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REVIEW ARTICLE

Emerging therapies for the treatment of relapsed or refractory follicular lymphoma

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ABSTRACT

With no treatment standard having been established for relapsed and refractory follicular lymphoma, a number of therapeutic approaches are used in Canada. In patients who relapse early or who eventually become resistant to subsequent treatment, prognosis is poor, and new approaches are needed. A number of novel therapies are being examined in this setting, including monoclonal antibodies, immunoconjugates, immunomodulatory agents, and signal transduction inhibitors. With the body of evidence for those emerging therapies accumulating and the standard upfront treatment changing from rituximab and CHOP (cyclophosphamide–doxorubicin–vincristine–prednisone) or rituximab and CVP (cyclophosphamide–vincristine–prednisone) to bendamustine and rituximab, treatment decisions in the relapsed and refractory setting have become more complex. The choice of subsequent treatment must consider type of upfront treatment; duration of remission; and patient-related factors such as age, comorbidities, and treatment preferences. This paper summarizes the evidence for novel therapies and proposes recommendations for subsequent treatment options by remission duration after induction and maintenance.

Key Words Follicular lymphoma, relapsed disease, refractory disease, novel treatments, emerging therapies

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INTRODUCTION

Non-Hodgkin lymphoma (NHL) is the most common hematologic malignancy in Canadian adults, accounting for 4.5% of all new cancer cases in men and 3.8% in women in 2015[1]. As the population ages, rates continue to rise, with the reported incidence having increased 0.3% per year in men and 0.4% per year in women between 2001 and 2010. Of the indolent NHLs, follicular lymphoma (FL) is the most common subtype, constituting up to 35% of all cases in North America, with an incidence of more than 1500 cases annually[2].

Although approximately 20% of patients will not require therapy for the first 10 years after diagnosis, most will experience progressive disease needing treatment[3]. Until recently, the standard initial treatment for FL was rituximab with either cyclophosphamide–doxorubicin–vincristine–prednisone (R-CHOP) or cyclophosphamide–vincristine–prednisone (R-CVP), with R-CVP being more commonly used in Canada. However, data from the STIL-1 study by Rummel *et al.* in 2013 reported a significantly higher response rate and longer progression-free survival (PFS) with bendamustine–rituximab (BR) than with R-CHOP (PFS: 69.5 months vs. 31.2 months; $p < 0.0001$) after a median follow-up of 45 months[4]. In addition, BR was clearly associated with an improved safety profile. Updated results presented at the American Society of Hematology 2014 annual meeting showed that median time to next treatment in the BR group still had not been reached after a median follow-up of 87 months[5]. In the STIL-1 trial, maintenance rituximab was not given, but maintenance is routinely used in Canada; therefore, time to next treatment could in reality be even longer with BR. Based on the results of that study, Canadian guidelines for the first-line treatment of FL now recommend BR as the preferred regimen in this setting[2]. Despite those recent advances in treatment, most patients with FL eventually relapse and require subsequent therapy[6].

Treatment in the Relapsed and Refractory Setting

Results of the BRIGHT study, which randomized patients with untreated indolent NHL or mantle cell lymphoma to BR or the investigator's choice of R-CHOP or R-CVP, demonstrated that 3% of patients given BR and 9% of those given R-CHOP or R-CVP did not respond, having stable or progressive disease after induction[7]. Additionally, after a median follow-up of 45 months in the STIL-1 trial, salvage treatment was needed in 74 of 274 patients (27%) given BR and in 116 of 275 patients (42%) given R-CHOP[4].

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Given the recurrent nature of FL, the goal of therapy is to balance improved disease-free survival with maintenance of a good quality of life. Most studies in the relapsed setting have included patients who received rituximab-based chemotherapy other than BR as induction, complicating the subsequent choice of treatment. However, duration of remission is one key factor in treatment decisions. Data from the National LymphoCare Study in the United States demonstrated that patients receiving R-CHOP in the first line whose disease progressed within 2 years after diagnosis experienced lesser 5-year overall survival (OS) than did those whose disease did not progress within 2 years (50% vs. 90%)[8]. Therefore, where relapse occurs more than 2–3 years after upfront treatment, it might be reasonable to use the same approach for subsequent treatment. However, where relapse occurs early, such as before 6 months, a novel approach is needed. In addition, patient factors such as proximity to infusion clinics, age, comorbidities, and preferences are important considerations in the choice of subsequent treatment. For the treatment of patients in the relapsed and refractory setting, there is therefore no accepted standard approach[6].

In practice, treatment strategies vary and include re-challenge with the initial treatment regimen, use of a non-cross-resistant treatment regimen with or without rituximab, high-dose chemotherapy with autologous or allogeneic stem-cell transplantation (SCT), or when possible, consideration of an appropriate clinical trial[6]. In the STIL-1 study, subsequent treatments for patients randomized to receive BR in the first line included repeat treatment with BR (22%) or treatment with R-CHOP (31%) or a fludarabine-based regimen (10%)[5]. In addition, the STIL-2 study compared treatment with BR or fludarabine–rituximab in the relapsed setting, in which 11% of patients receiving BR had previously received the same regimen as at induction[9]. After a median follow-up of 96 months, the overall response rates (ORRs) in the BR and fludarabine–rituximab groups were 82% and 51% respectively, and the associated median PFS durations were 34.2 months and 11.7 months ($p < 0.0001$). In addition, compared with patients receiving fludarabine–rituximab, those receiving BR experienced a longer median OS (109.7 months vs. 49.1 months, $p = 0.012$). However, a subgroup analysis of data for patients receiving upfront BR was not reported; it is therefore unclear whether the response in those patients was as good as it was in the patients who were bendamustine-naïve.

The purpose of the present paper is to provide an overview of novel therapies for patients with relapsed and refractory FL, and a discussion of how those agents might be used in the context of currently available treatment options. In all studies in which the patient population was refractory to rituximab, "refractory disease" was defined as failure to respond to, or progression within 6 months of, rituximab-based treatment[10–13]. For the sake of brevity, the discussion has been limited to novel agents with data available from phase II/III studies and does not include a discussion of autologous or allogeneic SCT. Because radioimmunotherapy is not used in Canada, a discussion of the associated agents has also been omitted.

EMERGING THERAPIES IN RELAPSED AND REFRACTORY FL

Monoclonal Antibodies and Immunoconjugates

Monoclonal antibodies (mAbs) are monospecific targeted agents that have direct anti-lymphoma activity and that also induce an immune response against lymphoma. Anti-CD20 monoclonal antibodies are classified based on their mode of action and CD20-binding properties[14]. Type I mAbs such as rituximab induce complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and signal apoptosis.

In FL, rituximab has revolutionized treatment, and it is recommended for use in combination with chemotherapy, followed by maintenance monotherapy[2]. However, not all patients respond to rituximab-containing regimens in the first line, as evidenced by data from STIL-1, in which about 8% of patients did not achieve a response to their randomized treatment[4]. Furthermore, a number of additional patients will relapse or progress during their 2 years of maintenance therapy, as was seen in the PRIMA study of maintenance rituximab after first-line treatment with either R-CHOP, R-CVP, or rituximab with fludarabine–cyclophosphamide–mitoxantrone[15,16]. In that study, about 20% of patients did not achieve at least a partial response with induction, and another 20% progressed during the 2 years of maintenance rituximab. The likelihood of response to subsequent rituximab-containing regimens decreases, as demonstrated by the ORR described earlier for STIL-2[9]. There is therefore an unmet need to develop alternative antibodies that are more effective and non-cross-resistant to rituximab. Table I summarizes the phase II/III studies examining novel mAbs for the treatment of relapsed and refractory FL.

Obinutuzumab

Obinutuzumab is a type II anti-CD20 mAb that was designed to improve on the therapeutic activity of rituximab[14]. In addition to inducing antibody-dependent cell-mediated cytotoxicity, type II mAbs induce non-apoptotic direct cell death, but only weakly induce complement activation. In preclinical studies comparing it with rituximab, obinutuzumab demonstrated superior activity, with increased direct cell death, antibody-dependent cell-mediated cytotoxicity, and B-cell depletion in whole human blood and lymphoid tissues from non-human primates[14]. Of all the novel mAbs, obinutuzumab is the furthest into development, with data available from a total of four studies examining its use either as monotherapy or in combination with chemotherapy. It is Health Canada–approved in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia[13,14,17–19].

The phase II GAUSS study compared obinutuzumab with rituximab monotherapy in patients with relapsed and refractory FL not refractory to rituximab[14]. A numerically superior ORR of 45% for obinutuzumab compared with 33% for rituximab was reported; however, results were not statistically significant, and no difference in PFS was observed between the groups after a median follow-up of 32 months (Table I). The safety profile in

TABLE I Monoclonal antibodies and immunoconjugates

Reference (trial name or ID)	Study population	Prior treatments (median *n*)	Study treatment	ORR (%)	DOR (months)	PFS (months)	OS (months)
Randomized trials							
Sehn *et al.*, 2015 (GAUSS, NCT00576758)	Relapsed, non-refractory to rituximab	2	GA-101 (*n*=88) vs. rituximab (*n*=87)	44.6 vs. 33.3 (*p*=0.08)	Not reached	No difference between groups	Not reached
Sehn *et al.*, 2016; Pott *et al.*, at ASH 2015 (GADOLIN, NCT01059630)	Rituximab-refractory	2	Obinutuzumab–bendamustine (*n*=194) vs. bendamustine (*n*=202)	69 vs. 63 (*p*=NS) MRD: 82 vs. 43 (*p*<0.0001)	Not available	Not reached vs. 14.9 (*p*=0.0001)	Not reached in either arm
Phase II trials							
Hagenbeek *et al.*, 2008 (NCT00092274)	Relapsed and refractory (4 rituximab-refractory)	1.5–3	Ofatumumab (*n*=40)	20–63	29.9	8.8–32.6	Not available
Czuczman *et al.*, 2012 (NCT00394836)	Rituximab-refractory	4	Ofatumumab (*n*=116)	10–13	Not available	5.8	Not available
Fayad *et al.*, 2013 (NCT00299494)	Relapsed, non-refractory to rituximab	2 Prior lines in 48% (pts with FL)	Rituximab plus inotuzumab ozogamicin (*n*=118, 42 with FL)	87 (pts with FL)	Not reached (pts with FL)	2-Year: 68% (pts with FL) Median: not reached	2-Year: 90% (pts with FL) Median: not reached
Radford *et al.*, 2013 (phase IB) (GAUDI, NCT00825149)	Relapsed and refractory (14 rituximab-refractory)	1 (G-CHOP) 2 (G-FC)	G–CHOP (*n*=28) vs. G–FC (*n*=28)	96 vs. 93 (rituximab-refractory: 100 vs. 100)	Not available	Not available	Not available
Salles *et al.*, 2013 (GAUGUIN, NCT00517530)	Relapsed and refractory (22 rituximab-refractory)	3	GA-101 (*n*=40, 34 with FL) (1600/80 vs. 400/400)	55 vs. 17	Not available	11.9 vs. 6.0	Not available
Morschhauser *et al.*, at ASH 2014 (ROMULUS, NCT01691898)	Relapsed and refractory (44% rituximab-refractory)	2 (pts with FL)	Rituximab plus polatuzumab vedotin (*n*=59, 20 with FL) vs. rituximab plus pinatuzumab vedotin (*n*=63, 21 with FL)	70% vs. 62%	Not available	Not available	Not available
Jurczak *et al.*, at EHA/ASCO 2016 (NCT01685008)	Relapsed and refractory	2	MOR208 (*n*=89, 31 with FL)	26 (pts with FL)	2.6 (pts with FL)	Not available	Not available

ORR = overall response rate; DOR = duration of response; PFS = progression-free survival; OS = overall survival; ASH = American Society of Hematology; NS = nonsignificant; MRD = minimal residual disease; FL = follicular lymphoma; G–CHOP = obinutuzumab with cyclophosphamide–doxorubicin–vincristine–prednisone; G–FC = obinutuzumab with fludarabine–cyclophosphamide; pts = patients; EHA = European Hematology Association; ASCO = American Society of Clinical Oncology.

both treatment groups was similar, with the exception of infusion-related reactions (IRRs) and cough, which were more frequent with obinutuzumab.

As with rituximab, results with obinutuzumab have been more promising when the mAb is combined with chemotherapy. In the phase Ib GAUDI study, patients with relapsed or refractory FL were randomized to one of two dosing regimens: obinutuzumab with CHOP (G-CHOP) or with fludarabine–cyclophosphamide[18]. Overall, patients achieved ORRs of 96% with G-CHOP and 93% with obinutuzumab–fludarabine–cyclophosphamide. In addition, all patients with rituximab-refractory disease achieved at least a partial response. Neutropenia was the most common treatment-related toxicity, occurring in 43% of patients receiving G-CHOP and in 50% of those receiving obinutuzumab–fludarabine–cyclophosphamide. Grade 3 or 4 IRRs occurred in 7% of patients and were restricted to the first infusion.

The efficacy of obinutuzumab in rituximab-refractory disease was explored further in the phase III GADOLIN study, in which patients with rituximab-refractory indolent NHL received either obinutuzumab–bendamustine (GB) induction followed by maintenance with obinutuzumab, or bendamustine monotherapy induction and no maintenance[13]. In that study, no statistical difference in ORR was observed between the groups after induction; however, patients in the GB group were more likely to be negative for minimal residual disease (82% vs. 43%, $p < 0.0001$)[20]. After a median follow-up of 21.9 months, treatment with GB was associated with superior PFS (not reached vs. 14.9 months with bendamustine monotherapy, $p = 0.0001$)[13]. Grades 3 and 4 toxicities occurring more frequently with GB included neutropenia (33% vs. 26%) and IRR (11% vs. 6%).

Other Novel Monoclonal Antibodies

A number of novel mAbs are being explored as potential alternatives to rituximab, with data from phase II/III trials being available for ofatumumab and MOR28[10,21–23] (Table I).

Results of two phase II studies using ofatumumab yielded disappointing results, reporting ORRs of 20%–63% in relapsed and refractory patients and 10%–13% in rituximab-refractory patients[10,21]. In addition, preliminary results of the phase III HOMER study demonstrated numerically superior PFS (21.2 months vs. 16.2 months) and ORR (63% vs. 50%) for rituximab compared with ofatumumab monotherapy[23]. An ongoing study is examining the novel anti-CD19 mAb MOR28-1, with preliminary results demonstrating an ORR of 26% and a median duration of response of 2.6 months in patients with FL[22].

Immunoconjugates

Immunoconjugates are antibodies that are joined to a second molecule such as a toxin to form an antibody–drug combination. Inotuzumab ozogamicin combines the humanized immunoglobulin G4 anti-CD22 antibody (G544) with the cytotoxic antibiotic calicheamicin and targets CD22, a B-cell antigen that is expressed in most B-cell NHLs[24]. A study by Fayad *et al.*[24] that included patients with relapsed, non-rituximab-refractory FL reported an ORR of 87% and 2-year PFS and OS of 68% and 90% respectively with that regimen after a median follow-up of 40 months. The most common grades 3 and 4 toxicities were thrombocytopenia (31%) and neutropenia (22%).

Other immunoconjugates—such as one containing the anti-mitotic monomethyl auristatin E targeting CD79b, polatuzumab vedotin, and one targeting CD22, pinatuzumab vedotin—are also being examined in clinical trials. Preliminary results of the ongoing phase II ROMULUS trial comparing the efficacy and safety of polatuzumab vedotin and pinatuzumab vedotin in patients with relapsed or refractory FL demonstrated ORRs of 70% and 62% respectively for those agents[25]. Both regimens had similar safety profiles, with the most common toxicities being fatigue (55%), diarrhea (43%), and nausea (37%).

Immunomodulatory Drugs

Immunomodulatory drugs are functional analogues of thalidomide that modulate the immune system and other biologic targets, not all of which have been fully elucidated[12]. To date, lenalidomide, a potent thalidomide derivative with immune, antiangiogenic, and direct anti-lymphoma effects, is the only immunomodulatory drug for which data from phase II/III trials are available[26] (Table II). Data from preclinical studies have suggested that the combination of lenalidomide and rituximab increases antitumour effects[26]. A number of phase II studies have therefore examined this combination in the relapsed and refractory setting.

A phase II study by Tuscano *et al.*[27] of rituximab–lenalidomide in patients with relapsed and refractory indolent NHL demonstrated an ORR of 77%, a median PFS of 12.4 months, and a median duration of response (DOR) of 15.4 months after a median follow-up of 43 months. The most common grades 3 and 4 toxicities included lymphopenia (45%), neutropenia (55%), fatigue (23%), and hyponatremia (9%). Subsequently, the phase II ALLIANCE trial randomized patients with relapsed FL not refractory to rituximab to treatment with lenalidomide with or without rituximab[26]. After a median follow-up of 30 months, the ORRs were 53% and 76% ($p = 0.029$) and the median times to progression were 13.2 months and 24 months ($p = 0.0023$) in the lenalidomide monotherapy and rituximab–lenalidomide groups respectively. The most common grades 3 and 4 toxicities included neutropenia (16% vs. 20%), fatigue (9% vs. 13%), and thrombosis (16% vs. 4%).

In rituximab-refractory patients, the combination of lenalidomide and rituximab has also been tested with the addition of dexamethasone[12]. That study by Ahmadi *et al.* reported an ORR of 29% and a median PFS of 23.7 months in rituximab-refractory NHL after a median follow-up of 12.2 months; however, only 18 patients in the study had FL. The most common grades 3 and 4 toxicities with this combination included neutropenia (30%), leucopenia (15%), hypokalemia (15%), and anemia (7%).

Signal Transduction Inhibitors

Phosphatidylinositol 3 Kinase Inhibitors

Phosphatidylinositol 3 kinase (PI3K) inhibitors are targeted agents that inhibit one or more of the PI3K enzymes that form the PI3K/Akt/mTOR (mammalian target of rapamycin) pathway linked to cell proliferation, survival, and

TABLE II Immunomodulatory drugs

Reference	Study population	Prior treatments (median *n*)	Study treatment	ORR (%)	DOR (months)	PFS or TTP (months)	OS (months)
Randomized trials							
Leonard *et al.*, 2015 (ALLIANCE, NCT00238238)	Relapsed, non-refractory to rituximab	Not available	Lenalidomide (*n*=45 with FL) vs. rituximab plus lenalidomide (*n*=44 with FL)	53 vs. 76 (*p*=0.029)	Not reached	TTP: 13.2 vs. 24 (*p*=0.002)	Not reached
Phase II trials							
Ahmadi *et al.*, 2014 (NCT01476787)	Rituximab-refractory	3	Rituximab plus lenalidomide plus dexamethasone (*n*=27, 18 with FL)	Overall: 29	Not available	Overall PFS: 23.7	Not available
Tuscano *et al.*, 2014 (NCT01316523)	Relapsed and refractory (15 of 30 rituximab-refractory)	3	Rituximab plus lenalidomide (*n*=30, 22 with FL)	77	Overall: 15.4	Overall PFS: 12.4	Not available

ORR = overall response rate; DOR = duration of response; PFS = progression-free survival; TTP = time to progression; OS = overall survival; FL = follicular lymphoma.

motility[11]. The PI3Ks have a catalytic subunit with 4 different isoforms; the α and β isoforms are widely expressed in tissues, and the γ and δ isoforms are highly restricted to hematopoietic cells.

Idelalisib: Idelalisib is a potent, small-molecule inhibitor of PI3Kd that is highly selective for the δ isoform[11]. The PI3Kδ signalling pathways are frequently hyperactive in B-cell cancers, making them an ideal target for the treatment of indolent NHLs. To date, two phase II studies have examined the efficacy and safety of idelalisib for the treatment of relapsed and refractory FL. A study by Gopal *et al.*[11] that used idelalisib monotherapy to treat patients with rituximab- and chemotherapy-refractory indolent lymphoma reported an ORR of 57%, a DOR of 12.5 months, and a PFS of 11 months after a median follow-up of 9.7 months. In the FL subgroup, the ORR was 56%, and the median PFS was 11 months[28]. The most common grades 3 and 4 events included neutropenia (22%), elevated serum aminotransferase (14%), diarrhea (14%), and pneumonitis (4%).

A second phase II study by de Vos *et al.* is examining the use of idelalisib in combination with bendamustine, rituximab, or both; in patients receiving bendamustine, 44% had already received treatment with that agent[29]. In addition, approximately 46% of patients were refractory to their last pre-study therapy, and 58% of patients were refractory to rituximab. Preliminary results demonstrated an ORR of 81% and a median PFS of 32.8 months after a follow-up of up to 4 years, with numerically improved outcomes in patients given bendamustine-based regimens. Median DOR has not been reached, except in the rituximab–idelalisib group, where it was reported to be 28.6 months. The most frequent grades 3 and 4 adverse events included diarrhea (15%), pneumonia (19%), rash (9%), fatigue (4%), and febrile neutropenia (3%). Recently, clinical trials using idelalisib as part of combination therapy have been halted because of reports of higher death and infection rates with those regimens. As stated in the updated product monograph, prophylaxis for *Pneumocystis jirovecii* (formerly *P. carinii*) pneumonia and monitoring for cytomegalovirus are now required during treatment with idelalisib[30].

Other PI3K Inhibitors: A number of novel PI3K inhibitors for the treatment of FL, such as copanlisib and duvelisib, are currently under development, with phase II data being available only for copanlisib. Preliminary results of the CHRONOS trial demonstrated an ORR of 40% and a median DOR of 13 months in patients with relapsed and refractory FL given copanlisib[31]. The most common grades 3 and 4 adverse events included hyperglycemia (59%), hypertension (54%), diarrhea (33%), and fatigue (28%).

Bruton Tyrosine Kinase Inhibitors

Bruton tyrosine kinase is another key component of the B-cell receptor signalling pathway that is critical to the survival and proliferation of malignant B-cells[32]. To date, ibrutinib is the only Bruton tyrosine kinase inhibitor for which phase II data are available with respect to the treatment of relapsed and refractory FL. Preliminary results of the ongoing CONSORTIUM trial examining ibrutinib monotherapy in relapsed and refractory FL demonstrated an

ORR of 30% and a median PFS of 9.9 months after a median follow-up of 6.5 months[32]. Only 2 of 18 patients (11%) with rituximab-refractory disease responded, compared with 8 of 19 patients (42%) with rituximab-sensitive disease ($p = 0.06$). The most common grades 3 and 4 adverse events included anemia (5%), neutropenia (8%), and infection (5%).

mTOR Inhibitors

The serine/threonine MTOR kinase also belongs to the PI3K family[33,34]. Thus far, temsirolimus, a water-soluble rapalog, is the only MTOR inhibitor for which phase II data are available in relapsed and refractory FL. A study by Smith *et al.* demonstrated an ORR of 53.8% and a median PFS of 12.7 months after a median follow-up of 34 months with temsirolimus monotherapy in patients with relapsed and refractory FL[33]. Key toxicities included mild or reversible myelosuppression and mucositis.

Subsequently, two phase II studies combined temsirolimus with additional agents. A study by Fenske *et al.*[34] that combined temsirolimus with bortezomib showed an ORR of 31% and a median PFS of 16.5 months in patients with relapsed and refractory FL. The most frequent grades 3 and 4 adverse events were thrombocytopenia (44%), neutropenia (26%), gastrointestinal toxicities (15%), and lymphopenia (15%). Most recently, an ongoing study examining the combination of temsirolimus with BR reported a preliminary ORR of 88% with that combination in patients having relapsed non-bendamustine-refractory FL[35]. Median PFS has not been reached after a median follow-up of 13 months. Key grades 3 and 4 adverse events included leucopenia (32%), neutropenia (24%), and thrombocytopenia (21%).

Proteasome Inhibitors

Proteasome inhibitors inhibit the action of proteasomes, resulting in a wide range of cellular alterations, including modulation of nuclear factor κB, pro- and antiapoptotic pathways, and cell cycles[36]. To date, bortezomib, which reversibly inhibits the 26S proteasome, is the only proteasome inhibitor for which phase II data in relapsed and refractory FL are available (Table III). Three phase II studies have examined bortezomib as monotherapy in relapsed and refractory FL, demonstrating variable ORRs ranging from 17% to 77%, with few complete remissions[37–39]. Median PFS and OS were available in one study and were reported to be 5.1 and 27.7 months respectively[38]. The most frequent grades 3 and 4 toxicities included thrombocytopenia, neutropenia, fatigue, neuropathy, and diarrhea.

Bortezomib has also been examined in combination with other agents with varying success. Two studies have combined bortezomib with BR, resulting in ORRs of 83%–88%, with a median PFS of 14.9 months and a DOR of 11.7 months being reported in one study after a median follow-up of 9.4 months[40,41]. The most frequent grades 3 and 4 hematologic toxicities included neutropenia, leucopenia, and thrombocytopenia; nonhematologic toxicities included fatigue, nausea, diarrhea, and peripheral neuropathy. As discussed earlier, a study by Fenske *et al.*[34] combined bortezomib with temsirolimus, demonstrating an ORR of 31% and a median PFS of 16.5 months in patients with relapsed and refractory FL, the most frequent grades 3 and 4 toxicities being thrombocytopenia, neutropenia, gastrointestinal toxicities, and lymphopenia. Finally, one randomized study demonstrated, for the addition of rituximab to bortezomib, a significantly improved ORR (49% vs. 63%, $p = 0.0004$) and median PFS (11.0 months vs. 12.8 months, $p = 0.039$) after a median follow-up of 33.9 months[42].

CLINICAL PERSPECTIVE ON TREATMENT

With the standard upfront treatment for FL in Canada recently changing from R-CVP or R-CHOP to BR, it is difficult to identify the optimal therapeutic approach to take in the relapsed and refractory settings. In addition, the abundance of novel agents makes treatment decisions even more challenging. In an attempt to provide guidance, we have developed a recommended approach to treatment categorized by previous therapy received and response to therapy (Table IV). Because no trial has focused on patients relapsing after BR chemotherapy (except for STIL-2, in which only 11% of patients met that criterion), much of the opinion provided here is an extrapolation from available data. In addition, although a review of the role of transplantation in FL is beyond the scope of this paper, it is important to note that many centres consider autologous SCT for young and high-risk patients with relapsed FL, given the long PFS durations achieved using that approach. Transplantation strategies should therefore be considered as an option in such patients. Furthermore, given that allogeneic SCT can be curative, transplantation can also be considered in selected young patients; however, the risk of treatment-related mortality remains high[43,44].

At all treatment-decision time points, participation in clinical trials should be prioritized, because such participation will lead to improved insight into management and will provide early access to novel therapies. Typically, conventional chemoimmunotherapy regimens such as R-CHOP, R-CVP, BR, and rituximab–fludarabine–mitoxantrone should be considered in the second-line setting when the response to first-line treatment extends to at least 2 years beyond the last dose of rituximab. In such cases, it is reasonable to re-challenge patients with chemoimmunotherapy. However, for patients whose disease is refractory or who experience a short remission after first-line therapy, or for those who eventually become resistant to subsequent lines of treatment, a need remains for alternative agents such as those reviewed here that are effective and well-tolerated. Of the novel mAbs, obinutuzumab has the greatest volume of available data, which has led to its approval (in combination with bendamustine) by the U.S. Food and Drug Administration in the relapsed and refractory setting. Obinutuzumab appears to be as effective as, or even more effective than, rituximab. An IRR at first infusion is the key toxicity; however, IRRs are easily managed and are rarely serious in nature.

Overall, obinutuzumab shows promise in the rituximab-refractory setting. The improvement in PFS seen in the GADOLIN study demonstrates that obinutuzumab maintains anti-lymphoma activity even in patients who relapse sooner than 6 months after prior rituximab-based regimens[13]. For such patients, GB followed by maintenance

TABLE III Signal transduction inhibitors

Reference	Study population	Prior treatments (median *n*)	Study treatment	ORR (%)	DOR (months)	PFS (months)	OS
PI3K inhibitors							
De Vos *et al.*, at ASH 2014	Relapsed and refractory (58% rituximab-refractory)	3	Idelalisib plus (A) bendamustine, (B) rituximab, or (C) bendamustine–rituximab (*n*=79, 59 with FL)	81 Overall; (A) 88; (B) 75; (C) 79	Not reached except 28.6 for (B)	32.8 Overall; (A) 32.8; (B) 29.7; (C) 37.1	Not reached
Gopal *et al.*, 2014; Zinzani *et al.*, at EHA 2016 (NCT01282424)	Rituximab-refractory and chemotherapy-refractory	4	Idelalisib (*n*=125, 72 with FL)	Overall: 57 FL: 56	Overall: 12.5 FL: 11.0	Overall: 11.0 FL: 11.0	Overall: 20.3 months (2-Year: 68%; median: not reached)
Dreyling *et al.*, at EHA 2016 (CHRONOS-1, NCT01660451)	Relapsed and refractory	4	Copanlisib (*n*=20, 16 with FL)	FL: 40	13.0 (indolent NHL)	Not available	Not available
BTK inhibitors							
Bartlett *et al.*, at ASH 2014 (CONSORTIUM/NCI 9271)	Relapsed and refractory (45% rituximab-refractory)	3	Ibrutinib (*n*=40 with FL)	30	Not available	9.9	Not available
mTOR inhibitors							
Smith *et al.*, 2010 (NCT00290472)	Relapsed and refractory	2	Temsirolimus (*n*=89, 39 with FL)	FL: 53.8	Not available	FL: 12.7	Not reached
Fenske *et al.*, 2015 (NCT01281917)	Relapsed and refractory (1 bortezomib–refractory)	4	Temsirolimus plus bortezomib (*n*=39, 9 with FL)	31	Not available	FL: 16.5	Not available
Hess *et al.*, at ASH 2015 (NCT01078142)	Relapsed, non-refractory to bendamustine	2	Temsirolimus plus bendamustine–rituximab (*n*=34, 9 with FL)	FL: 88	Not available	Not reached (FL)	Not available
Proteasome inhibitors, randomized trials							
Coiffier *et al.*, 2011 (NCT00312845)	Relapsed, non-refractory to rituximab	33% ≥3 (rituximab) 32% ≥3 (rituximab plus bortezomib)	Rituximab (*n*=340 with FL) vs. rituximab plus bortezomib (*n*=336 with FL)	49 vs. 63 (*p*=0.0004)	13.8 vs. 16 (*p*=NS)	11.0 vs. 12.8 (*p*=0.039)	Median: not reached 1-Year: 90.5% vs. 90.1%
Proteasome inhibitors, phase II trials							
Goy *et al.*, 2005 (NCT00038571)	Relapsed and refractory	3–4	Bortezomib (*n*=60, 5 with FL)	19 (non-MCL)	Not available	Not available	Not available
O'Connor *et al.*, 2005 (NCT00023764)	Relapsed and refractory	3	Bortezomib (*n*=26, 10 with FL)	FL: 77	≥3	Not available	Not available
Di Bella *et al.*, 2010	Relapsed and refractory (30 rituximab-refractory)	3	Bortezomib (*n*=59, 36 with FL)	FL: 17	Overall: 7.9	Overall: 5.1	Overall: 27.7 months
Fowler *et al.*, 2011 (VERTICAL, NCT00636792)	Relapsed, non-refractory to rituximab or bortezomib	2	Bortezomib plus bendamustine–rituximab (*n*=73 with FL)	88	11.7	14.9	Not available
Friedberg *et al.*, 2011 (NCT00547534)	Relapsed and refractory, no prior bendamustine (10 rituximab-refractory)	4	Bortezomib plus bendamustine–rituximab (*n*=30, 16 with FL)	83	Not available	2-Year: 47%	Not available
Fenske *et al.*, 2015 (NCT01281917)	Relapsed and refractory (1 bortezomib-refractory)	4	Temsirolimus plus bortezomib (*n*=39, 9 with FL)	31	Not available	FL: 16.5	Not available

ORR = overall response rate; DOR = duration of response; PFS = progression-free survival; OS = overall survival; PI3K = phosphoinositide 3 kinase; ASH = American Society of Hematology; FL = follicular lymphoma; EHA = European Hematology Association; NHL = non-Hodgkin lymphoma; NS = nonsignificant; MCL = mantle cell lymphoma.

TABLE IV Suggested approach to treatment with novel agents in follicular lymphoma (FL), including off-label use[a]

Agent	Pivotal FL trials	Health Canada label indications	Suitable patients
Obinutuzumab plus chemotherapy (plus obinutuzumab maintenance)	Sehn *et al.*, 2015 (GAUSS, NCT00576758)[b] Radford *et al.*, 2013 (GAUDI, NCT00825149)[c] Sehn *et al.*, 2016; and Pott *et al.*, at ASH 2015 (GADOLIN, NCT01059630)[d]	■ With chlorambucil in untreated chronic lymphocytic leukemia ■ No indication in FL; under consideration in combination with bendamustine in rituximab-refractory FL	Consider in patients who have had no response or relapse within 6 months of completing a rituximab-containing regimen (as monotherapy or with chemotherapy with or without maintenance rituximab)
Idelalisib	Gopal *et al.*, 2014; and Zinzani *et al.*, at EHA 2016 (NCT01282424)[e] De Vos*et al.*, at ASH 2014[f]	■ Monotherapy in FL after receipt of 2 or more prior regimens and refractory to rituximab and alkylator (NOC/c) ■ With rituximab in relapsed chronic lymphocytic leukemia	Consider in patients with no response, early relapse, or moderate remission after completion of at least 2 lines of chemotherapy (with or without monoclonal antibody), or in patients in whom intravenous treatment is not feasible
Lenalidomide plus rituximab	Leonard *et al.*, 2015 (ALLIANCE, NCT00238238)[g]	■ With dexamethasone in multiple myeloma ■ Transfusion-dependent anemia in myelodysplastic syndrome ■ No indication in FL	Consider in patients who relapse after completing treatment with idelalisib

[a] Other novel agents should be considered in clinical trials in which early relapse or no response is seen after chemotherapy with or without monoclonal antibody.
[b] Obinutuzumab compared with rituximab in non- rituximab-refractory FL.
[c] Obinutuzumab and CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) compared with obinutuzumab and fludarabine– cyclophosphamide in relapsed or refractory FL.
[d] Obinutuzumab–bendamustine plus obinutuzumab maintenance compared with bendamustine monotherapy in rituximab-refractory FL.
[e] Idelalisib alone in rituximab-refractory FL.
[f] Idelalisib plus bendamustine, or rituximab, or bendamustine–rituximab in relapsed or refractory FL.
[g] Rituximab–lenalidomide in relapsed, non-rituximab-refractory FL.
ASH = American Society of Hematology; EHA = European Hematology Association; NOC/c = notice of compliance with conditions.

obinutuzumab appears to be a reasonable therapeutic approach. However, for patients who are refractory to BR, it might be preferable to use a different chemotherapy backbone or a novel targeted agent instead of chemoimmunotherapy. The use of GB might therefore be more appropriate in patients who respond well to BR, but who subsequently relapse while on rituximab maintenance, or who were initially given R-CHOP or R-CVP and who either relapsed or were refractory to treatment. Based on the results of the GAUDI trial, G-CHOP could, in addition to CHOP or CVP, be a reasonable option for patients in whom early relapse occurs after BR; promising outcomes have been demonstrated with the former regimen[18].

The use of idelalisib as monotherapy has been approved by Health Canada for the treatment of rituximab- and chemotherapy-refractory FL in patients who have been treated with at least 2 prior lines of therapy. That decision was based on the promising results of the study by Gopal *et al.*[11,45], which demonstrated an ORR of 57% and a median PFS of 11 months in such patients. For patients that relapse less than 6 months after chemoimmunotherapy, idelalisib is therefore a reasonable treatment option in preference to re-treating with chemoimmunotherapy; however, the PFS is evidently short.

The immunomodulatory drug lenalidomide, in combination with rituximab, has demonstrated significant promise and could be considered in patients for whom standard options have failed. The roles of other novel agents, either as monotherapy or in combination, will await further data from clinical trials.

CONCLUSIONS

For patients with FL, treatment decisions in the relapsed and refractory setting are complex, given the change to BR from R-CHOP or R-CVP in standard upfront treatment. Disease factors such as duration of remission and patient factors such as age, comorbidities, and treatment preferences have to be taken into account, and there is therefore no standard approach to treatment in Canada for these patients. A growing number of novel agents are being examined that might provide additional treatment options in this setting. To date, the most data are available for obinutuzumab, idelalisib, and lenalidomide. In patients for whom standard therapies fail, those agents provide valuable therapeutic options that can be selected based on duration of remission after induction, with or without maintenance. Future studies will help to clarify the role of newer regimens such as immunoconjugates and BR-based combination therapies.

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