.org/0000-0002-1311-6227
Brian K Link https://orcid.org/0000-0001-5084-0698

References

1. Teras LR, DeSantis CE, Cerhan JR, *et al*. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. *CA Cancer J Clin*. Epub ahead of print 12 September 2016. DOI: 10.3322/caac.21357.
2. Morrison VA, Bell JA, Hamilton L, *et al*. Economic burden of patients with diffuse large B-cell and follicular lymphoma treated in the USA. *Future Oncol* 2018; 14: 2627–2642.
3. Nabhan C, Aschebrook-Kilfoy B, Chiu BC, *et al*. The impact of race, age, and sex in follicular lymphoma: a comprehensive SEER analysis across consecutive treatment eras. *Am J Hematol* 2014; 89: 633–638.
4. Tan D, Horning SJ, Hoppe RT, *et al*. Improvements in observed and relative survival in follicular grade 1–2 lymphoma during 4 decades: the Stanford University experience. *Blood* 2013; 122: 981–987.
5. Casulo C, Byrtek M, Dawson KL, *et al*. Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: an analysis from the national lymphocare study. *J Clin Oncol* 2015; 33: 2516–2522.
6. Maurer MJ, Bachy E, Ghesquieres H, *et al*. Early event status informs subsequent outcome in newly diagnosed follicular lymphoma. *Am J Hematol* 2016; 91: 1096–1101.
7. Solal-Celigny P, Roy P, Colombat P, *et al*. Follicular lymphoma international prognostic index. *Blood* 2004; 104: 1258–1265.
8. Mercadal S, Pomares H, Sancho JM, *et al*. Clinico-biological features, treatment and survival of 457 patients with histological Grades 3A and 1–2 follicular lymphoma mostly treated with immunochemotherapy. *Br J Haematol* 2016; 172: 470–473.
9. Arcaini L, Merli M, Passamonti F, *et al*. Validation of follicular lymphoma international prognostic index 2 (FLIPI2) score in an independent series of follicular lymphoma patients. *Br J Haematol* 2010; 149: 455–457.
10. Press OW, Unger JM, Rimsza LM, *et al*. A comparative analysis of prognostic factor models for follicular lymphoma based on a phase III trial of CHOP-rituximab versus CHOP + 131iodine–tositumomab. *Clin Cancer Res* 2013; 19: 6624–6632.
11. Federico M, Bellei M, Marcheselli L, *et al*. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. *J Clin Oncol* 2009; 27: 4555–4562.
12. Jurinovic V, Kridel R, Staiger AM, *et al*. Clinicogenetic risk models predict early progression of follicular lymphoma after first-line immunochemotherapy. *Blood* 2016; 128: 1112–1120.
13. Bachy E, Maurer MJ, Habermann TM, *et al*. A simplified scoring system in de novo follicular lymphoma treated initially with immunochemotherapy. *Blood* 2018; 132: 49–58.
14. Meignan M, Cottereau AS, Versari A, *et al*. Baseline metabolic tumor volume predicts outcome in high-tumor-burden follicular lymphoma: a pooled analysis of three multicenter studies. *J Clin Oncol* 2016; 34: 3618–3626.
15. Cottereau AS, Versari A, Luminari S, *et al*. Prognostic model for high-tumor-burden

follicular lymphoma integrating baseline and end-induction PET: a LYSA/FIL study. *Blood* 2018; 131: 2449–2453.

16. Casulo C. Risk stratification in follicular lymphoma. *Best Pract Res Clin Haematol* 2018; 31: 15–22.

17. Delfau-Larue MH, van der Gucht A, Dupuis J, *et al*. Total metabolic tumor volume, circulating tumor cells, cell-free DNA: distinct prognostic value in follicular lymphoma. *Blood Adv* 2018; 2: 807–816.

18. Della Starza I, Cavalli M, Del Giudice I, *et al*. Comparison of two real-time quantitative polymerase chain reaction strategies for minimal residual disease evaluation in lymphoproliferative disorders: correlation between immunoglobulin gene mutation load and real-time quantitative polymerase chain reaction performance. *Hematol Oncol* 2014; 32: 133–138.

19. Brice P, Bastion Y, Lepage E, *et al*. Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol* 1997; 15: 1110–1117.

20. Casadei B, Pellegrini C, Pulsoni A, *et al*. 90-yttrium-ibritumomab tiuxetan consolidation of fludarabine, mitoxantrone, rituximab in intermediate/high-risk follicular lymphoma: updated long-term results after a median follow-up of 7 years. *Cancer Med* 2016; 5: 1093–1097.

21. Eastern Cooperative Oncology Group and National Cancer Institute. Bendamustine hydrochloride and rituximab with or without bortezomib followed by rituximab with or without lenalidomide in treating patients with high-risk stage II, stage III, or stage IV follicular lymphoma, https://ClinicalTrials.gov/show/NCT01216683 (accessed 30 April 2018).

22. Gine E, Montoto S, Bosch F, *et al*. The Follicular Lymphoma International Prognostic Index (FLIPI) and the histological subtype are the most important factors to predict histological transformation in follicular lymphoma. *Ann Oncol* 2006; 17: 1539–1545.

23. Link BK, Maurer MJ, Nowakowski GS, *et al*. Rates and outcomes of follicular lymphoma transformation in the immunochemotherapy era: a report from the University of Iowa/MayoClinic Specialized Program of Research Excellence Molecular Epidemiology Resource. *J Clin Oncol*. 2013; 31: 3272–3278.

24. Link BK. Transformation of follicular lymphoma: why does it happen and can it be prevented? *Best Pract Res Clin Haematol* 2018; 31: 49–56.

25. Horning SJ and Rosenberg SA. The natural history of initially untreated low-grade non-Hodgkin's lymphomas. *N Engl J Med* 1984; 311: 1471–1475.

26. Kahl BS, Hong F, Williams ME, *et al*. Rituximab extended schedule or re-treatment trial for low-tumor burden follicular lymphoma: eastern cooperative oncology group protocol e4402. *J Clin Oncol* 2014; 32: 3096–3102.

27. Rummel MJ, Niederle N, Maschmeyer G, *et al*. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet* 2013; 381: 1203–1210.

28. Rummel MJ, Maschmeyer G, Ganser A, *et al*. Bendamustine plus rituximab (B-R) versus CHOP plus rituximab (CHOP-R) as first-line treatment in patients with indolent lymphomas: nine-year updated results from the StiL NHL1 study. *J Clin Oncol* 2017; 35(Suppl. 15): 7501.

29. Flinn IW, van der Jagt R, Kahl BS, *et al*. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. *Blood* 2014; 123: 2944–2952.

30. Flinn I, Jagt Rvd, Chang JE, *et al*. First-line treatment of iNHL or MCL patients with BR or R-CHOP/R-CVP: results of the BRIGHT 5-year follow-up study. *J Clin Oncol* 2017; 35(Suppl. 15): 7500.

31. Marcus R, Davies A, Ando K, *et al*. Obinutuzumab for the first-line treatment of follicular lymphoma. *N Engl J Med* 2017; 377: 1331–1344.

32. Hiddemann W, Barbui AM, Canales MA, *et al*. Immunochemotherapy with obinutuzumab or rituximab for previously untreated follicular lymphoma in the gallium study: influence of chemotherapy on efficacy and safety. *J Clin Oncol* 2018; 36: 2395–2404.

33. Ahmed MA, Fowler N, Ma L, *et al*. SUVmax on pre-treatment FDG PET scan is not predictive of outcome in follicular lymphoma after R-CHOP threapy. *Blood* 2014; 124: 1629.

34. Strati P, Fowler N, Pina-Oviedo S, *et al*. Long-term remissions of patients with follicular lymphoma grade 3 treated with

R-CHOP. *Clin Lymphoma Myeloma Leuk* 2018; 18: e103–e108.

35. Salles G, Seymour JF, Offner F, *et al*. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. *Lancet* 2011; 377: 42–51.
36. Salles GA, Seymour JF, Feugier P, *et al*. Long term follow-up of the PRIMA study: half of patients receiving rituximab maintenance remain progression free at 10 years. *Blood* 2017; 130: 486.
37. Kahl BS, Burke JM, van der Jagt R, *et al*. Assessment of maintenance rituximab after first-line bendamustine-rituximab in patients with follicular lymphoma: an analysis from the BRIGHT trial. *Blood*. 2017; 130: 484.
38. Hill BT, Nastoupil L, Winter AM, *et al*. Maintenance rituximab or observation after frontline treatment with bendamustine-rituximab (br) for follicular lymphoma: a real world analysis across 13 us cancer centers. *Blood* 2017; 130: 2779.
39. Maddocks K, Barr PM, Cheson BD, *et al*. Recommendations for clinical trial development in follicular lymphoma. *J Natl Cancer Inst* 2017; 109.
40. Hiddemann W, Kneba M, Dreyling M, *et al*. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood* 2005; 106: 3725–3732.
41. Marcus R, Imrie K, Belch A, *et al*. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. *Blood* 2005; 105: 1417–1423.
42. Kimby E, Rondeau S, Vanazzi A, *et al*. Rituximab plus lenalidomide versus rituximab monotherapy in untreated follicular lymphoma patients in need of therapy. First analysis of survival endpoints of the randomized phase-2 trial SAKK 35/10. *Blood* 2016; 128: 1099.
43. Morschhauser F, Fowler NH, Feugier P, *et al*. Rituximab plus lenalidomide in advanced untreated follicular lymphoma. *N Engl J Med* 2018; 379: 934–947.
44. Akinleye A, Furqan M and Adekunle O. Ibrutinib and indolent B-cell lymphomas. *Clin Lymphoma Myeloma Leuk* 2014; 14: 253–260.
45. Fowler N, Nastoupil L, de Vos S, *et al*. Ibrutinib combined with rituximab in treatment-naive patients with follicular lymphoma: arm 1 + arm 2 results from a multicenter, open-label phase 2 study. *Blood* 2016; 128: 1804.
46. Ujjani CS, Jung SH, Pitcher B, *et al*. Phase 1 trial of rituximab, lenalidomide, and ibrutinib in previously untreated follicular lymphoma: alliance A051103. *Blood* 2016; 128: 2510–2516.
47. Furman RR, Sharman JP, Coutre SE, *et al*. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N Engl J Med* 2014; 370: 997–1007.
48. Casulo C, Sancho JM, Van Eygen K, *et al*. Contempo: preliminary results in first-line treatment of follicular lymphoma with the oral dual PI3K-δ,γ inhibitor, duvelisib, in combination with rituximab or obinutuzumab. *Blood* 2016; 128: 2979.
49. Vaandrager JW, Schuuring E, Raap T, *et al*. Interphase FISH detection of BCL2 rearrangement in follicular lymphoma using breakpoint-flanking probes. *Genes Chromosom Cancer* 2000; 27: 85–94.
50. Roberts AW, Davids MS, Pagel JM, *et al*. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. *N Engl J Med* 2016; 374: 311–322.
51. Davids MS, Roberts AW, Seymour JF, *et al*. Phase I first-in-human study of venetoclax in patients with relapsed or refractory non-Hodgkin lymphoma. *J Clin Oncol* 2017; 35: 826–833.
52. Yang ZZ, Novak AJ, Stenson MJ, *et al*. Intratumoral CD4+CD25+ regulatory T-cell-mediated suppression of infiltrating CD4+ T cells in B-cell non-Hodgkin lymphoma. *Blood* 2006; 107: 3639–3646.
53. Dave SS, Wright G, Tan B, *et al*. Prediction of survival in follicular lymphoma based on molecular features of tumor-infiltrating immune cells. *N Engl J Med* 2004; 351: 2159–2169.
54. Yang ZZ, Grote DM, Ziesmer SC, *et al*. PD-1 expression defines two distinct T-cell sub-populations in follicular lymphoma that differentially impact patient survival. *Blood Cancer J* 2015; 5: e281.
55. Carreras J, Lopez-Guillermo A, Roncador G, *et al*. High numbers of tumor-infiltrating programmed cell death 1-positive regulatory lymphocytes are associated with improved

overall survival in follicular lymphoma. *J Clin Oncol* 2009; 27: 1470–1476.

56. Richendollar BG, Pohlman B, Elson P and Hsi ED. Follicular programmed death 1-positive lymphocytes in the tumor microenvironment are an independent prognostic factor in follicular lymphoma. *Hum Pathol* 2011; 42: 552–557.

57. Lesokhin AM, Ansell SM, Armand P, *et al.* Nivolumab in patients with relapsed or refractory hematologic malignancy: preliminary results of a phase Ib study. *J Clin Oncol* 2016; 34: 2698–2704.

58. Morschhauser F, Radford J, Van Hoof A, *et al.* 90Yttrium-ibritumomab tiuxetan consolidation of first remission in advanced-stage follicular non-Hodgkin lymphoma: updated results after a median follow-up of 7.3 years from the international, randomized, phase III first-lineindolent trial. *J Clin Oncol* 2013; 31: 1977–1983.

59. Provencio M, Cruz Mora MA, Gomez-Codina J, *et al.* Consolidation treatment with Yttrium-90 ibritumomab tiuxetan after new induction regimen in patients with intermediate- and high-risk follicular lymphoma according to the Follicular Lymphoma International Prognostic Index: a multicenter, prospective phase II trial of the Spanish Lymphoma Oncology Group. *Leuk Lymphoma* 2014; 55: 51–55.

60. Provencio-Pulla M, Franco F, Gómez-Codina J, *et al.* 90 yttrium-ibritumomab tiuxetan consolidation of first remission in advanced-stage follicular non-Hodgkin lymphoma: updated results after a median follow-up of 8.5years from the GOTEL trial. *J Clin Oncol* 2018; 36(Suppl. 15): 7550.

61. Schaefer NG, Ma J, Huang P, *et al.* Radioimmunotherapy in non-Hodgkin lymphoma: opinions of U.S. medical oncologists and hematologists. *J Nucl Med* 2010; 51: 987–994.

62. Launonen A, Hiddemann W, Duenzinger U, *et al.* Early disease progression predicts poorer survival in patients with follicular lymphoma (FL) in the GALLIUM study. *Blood* 2017; 130: 1490.

63. Kahl BS and Yang DT. Follicular lymphoma: evolving therapeutic strategies. *Blood* 2016; 127: 2055–2063.

64. National Cancer Institute. Obinutuzumab with or without umbralisib, lenalidomide, or combination chemotherapy in treating patients with relapsed or refractory grade I-IIIa follicular lymphoma, https://ClinicalTrials.gov/show/NCT03269669 (accessed 31 December 2017).

65. Fowler NH, Pearlberg J, Brail LH, *et al.* FRESCO: a phase 2, randomized study of duvelisib plus rituximab vs R-CHOP in patients with relapsed/refractory follicular lymphoma who have progressed within 24 months of receiving an alkylator-based chemotherapy regimen. *J Clin Oncol* 2016; 34: TPS7578-TPS.

66. Trotman J, Fournier M, Lamy T, *et al.* Positron emission tomography-computed tomography (PET-CT) after induction therapy is highly predictive of patient outcome in follicular lymphoma: analysis of PET-CT in a subset of PRIMA trial participants. *J Clin Oncol* 2011; 29: 3194–3200.

67. Dupuis J, Berriolo-Riedinger A, Julian A, *et al.* Impact of [(18)F]fluorodeoxyglucose positron emission tomography response evaluation in patients with high-tumor burden follicular lymphoma treated with immunochemotherapy: a prospective study from the Groupe d'Etudes des Lymphomes de l'Adulte and GOELAMS. *J Clin Oncol* 2012; 30: 4317–4322.

68. Rivas-Delgado A, Magnano L, Moreno-Velazquez M, *et al.* Progression-free survival shortens after each relapse in patients with follicular lymphoma treated in the rituximab era. *Hematological Oncology* 2017; 35: 360–361.

69. Conconi A, Lobetti-Bodoni C, Montoto S, *et al.* Life expectancy of young adults with follicular lymphoma. *Ann Oncol* 2015; 26: 2317–2322.

70. Sehn LH, Chua N, Mayer J, *et al.* Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. *Lancet Oncol* 2016; 17: 1081–1093.

71. Cheson BD, Chua N, Mayer J, *et al.* Overall survival benefit in patients with rituximab-refractory indolent non-hodgkin lymphoma who received obinutuzumab plus bendamustine induction and obinutuzumab maintenance in the GADOLIN study. *J Clin Oncol* 2018; 36: 2259–2266.

72. Sawas A, Farber CM, Schreeder MT, *et al.* A phase 1/2 trial of ublituximab, a novel anti-CD20 monoclonal antibody, in patients with B-cell non-Hodgkin lymphoma or chronic

lymphocytic leukaemia previously exposed to rituximab. *Br J Haematol* 2017; 177: 243–253.

73. Goy A, Forero A, Wagner-Johnston N, *et al*. A phase 2 study of inotuzumab ozogamicin in patients with indolent B-cell non-Hodgkin lymphoma refractory to rituximab alone, rituximab and chemotherapy, or radioimmunotherapy. *Br J Haematol* 2016; 174: 571–581.
74. Ogura M, Tobinai K, Hatake K, *et al*. Phase I study of inotuzumab ozogamicin combined with R-CVP for relapsed/refractory CD22+ B-cell non-hodgkin lymphoma. *Clin Cancer Res* 2016; 22: 4807–4816.
75. Sehn LH, Kamdar M, Herrera AF, *et al*. Randomized phase 2 trial of polatuzumab vedotin (pola) with bendamustine and rituximab (BR) in relapsed/refractory (r/r) FL and DLBCL. *J Clin Oncol* 2018; 36(Suppl. 15): 7507.
76. Goebeler ME, Knop S, Viardot A, *et al*. Bispecific T-Cell Engager (BiTE) antibody construct blinatumomab for the treatment of patients with relapsed/refractory non-hodgkin lymphoma: final results from a phase I study. *J Clin Oncol* 2016; 34: 1104–1111.
77. Roy R, Evens AM, Patton D, *et al*. Bortezomib may be safely combined with Y-90-ibritumomab tiuxetan in patients with relapsed/refractory follicular non-Hodgkin lymphoma: a phase I trial of combined induction therapy and bortezomib consolidation. *Leuk Lymphoma* 2013; 54: 497–502.
78. Andorsky DJ, Yacoub A, Bitran JD, *et al*. MAGNIFY: phase IIIb randomized study of lenalidomide plus rituximab (R2) followed by lenalidomide vs. rituximab maintenance in subjects with relapsed/refractory follicular, marginal zone, or mantle cell lymphoma. *Blood* 2016; 128: 1798.
79. Bartlett NL, Costello BA, LaPlant BR, *et al*. Single-agent ibrutinib in relapsed or refractory follicular lymphoma: a phase 2 consortium trial. *Blood* 2018; 131: 182–190.
80. Zinzani P, Wagner-Johnston N, Miller C, *et al*. DYNAMO: a phase 2 study demonstrating the clinical activity of duvelisib in patients with double-refractory indolent non-hodgkin lymphoma. *Hematol Oncol* 2017; 35: 69–70.
81. Zinzani PL, Topp MS, Yuen SL, *et al*. Phase 2 study of venetoclax plus rituximab or randomized ven plus bendamustine+rituximab (BR) versus BR in patients with relapsed/refractory follicular lymphoma: interim data. *Blood* 2016; 128: 617.
82. Westin JR, Chu F, Zhang M, *et al*. Safety and activity of PD1 blockade by pidilizumab in combination with rituximab in patients with relapsed follicular lymphoma: a single group, open-label, phase 2 trial. *Lancet Oncol* 2014; 15: 69–77.
83. Palomba ML, Till BG, Park SI, *et al*. A phase Ib study evaluating the safety and clinical activity of atezolizumab combined with obinutuzumab in patients with relapsed or refractory non-hodgkin lymphoma (Nhl). *Hematol Oncol* 2017; 35: 137–138.
84. Nastoupil LJ, Westin JR, Fowler NH, *et al*. Response rates with pembrolizumab in combination with rituximab in patients with relapsed follicular lymphoma: interim results of an on open-label, phase II study. *J Clin Oncol* 2017; 35: 7519.
85. McDonald A, Clawson A, Chaidos A, *et al*. Interim update from a phase 2 multicenter study of tazemetostat, an EZH2 inhibitor, in patients with relapsed or refractory follicular lymphoma 2018, https://ehaweb.org/congress/previous-congresses/23rd-c/program/online-program/ (accessed 27 August 2018).
86. Ogura M, Ando K, Suzuki T, *et al*. A multicentre phase II study of vorinostat in patients with relapsed or refractory indolent B-cell non-Hodgkin lymphoma and mantle cell lymphoma. *Br J Haematol* 2014; 165: 768–776.
87. Hagenbeek A, Gadeberg O, Johnson P, *et al*. First clinical use of ofatumumab, a novel fully human anti-CD20 monoclonal antibody in relapsed or refractory follicular lymphoma: results of a phase 1/2 trial. *Blood* 2008; 111: 5486–5495.
88. Czuczman MS, Fayad L, Delwail V, *et al*. Ofatumumab monotherapy in rituximab-refractory follicular lymphoma: results from a multicenter study. *Blood* 2012; 119: 3698–3704.
89. Genmab. Genmab announces topline results in phase III study of Arzerra® in indolent non-Hodgkin's lymphoma 2018, https://globenewswire.com/news-release/2018/05/24/1511714/0/en/Genmab-Announces-Topline-Results-in-Phase-III-study-of-Arzerra-in-Indolent-Non-Hodgkin-s-Lymphoma.html (accessed 20 August 2018).

90. Ganjoo KN, de Vos S, Pohlman BL, *et al.* Phase 1/2 study of ocaratuzumab, an Fc-engineered humanized anti-CD20 monoclonal antibody, in low-affinity FcgammaRIIIa patients with previously treated follicular lymphoma. *Leuk Lymphoma* 2015; 56: 42–48.

91. Palanca-Wessels MC, Czuczman M, Salles G, *et al.* Safety and activity of the anti-CD79B antibody-drug conjugate polatuzumab vedotin in relapsed or refractory B-cell non-Hodgkin lymphoma and chronic lymphocytic leukaemia: a phase 1 study. *Lancet Oncol* 2015; 16: 704–715.

92. Witzig TE, Flinn IW, Gordon LI, *et al.* Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. *J Clin Oncol* 2002; 20: 3262–3269.

93. Gribben JG, Fowler N and Morschhauser F. Mechanisms of action of lenalidomide in B-Cell non-hodgkin lymphoma. *J Clin Oncol* 2015; 33: 2803–2811.

94. Celgene. Celgene announces phase III 'AUGMENT' study of REVLIMID® in combination with rituximab (R^2) for the treatment of patients with relapsed/refractory indolent lymphoma met primary endpoint, http://ir.celgene.com/releasedetail.cfm?releaseid=1072723 (2018, accessed 23 July 2018).

95. Fowler NH, Neelapu SS, Samaniego F, *et al.* Activity of the immunologic doublet of lenalidomide plus obinutuzumab in relapsed follicular lymphoma: results of a phase I/II study. *J Clin Oncol* 2017; 35: 7531.

96. Michot JM, Doorduijn JK, Bouabdallah R, *et al.* A phase 1B study of CC-122 in combination with Obinutuzumab (GA101) in relapsed or refractory diffuse large B-Cell lymphoma and indolent non-hodgkin lymphoma. *Blood* 2016; 128: 4199.

97. Gopal AK, Schuster SJ, Fowler NH, *et al.* Ibrutinib as treatment for patients with relapsed/refractory follicular lymphoma: results from the open-label, multicenter, phase II DAWN study. *J Clin Oncol* 2018; 36: 2405–2412.

98. Fowler N, Coleman M, Stevens DA, *et al.* Acalabrutinib alone or in combination with rituximab (R) in follicular lymphoma (FL). *J Clin Oncol* 2018; 36(Suppl. 15): 7549.

99. Swinnen LJ, Flowers CR, Wang D, *et al.* Venetoclax, bendamustine and rituximab in patients with relapsed or refractory (r/r) non-Hodgkin lymphoma (NHL): final results of a phase I study. *Hematol Oncol* 2017; 35: 90.

100. Mocsai A, Ruland J and Tybulewicz VL. The SYK tyrosine kinase: a crucial player in diverse biological functions. *Nat Rev Immunol* 2010; 10: 387–402.

101. Friedberg JW, Sharman J, Sweetenham J, *et al.* Inhibition of Syk with fostamatinib disodium has significant clinical activity in non-Hodgkin lymphoma and chronic lymphocytic leukemia. *Blood* 2010; 115: 2578–2585.

102. Hamlin PA, Cheson BD, Farber CM, *et al.* The dual SYK/JAK inhibitor cerdulatinib demonstrates rapid tumor responses in a phase 2 study in patients with relapsed/refractory B- and T-cell non-Hodgkin lymphoma (NHL). *J Clin Oncol* 2018; 36(Suppl. 15): 7511.

103. Study of nivolumab in subjects with relapsed or refractory follicular lymphoma (FL) (CheckMate 140) 2018, https://ClinicalTrials.gov/show/NCT02038946 (accessed 12 July 2018).

104. Advani R, Flinn I, Popplewell L, et al. CD47 blockade by Hu5F9-G4 and Rituximab in non-Hodgkin's lymphoma. *N Engl J Med* 2018; 379: 1711–1721.

105. Rosenquist R, Bea S, Du MQ, *et al.* Genetic landscape and deregulated pathways in B-cell lymphoid malignancies. *J Intern Med* 2017; 282: 371–394.

106. Korfi K, Ali S, Heward JA, *et al.* Follicular lymphoma, a B cell malignancy addicted to epigenetic mutations. *Epigenetics* 2017; 12: 370–377.

107. Pastore A, Jurinovic V, Kridel R, *et al.* Integration of gene mutations in risk prognostication for patients receiving first-line immunochemotherapy for follicular lymphoma: a retrospective analysis of a prospective clinical trial and validation in a population-based registry. *Lancet Oncol* 2015; 16: 1111–1122.

108. Brudno JN and Kochenderfer JN. Chimeric antigen receptor T-cell therapies for lymphoma. *Nat Rev Clin Oncol* 2018; 15: 31–46.

109. Maude SL, Laetsch TW, Buechner J, *et al.* Tisagenlecleucel in children and young adults with B-Cell lymphoblastic leukemia. *N Engl J Med* 2018; 378: 439–448.

110. Neelapu SS, Locke FL, Bartlett NL, *et al.* Axicabtagene ciloleucel CAR T-Cell therapy in refractory large B-Cell lymphoma. *N Engl J Med* 2017; 377: 2531–2544.