Novel agents in follicular lymphoma: choosing the best target

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Outcomes in patients with follicular lymphoma (FL) have improved dramatically over the last decade. However, novel agents are greatly needed for those who exhibit treatment resistance, in order to minimize lifelong toxicity and to enable combinations that may allow us to achieve the elusive goal of cure. Biological advances have led to the discovery of a large number of potential therapeutic targets and the development of a plethora of novel agents designed to exploit these processes. Possible targets include tumor cell surface markers, key components of intracellular pathways and epigenetic mechanisms, and reactive cells of the microenvironment. Given the large number of candidate drugs and potential combinations, it will be crucial to prioritize evaluation based on sound preclinical and early clinical studies. Combinations that exploit driver mechanisms within tumor cells and target parallel pathways to minimize the development of drug resistance, as well as harness the potential of the immune system would seem most logical. In order to expedite progress, future studies will need to use innovative trial designs and employ surrogate end points. The development of validated prognostic tools to identify higher risk patients and reliable predictive markers to select subgroups most likely to benefit from targeted agents will be paramount. The potential for unexpected toxicity with novel combinations must be recognized, necessitating both short- and long-term vigilance. Finally, as a greater number of treatment options become available, optimal sequencing must be determined in order to both prolong life and maintain its quality.

Learning Objectives

- To recognize the potential therapeutic targets, which have been discovered as a consequence of greater biological insight into the pathogenesis of FL
- To consider the novel agents in clinical development and how they may influence the management for patients with FL

Introduction

The challenge of follicular lymphoma (FL) is that although the disease generally follows an indolent course and is responsive to various treatments, advanced stage patients remain incurable and must be managed over a lifetime. In addition, although outcome is favorable for the majority of patients, a subset will exhibit more rapidly evolving treatment-resistant disease that will significantly affect their longevity. Finally, because the median age at diagnosis is in the mid 60s, both short- and long-term toxicities are a major concern.

The mainstay of therapy continues to rely on cytotoxic chemotherapy, with alkylators and purine analogs most frequently used. Approximately a decade ago, the addition of the chimeric anti-CD20 monoclonal antibody (mAb) rituximab, lead to improved response rates, duration of response, and overall survival, establishing immunochemotherapy as the standard of care.¹⁻⁵ However, not all patients have a favorable outcome with this approach. The 20% of patients who experience

disease progression within 2 years of diagnosis despite receiving treatment with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), have a 5-year survival rate of ~50%, compared with a 5-year survival rate of 90% for the remaining patients.⁶ This poor-risk subgroup represents the patients with the greatest need in FL.

Innovative therapies will be required to impact this high-risk subgroup, as well as to provide patients with additional therapeutic options once standard therapies are no longer effective. In addition, novel targeted agents with a reduced toxicity profile are needed to offer safer treatment options for patients with limited tolerance and to more easily combine with existing platforms to generate more effective strategies.

Over the last decade, biological advances have lead to improved insight into the underlying pathogenic mechanisms that promote and sustain FL. It is now understood that disease behavior is influenced by a complex interplay between the clonal FL cells and polyclonal cells of the microenvironment. This understanding has lead to the discovery of a large number of potential therapeutic targets and the development of a plethora of novel agents designed to exploit these processes. Possible targets include tumor cell surface markers, key components of intracellular pathways and epigenetic mechanisms, and reactive cells of the microenvironment. The goal of this review is to highlight some of the key compounds in development, focusing on prototypic drugs and those that are furthest along in development.

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Off-label drug use: Majority of novel agents discussed are either off-label in FL or in development.

Tumor cell surface targets

Novel anti-CD20 mAbs

Given the impact of rituximab, the development of novel anti-CD20 mAbs with improved efficacy would seem rational. By design, these agents have been engineered to optimize one or more of the modalities by which rituximab exerts its effects; including antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), or direct cell death. Based on their mode of CD20 binding and cell-killing mechanism, anti-CD20 mAbs can be categorized as type I (eg, rituximab) or type II. Novel type I mAbs in development include agents such as ofatumumab, veltuzumab, ocaratuzumab, and ublituximab (Table 1).

Ofatumumab was initially approved by the US Food and Drug Administration (FDA) in 2009 for chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab. Similar to rituximab, it is an immunoglobulin G1 (IgG1) mAb, but has been fully humanized for lower immunogenicity. In addition, ofatumumab targets a distinct epitope on CD20 and has a slower off-rate, potentially yielding higher CDC and direct cell death than rituximab. When tested in patients with relapsed/refractory FL in a phase 1/2 trial, the overall response rate (ORR) ranged from 20% to 63%, with a median time to progression of 8.8 months.⁷ However, when evaluated in patients with rituximab-refractory FL, the ORR was only 11% and the median progression-free survival (PFS) was 5.8 months.⁸ Recently, a phase 3 trial of ofatumumab vs rituximab in patients with relapsed indolent lymphoma who had previously received rituximab was prematurely stopped due to presumed futility.⁹ The role of this drug in FL remains unclear, although an ongoing phase 3 trial will evaluate the benefit of ofatumumab when added to bendamustine in rituximab-refractory FL (#NCT01077518).

Veltuzumab, a humanized IgG1 mAb, was constructed on the framework of the anti-CD22 mAb epratuzumab, but has identical anti-CD20 complementarity-determining regions as rituximab. Preclinically, it was shown to have a slower off-rate and improved CDC compared with rituximab.¹⁰ In a phase 1/2 dose-finding study in relapsed/refractory B-cell non-Hodgkin lymphoma (NHL), the ORR in patients with FL was 44%, including a complete remission (CR) rate of 27%, many of which were durable (median duration, 19.7 months).¹¹ In a separate trial, subcutaneous administration was demonstrated to be safe and effective.¹² A recent phase 1/2 trial of veltuzumab in combination with the anti-CD74 mAb milatuzumab in relapsed/refractory NHL, demonstrated safety and an ORR of 33% in patients with FL.¹³

Ocaratuzumab (AME-133) is a humanized IgG1 mAb that was optimized through protein engineering for increased CD20 affinity and enhanced binding to FcγRIIIa to augment ADCC. A phase 1/2 trial in 50 patients with previously treated FL and a low affinity genotype of FcγRIIIa demonstrated an ORR of 30% (CR/CRu 14%), median PFS of 38 weeks, and a favorable safety profile.¹⁴ Further studies will be required to assess its comparative benefit with rituximab. Ublituximab (TG-1101) targets a unique epitope on CD20 and has been glycoengineered for greater ADCC. A phase 1 trial in patients with B-cell NHL and prior exposure to rituximab confirmed activity and safety, and combination studies are underway^{15,16} (#NCT01744912 and #NCT02006485).

Obinutuzumab (GA101) is the first type II anti-CD20 mAb evaluated in NHL. It has been uniquely glycoengineered, and shown to have

Table 1. Tumor cell surface targets and potential therapies

Category	Target	Potential agents
Anti-CD20 mAbs, type I	CD20	Rituximab
	CD20	Ofatumumab
	CD20	Veltuzumab
	CD20	Ocaratuzumab
	CD20	Ublituximab
Anti-CD20 mAbs, type II	CD20	Obinutuzumab
Other mAbs	CD22	Epratuzumab*
	CD80	Galiximab*
	CD37	Otlertuzumab
	CD37	BI 836826
Bispecific antibodies	HLA-DR	IMMU-114
	CD3/CD19	Blinatumumab
	CD3/CD20	BTCT4465A
	CD3/CD20	REGN1979
	CD3/CD19	AFM11
ADCs	CD22	Inotuzumab Ozogamycin
	CD19	Coltuzumab Ravtansine
	CD79b	Polatuzumab Vedotin
	CD37	IMGN529
	CD37	AGS67E
	CD19	ADCT-402
	CD25	ADCT-301
	CD19/CD22	DT2219ARL

ADCs, antibody-drug conjugates.

*No longer in development in NHL.

enhanced ADCC and increased induction of direct cell death by an alternate mechanism but lower CDC than rituximab.¹⁷ In 2013, obinutuzumab in combination with chlorambucil, was approved by the FDA for patients with untreated CLL.¹⁸ Phase 1/2 trials of obinutuzumab in patients with relapsed/refractory NHL demonstrated promising efficacy and a favorable safety profile, although with a higher rate of infusion-related reactions compared with rituximab.¹⁹⁻²¹ A phase 2 comparison of obinutuzumab vs rituximab in patients with relapsed CD20-positive indolent NHL demonstrated a promising ORR, but no difference in PFS was seen at the time of analysis.²¹ The GADOLIN phase 3 trial compared bendamustine monotherapy vs bendamustine and obinutuzumab followed by obinutuzumab maintenance in patients with rituximab-refractory indolent NHL.²² PFS was significantly improved in the obinutuzumab cohort (median PFS not reached vs 14.9 months; hazard ratio, 0.55; $P = .0001$), leading to recent FDA approval for patients with relapsed or refractory FL and the establishment of a new standard of care.

Other tumor cell surface targets

Numerous mAbs targeting other B-cell surface markers have been undergoing evaluation. CD22 is commonly expressed on B-cell malignancies, including FL. Epratuzumab, a humanized IgG1 mAb targeting CD22 demonstrated a modest ORR of 18% in a phase 1 study in multiply-treated patients with indolent NHL.²³ Phase 2 studies in combination with rituximab demonstrated feasibility and activity in patients with relapsed/refractory and untreated indolent NHL, but the degree of benefit provided by epratuzumab was unclear and further development is unlikely.²⁴⁻²⁶ Similarly, the mAb galiximab targeting the co-stimulatory molecule CD80 showed modest activity as a single agent and in combination with rituximab in patients with relapsed/refractory FL, and is no longer in development.^{27,28}

CD37 is a glycosylated cell surface protein (member of the tetraspanin superfamily) that is primarily expressed on B cells and B-cell

lymphomas, making it a logical therapeutic target. Otlertuzumab (TRU-016) is a single-chain peptide therapeutic composed of an IgG1 variable region and an engineered constant region that binds CD37, and induces both ADCC and direct apoptosis.²⁹ After initial demonstration of safety and efficacy in CLL,³⁰ otlertuzumab was evaluated in a phase 1 trial in 16 patients with multiply-treated NHL (8 with FL), administered at a dose of 20 mg/kg weekly for up to 8 weeks, then monthly for 4 doses. Toxicities were mainly low grade, including neutropenia, fatigue, thrombocytopenia, diarrhea, and peripheral edema. Three of 12 (25%) evaluable patients (2 with FL) experienced lymph node reduction $\geq 50\%$.³¹ A phase 1b study with bendamustine and rituximab demonstrated feasibility, but further development in NHL is uncertain.³² Another agent in development targeting CD37 is the chimeric IgG1 mAb BI 836826 (#NCT01403948).

Human leukocyte antigen-antigen D-related (HLA-DR), a major histocompatibility complex class II molecule, is present on many BCLs. IMMU-114 is a humanized IgG4 anti-HLA-DR mAb that directly induces apoptosis via the AKT survival pathway and does not induce CDC or ADCC. Preliminary results of an ongoing phase 1 study of IMMU-114 in 11 patients with relapsed/refractory CLL and NHL (given subcutaneously on a variable dosing schedule), demonstrated only low-grade administration reactions and evidence of activity, including patients with FL³³ (#NCT01728207).

Bispecific antibodies

By combining 2 antibodies recognizing different epitopes, bispecific antibodies may have multiple applications, such as redirecting T cells toward tumor cells, blocking 2 different signaling pathways simultaneously, or the dual targeting of different disease mediators.

Blinatumomab is a bispecific T-cell-engaging antibody that transiently links CD3-positive T cells to CD19-positive B cells, inducing T-cell activation and proliferation, and tumor cell lysis.³⁴ In 2014, blinatumomab became the first bispecific antibody to receive FDA approval for lymphoid cancer, based on efficacy demonstrated in a phase 2 trial in patients with relapsed/refractory B-precursor acute lymphoblastic leukemia.³⁵ Blinatumomab was evaluated in a phase 1 trial in relapsed/refractory NHL, including 28 patients with FL.³⁶ Neurologic events were dose limiting, which prompted a step-wise dosing scheme and established 60 $\mu\text{g}/\text{m}^2$ per day as the maximum-tolerated dosage (MTD). Among the 35 patients treated at this target dose, the ORR was 69% (37% CR/CRu) and the median response duration was 404 days; the ORR in FL was encouraging at 80%. A phase 2 trial of blinatumomab in relapsed/refractory indolent NHL is planned (#NCT02811679) and a combination trial with lenalidomide in relapsed NHL is underway (#NCT02568553).

Additional bispecific antibodies under investigation in NHL include BTCT4465A, a humanized full-length T-cell-dependent bispecific antibody designed to target both CD20 and CD3 (#NCT02500407) and REGN1979, which also targets CD20 and CD3 (#NCT02290951). AFM11, a humanized tetravalent bispecific antibody, which has 2 binding sites for CD3 and 2 for CD19 is also being evaluated in CD19-positive B-cell NHL (#NCT02106091).

ADCs

By conjugating a toxin to a B-cell-specific mAb, ADCs provide a mechanism of targeted delivery of cytotoxic therapy with the potential to minimize toxicity to normal tissues. An ADC consists of the targeting antibody, the effector molecule (most commonly

microtubule inhibitors and DNA damaging agents), and the linker joining the two, with each component contributing to its activity.³⁷ For example, membrane permeability of the released toxin can contribute to both severity of toxicities as well as bystander effects, which may prove beneficial in bulky tumors or when the target is heterogeneously expressed. Multiple ADCs are in clinical development for NHL, with targets including CD19, CD22, CD25, CD37, and CD79b.

Inotuzumab ozogamycin (CMC-544), a humanized anti-CD22 antibody conjugated to calicheamicin, was one of the first ADCs evaluated in NHL. A phase 1 trial demonstrated an ORR of 68% in patients with FL treated at the MTD,³⁸ whereas an ORR of 87% and a 2-year PFS of 68% were reported in a phase 2 trial in combination with rituximab.³⁹ Toxicities included thrombocytopenia, neutropenia, hyperbilirubinemia, and transaminitis. Unfortunately, a phase 3 study of inotuzumab ozogamycin in combination with rituximab compared with investigators choice in relapsed/refractory FL was terminated early due to poor enrollment, but both single-agent and combination studies have continued.⁴⁰ A recent trial of inotuzumab ozogamycin in patients with indolent B-cell NHL refractory to rituximab or CD20-directed radioimmunotherapy demonstrated an ORR of 67% with median PFS of 12.7 months, but 58% of patients experienced adverse events (primarily hematologic toxicity) leading to treatment discontinuation.⁴¹

Coltuximab ravtansine (SAR3419) is an ADC comprised of a humanized anti-CD19 antibody linked to DM4, a tubulin inhibitor.⁴² In an initial phase 1 trial in 39 patients with relapsed/refractory NHL (17 with FL), the MTD was 160 mg/m^2 administered every 3 weeks.⁴³ The reported dose-limiting toxicity was blurred vision caused by reversible corneal epitheliopathy. Tumor reduction was seen in 74%, with 6/35 evaluable patients achieving a CR or partial remission. In a second dose-escalation trial in patients with relapsed/refractory NHL, coltuximab ravtansine administered at a dose of 55 mg/m^2 weekly for 4 weeks, then biweekly for 4 weeks, was determined to be tolerable with an ORR of $\sim 30\%$ and fewer ocular events noted.⁴⁴ A recent phase 2 trial in combination with rituximab in patients with relapsed/refractory diffuse large BCL (DLBCL) demonstrated an ORR of 30%, below the positivity threshold set by the study, and it is unclear at this time whether further trials in indolent lymphoma will be planned.⁴⁵

Another ADC undergoing evaluation is polatuzumab vedotin, which uses the same protease-cleavable linker to monomethyl aurastatin E as brentuximab, but targets CD79b, a component of the B-cell receptor (BCR).⁴⁶ A phase 1 study with an expansion cohort included 77 patients with relapsed/refractory NHL (30 with indolent lymphoma) and identified 2.4 mg/kg every 3 weeks as the recommended phase 2 dose.⁴⁶ Objective responses were observed in 7 of 15 evaluable patients with indolent NHL treated at the recommended phase 2 dose, with a median PFS of 7.9 months. Preliminary analysis of the Romulus phase 2 study comparing rituximab in combination with polatuzumab or pinatuzumab vedotin (an identical molecule targeting CD22, which is no longer being developed) demonstrated an ORR of 70% in patients with relapsed/refractory FL,⁴⁷ supporting combination studies that are currently underway (#NCT02257567 and #NCT02600897).

IMGN529 is an ADC directed against CD37 conjugated to the maytansinoid anti-mitotic DM1. Preliminary findings from a phase 1 trial in relapsed/refractory NHL revealed activity, with hematologic toxicity (including transient neutropenia) and neuropathy seen.⁴⁸

A phase 2 study in combination with rituximab in relapsed/refractory NHL is ongoing (#NCT02564744). Recently, results of an ongoing first-in-human phase 1 study were reported for AGS67E, an ADC targeting CD37 linked to the microtubule toxin monomethyl aurastatin E.⁴⁹ Preliminary results in 30 patients with lymphoid malignancies demonstrated evidence of activity and a favorable safety profile, with mainly hematologic toxicity and low-grade neuropathy noted. Additional ADCs undergoing evaluation in indolent NHL include ADCT-402, targeting CD19 (#NCT02669017) and ADCT-301, targeting CD25 (NCT02432235). DT2219ARL is a bispecific ADC targeting both CD19 and CD22 linked to diphtheria toxin that is also undergoing evaluation (#NCT02370160).

Key intracellular pathway and epigenetic targets

BCR/tyrosine kinase inhibitors

Signaling from the BCR mediates multiple cellular processes including proliferation, differentiation, apoptosis, and cell migration, and is essential for B-cell development and survival.⁵⁰ Constitutive activation of the BCR is a hallmark in B-cell malignancies, including FL. Small molecule inhibitors targeting key signaling molecules downstream of the BCR and other parallel pathways represent a major area of therapeutic investigation (Table 2).

Bruton tyrosine kinase (BTK) inhibitors. BTK is an integral signaling molecule positioned early within the BCR-signaling cascade and is critical for B-cell function and survival. Ibrutinib is a first-in-class, selective, and irreversible small molecule inhibitor of BTK, which has shown efficacy in multiple B-cell malignancies and is currently FDA approved in CLL, mantle cell lymphoma, and Waldenstrom macroglobulinemia.⁵¹⁻⁵³ A phase 1 dose escalation study of ibrutinib in relapsed B-cell malignancies established the recommended dose of 560 mg daily for further evaluation and confirmed tolerability, with mainly grade 1 and 2 toxicities observed.⁵⁴ This trial included 16 patients with FL who exhibited an ORR of 38%. Preliminary results from a phase 2 consortium trial of 40 patients with relapsed/refractory FL demonstrated an ORR of 30% (1 CR) and median PFS of 9.9 months.⁵⁵ Based on this encouraging but modest benefit, ibrutinib combination trials are underway. In a phase 1 trial of ibrutinib and rituximab, the ORR in 60 patients with untreated FL was 82% (27% CR) and median PFS has not yet been reached.⁵⁶ Based on its favorable toxicity profile, combinations with ibrutinib and cytotoxic agents appear feasible, with no dose-limiting toxicities observed in a phase 1 study of bendamustine, rituximab, and ibrutinib in relapsed/refractory NHL.⁵⁷ A randomized phase 3 trial of immunochemotherapy (bendamustine/rituximab or R-CHOP) with or without ibrutinib in previously treated indolent NHL including FL has been completed but not yet reported (#NCT01974440). Second-generation BTK inhibitors that are potentially more selective than ibrutinib, including acalabrutinib (ACP-196), ONO/GS-4059, BGB-3111, and CC-292 are also being explored.

Phosphatidylinositol 3-kinase (PI3K) inhibitors. PI3K is a lipid kinase that has 4 catalytic forms, α , β , γ , and δ . Although the α and β forms are widely expressed in many tissues, the γ and δ forms are largely restricted to hematopoietic cells. PI3K is an enzyme downstream from the BCR that signals through several pathways, including the AKT/mammalian target of rapamycin (mTOR) pathway and regulates cellular proliferation, survival, and cellular motility.⁵⁸ PI3K signaling pathways are frequently hyperactive in BCLs, including FL, making it an attractive target.

Idelalisib, a potent small molecule inhibitor of PI3K δ , received accelerated approval by the FDA in 2014 for relapsed/refractory FL

Table 2. Key intracellular pathway and epigenetic targets and potential therapies

Category	Target	Potential agents
BTK inhibitors	BTK	Ibrutinib
	BTK	Acalabrutinib
	BTK	ONO/GS-4059
	BTK	BGB-3111
	BTK	CC-292
PI3K inhibitors	PI3K δ	Idelalisib
	PI3K δ and γ	Duvelisib
	PI3K δ and α	Copanlisib
	PI3K δ	TGR1202
Syk inhibitors	Syk	Fostamatinib*
	Syk	Entospletinib
BCL2 inhibitors	BCL2	Venetoclax
MDM2 inhibitors	MDM2	Idasanutlin
	MDM2	DS-3032b
Epigenetic modifiers	EZH2	Tazemetostat
	EZH2	CPI-1205
	EZH2	GSK2816126

*No longer in development in NHL.

following 2 prior lines of therapy, based on results from a pivotal phase 2 study.⁵⁹ In this trial, 125 patients with indolent NHL (72 with FL) refractory to both rituximab and alkylators were treated with idelalisib 150 mg twice daily until progression or intolerance. The ORR was 57% with a median duration of 12.5 months, and was similar in the FL subset. Although overall tolerability was favorable, grade 3 or higher toxicities included neutropenia (27%), transaminitis (13%), diarrhea (13%), and pneumonia (7%). A subset analysis limited to high-risk patients with relapse within 2 years of first-line therapy exhibited similar results.⁶⁰ Based on this promising activity, numerous combination trials were initiated in NHL. Recently, several of these trials were terminated prematurely due to excess toxicities, primarily atypical infections. As a consequence, the role of idelalisib in combination therapy for NHL remains uncertain at this time.

Second-generation PI3K inhibitors including duvelisib (IPI-145), copanlisib (BAY 80-6946), and TGR1202, are undergoing evaluation. Duvelisib, a PI3K δ and γ isoform inhibitor demonstrated an ORR of 69% in a phase 1 trial in patients with heavily pretreated FL,⁶¹ and is also undergoing evaluation in combination studies,⁶² including a randomized phase 2 trial of duvelisib and rituximab vs R-CHOP in patients with relapsed/refractory FL who have relapsed within 24 months of alkylator therapy (#NCT02605694). Currently, it remains unknown whether PI3K inhibitors that are more broadly targeted will have an efficacy advantage or different toxicity profile.

Spleen tyrosine kinase (SYK) inhibitors. Syk is a mediator of BCR signaling. Fostamatinib, an orally available inhibitor of Syk was evaluated in a phase 1/2 trial in patients with relapsed/refractory NHL and CLL. Although the drug was reasonably well tolerated with common toxicities including neutropenia, diarrhea, and fatigue, the ORR in 21 patients with FL was only 10%.⁶³ Entospletinib is a second-generation oral selective inhibitor of Syk that is undergoing evaluation in lymphoid malignancies. A phase 2 trial in 69 patients with relapsed/refractory indolent NHL (including 41 with FL) demonstrated an ORR of only 13%, although 62% had a decrease in tumor burden.⁶⁴ Primary toxicities included fatigue, nausea, diarrhea, transaminitis, and cytopenias. Although considerable toxicity

was seen when combined with idelalisib,⁶⁵ ongoing studies will evaluate entospletinib combined with vincristine (#NCT02568683) or the BTK inhibitor ONO/GS-4059 (#NCT02457598).

BCL2 inhibitors

The BCL2 family is a group of proteins that share one of four BCL homology domains (BH1-BH4) and include proapoptotic effectors (BAX, BAK), antiapoptotic proteins (BCL2, BCL-X_L, BCL-w, mantle cell lymphoma-1, A1), and BCL2 homology 3 (BH3)-only regulators (eg, BID, BIM, PUMA, BAD).⁶⁶ The t(14,18)(q32;q21) translocation, observed in the majority of patients with FL, leads to constitutive overexpression of BCL2 by placing the *BCL2* gene under direct control of IgH regulators. BH3-mimetic drugs mimic the activity of the physiologic antagonists of BCL2 and related proteins, triggering apoptosis. Navitoclax (ABT-263), a small molecule BH3 mimetic, was one of the first BCL2 inhibitors evaluated that showed some clinical activity against CLL, but demonstrated an unfavorable toxicity profile due to concurrent inhibition of BCL-X_L, causing thrombocytopenia.⁶⁷

Venetoclax (ABT-199/GDC-0199) is a highly selective orally available inhibitor of BCL2 that is more potent than navitoclax, with little activity against BCL-X_L.⁶⁸ Venetoclax has demonstrated significant efficacy in patients with CLL and was recently approved by the FDA for the treatment of CLL with 17p deletion following 1 prior line of therapy.^{69,70} Due to its rapid onset of activity and potential for tumor lysis syndrome, a ramp-up dosing schedule was designed to mitigate this risk. Additional side effects include myelosuppression (primarily neutropenia) and gastrointestinal symptoms such as nausea and diarrhea. Venetoclax has also been evaluated in a phase 1 trial in patients with relapsed/refractory NHL, with doses ranging up to 1200 mg daily until progression or unacceptable toxicity.⁷² At a recent update, 29 patients with FL (median = 3 prior lines of therapy) had been treated on the 1200 mg dose level, with an ORR of 34% (10% CR) and a median duration of response of 10 months.⁷² Although a clinical benefit was seen, the ORR was lower than anticipated in view of the key role of BCL2 in FL. It is possible that FL cells may require a concurrent proapoptotic signal for the full potential of venetoclax to be realized. Combination trials with venetoclax are currently ongoing in patients with NHL, including venetoclax in combination with bendamustine/rituximab (#NCT01594229).⁷³

Murine double minute 2 (MDM2) inhibitors

Dysregulation of the p53 tumor suppressor has been implicated in solid tumors and hematologic malignancies. MDM2, a negative regulator of the p53 pathway, may be overexpressed and represents a potential therapeutic target.⁷⁴ Idasanutlin (RG7388) is an oral selective inhibitor of MDM2 that prevents MDM2-p53 interaction, thereby restoring function of the p53 pathway and inducing cellular apoptosis.⁷⁵ The combination of idasanutlin and obinutuzumab has shown promise in preclinical studies,⁷⁶ and is being evaluated in a phase 1b/2 study in patients with relapsed/refractory FL and DLBCL (#NCT02624986). Additional MDM2 inhibitors are undergoing evaluation, such as DS-3032b, which is being tested in a phase 1 trial in patients with solid tumors and relapsed/refractory lymphoma (#NCT01877382).

Epigenetic modifiers

It has recently been recognized that mutations in epigenetic mechanisms and alterations of epigenomic patterning are a hallmark of FL. Inactivating mutations of the histone methyltransferase *MLL2* have

Table 3. Tumor microenvironment targets and potential therapies

Category	Target	Potential agents
Immunomodulatory agents Immune checkpoint inhibitors	Multiple	Lenalidomide
	PD-1	Pidilizumab
	PD-1	Nivolumab
	PD-1	Pembrolizumab
	PD-1	MEDI-0680
	PD-L1	Durvalumab
	PD-L1	Atezolizumab
	CTLA-4	Ipilimumab
Other immunomodulatory agents	CD47	TTI-621
	CD137	Urelumab
	KIR	Lirilumab

been found in >80% of cases, which limits the ability of *MLL2* to activate gene transcription through H3K4 methylation.⁷⁷ Recurring mutations in other histone modifiers have also been identified, including *CREBBP*, *EZH2*, *MEF2B*, and *EP300*.⁷⁷⁻⁸⁰ These mutations result in the disruption of chromatin structure and function of various proteins, ultimately causing aberrant transcription affecting a wide network of genes. Strategies targeted at overcoming abnormal epigenetic mechanisms may represent a therapeutic avenue.

The histone transferase *EZH2* is the catalytic subunit of polycomb repressive complex 2 responsible for methylating lysine 27 of histone H3, a modification that is associated with repressed transcription when trimethylated. Somatic gain-of-function mutations of *EZH2* at codon Y646 (and rare variants) occur in ~25% of cases with FL and appear to remain stable with time.^{78,81} Preclinical studies have demonstrated the potential therapeutic value of *EZH2* inhibitors in lymphoma.^{82,83} Tazemetostat (EPZ-6438) is an orally available selective inhibitor of both wild-type and mutated forms of *EZH2*. A phase 1 dose-escalation trial of tazemetostat included 19 patients with relapsed/refractory NHL; responses were observed in 9 of 15 evaluable patients (3 of 5 patients with FL), including those with wild-type *EZH2*.⁸⁴ Overall, the drug was well tolerated, with mainly low-grade adverse events reported. The ongoing phase 2 component is evaluating tazemetostat in patients with DLBCL and FL, and will correlate outcome with mutation status (#NCT01897571). Additional *EZH2* inhibitors undergoing phase 1 evaluation include CPI-1205 (#NCT02395601) and GSK2816126 (#NCT02082977).

Targeting the tumor microenvironment

The interplay between the malignant cell and the tumor microenvironment plays a crucial role in the pathogenesis of FL. In a landmark study, survival duration of patients with FL correlated with gene-expression signatures of infiltrating nonmalignant immune cells.⁸⁵ Approaches that manipulate this relationship by enhancing immune function against lymphoma cells have tremendous therapeutic potential (Table 3).

Immunomodulatory agents

To date, lenalidomide has been the most widely evaluated immunomodulatory drug in FL. Its mechanism of action includes activation of natural killer (NK) cells and T cells with restoration of immune synapse formation and augmentation of ADCC, modification of both inflammatory and anti-inflammatory cytokines, as well as direct antineoplastic activity resulting in decreased proliferation and apoptosis.⁸⁶ As a single agent, lenalidomide demonstrates only modest activity in patients with relapsed/refractory FL (ORR of ~30% to 50%), but activity is accentuated when combined with

rituximab (ORR >75%, with median time to progression of ~2 years).^{87,88} Responses and response duration are more dramatic in the front-line setting, where ORRs up to 98% (87% CR) have been reported, with 3-year PFS of 78.5%.⁸⁹ Based on these impressive results, a phase 3 trial comparing rituximab and lenalidomide with immunochemotherapy (RELEVANCE trial) in untreated patients with FL has been completed and is awaiting analysis (#NCT01650701). Numerous combination studies of lenalidomide with immunochemotherapy or novel targeted agents are underway and have been preliminarily reported.^{90,91} At this time, it is unclear whether these combinations will offer an additional benefit, but careful observation for unexpected toxicities is warranted because excessive toxicity (primarily hepatic) has been reported with the combination of lenalidomide, idelalisib, and rituximab.^{92,93}

Immune checkpoint inhibitors

In order to maintain self-tolerance and prevent autoimmunity, the immune system is carefully regulated by a set of cell surface proteins to downregulate T-cell activation.⁹⁴ This process can be exploited by tumor cells to allow them to evade T-cell-mediated antitumor immunity. One checkpoint system involves the engagement between programmed death-1 (PD-1) expressed on T cells, and its ligands PD-L1 and PD-L2 (on tumor and stromal cells), leading to inhibition of T-cell activation. Overexpression of PD-1 in the intratumoral T cells of patients with FL can lead to impairment in antitumor immune surveillance.⁹⁵ Strategies aimed at inhibiting PD-1 or its ligands, PD-L1 and PD-L2, are being explored in FL.

Pidilizumab (CT-011), a humanized anti-PD-1 mAb demonstrated modest activity as a single agent in a phase 1 trial in patients with hematologic malignancies, although the solitary patient with FL achieved a CR.⁹⁶ In a phase 2 trial of pidilizumab combined with rituximab in patients with relapsed FL, therapy was well tolerated with no grade 3 or 4 toxicities seen, and the ORR in 29 evaluable patients was 66% (52% CR) with a median PFS of 18.8 months.⁹⁷ Nivolumab, another humanized anti-PD-1 mAb that has shown efficacy in Hodgkin lymphoma, has recently been evaluated in a phase 1 dose-escalation trial in patients with relapsed/refractory hematologic malignancies and demonstrated an encouraging ORR of 40% (10% CR) in 10 patients with FL.^{98,99} Additional PD-1 inhibitors undergoing evaluation in hematologic malignancies include pembrolizumab (#NCT02332980) and MEDI-0680 (#NCT02271945). Finally, trials are also underway evaluating the utility of PD-L1 inhibition with agents such as durvalumab (MEDI-4736) (#NCT02401048) and atezolizumab (#NCT02596971).

Another immune checkpoint protein that is undergoing evaluation as a potential therapeutic target is cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). CTLA-4 is expressed on the surface of T cells and binds to its ligands CD80 or CD86, which are typically expressed by antigen-presenting cells. Engagement of CTLA-4 with its ligands results in T-cell inactivation. A phase 1 study of the anti-CTLA-4 mAb ipilimumab in patients with relapsed/refractory NHL demonstrated some activity, including a partial remission in 1 patient with FL.¹⁰⁰ Combination trials with ipilimumab are ongoing (#NCT01729806).

Other immunomodulatory agents

Although early in development, molecules targeting alternative immunomodulatory axes are being explored. CD47 is highly expressed on NHL cells and inhibits phagocytosis through activation of signal-regulatory protein α expressed on the surface of macrophages.

TTI-621, a fusion protein that binds CD47 and blocks interaction with signal-regulatory protein α resulting in macrophage activation and phagocytosis of tumor cells, is being evaluated in a phase 1 study in hematologic malignancies (#NCT02663518). CD137 is a costimulatory molecule that belongs to the tumor necrosis factor superfamily that is upregulated on activated lymphocytes, NK cells, and dendritic cells, and plays an important role in the potentiation of antigen-specific immune responses as well as in ADCC. Urelumab, a fully humanized IgG4 agonistic mAb targeting CD137 is being evaluated in combination with rituximab (#NCT01775631) or nivolumab (#NCT02253992) in B-cell NHL. Major histocompatibility complex class I antigens on lymphoma cells can interact with the killer Ig-like receptor (KIR) on the surface of NK cells and diminish NK-cell-mediated antitumor response. Lirilumab, a humanized mAb against KIR, which blocks the binding of KIR ligands leading to NK-cell activation, is being evaluated in combination with nivolumab in patients with lymphoma (#NCT01592370).

Conclusion

Greater insight into the biology of FL has led to the development of a multitude of therapeutic agents directed against novel targets, which include tumor cellular surface markers, intracellular mediators, epigenetic mechanisms, and cells of the microenvironment. Given the large number of candidate drugs, and even larger number of potential combinations, it will be crucial to prioritize evaluation based on sound preclinical and early clinical studies. Combinations that exploit driver mechanisms within tumor cells and target parallel pathways to minimize the development of drug resistance, as well as harness the potential of the immune system would seem most logical.

Currently, initial treatment with immunochemotherapy remains the standard of care for patients with FL; although, “chemotherapy-free” alternatives may challenge this paradigm and comparative trials are greatly anticipated. There is no standard of care for patients with relapsed/refractory FL, because numerous options exist and treatment selection should be individualized based on clinical status and responsiveness to prior therapy. The recent approval of obinutuzumab in patients previously treated with rituximab highlights the importance of anti-CD20 mAbs in the relapsed/refractory setting. The approval of idelalisib represents the first of many small molecule inhibitors targeting important pathways in FL that will inevitably emerge as future options. Drugs targeting key pathogenic mediators (such as the BCR pathway, BCL2, and epigenetic mechanisms) appear highly promising and studies involving combinations of these agents should be prioritized. In view of the instrumental role of the microenvironment, drugs that augment antitumor immune responses should also be incorporated.

The practical challenge moving forward is that given the favorable outcomes for the majority of patients with FL, it is no longer feasible to evaluate drugs in unselected patients. With standard approaches, large patient trials and decades of follow up will be required to demonstrate further benefit. Future studies will need to use innovative trial designs and employ surrogate end points in order to expedite progress. Validated prognostic tools incorporating biological markers (such as the recently described M7-FLIPI),^{101,102} are required in order to identify higher risk patients in whom alternative strategies should be sought. Ultimately, given the genetic diversity of FL, reliable predictive markers will be paramount to guide the selection of targeted therapies for the subgroup of patients who will most likely benefit.

In addition to the elusive goal of cure, toxicity reduction is a major aim. The selective nature of targeted agents may allow for a more

favorable side effect profile as normal cells are spared. However, it is clear that even well-tolerated drugs have the potential for unexpected and serious harm when administered within novel combinations.¹⁰³ Given the chronicity of FL management, both short- and long-term vigilance will be necessary to ensure safety. Finally, as a greater number of treatment options become available, optimal sequencing must be determined, in order to both prolong life and maintain its quality.

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