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Front-line Management of Follicular Lymphoma

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Introduction

Follicular lymphoma (FL) is the second most common type of non-Hodgkin lymphoma (NHL) in Western countries. Most patients have an indolent disease course with 10-year survival estimates of 80% among all patients in the rituximab era.[1] However, risk stratification schema can identify subgroups of patients at higher risk of early death and/or progression following front-line therapy. In addition, histologic transformation to an aggressive NHL occurs in approximately 2% of patients per year.[1] Many patients can initially be observed, but ultimately, most will be treated with multiple lines of therapy during their lifetimes. Current Health Canada-approved systemic treatment options include chemoimmunotherapy and lenalidomide plus rituximab. Phosphoinositide 3-kinase (PI3K) inhibitors were initially approved but were later withdrawn because of toxicity considerations. Newer therapies likely to impact care in Canada include bispecific T cell engagers (BiTEs) and chimeric antigen receptor (CAR)-T cell therapy.

Biology as it Pertains to Targeted Therapies

Several new targeted therapies have been developed for B cell NHL (**Table 1**). These targeted therapies have been developed based on an understanding of the role of several intracellular pathways in the pathogenesis of B cell lymphomas. Agents that target the NF-Kb pathway, such as PI3K inhibitors or Bruton's tyrosine kinase inhibitors (BTKi), anti-apoptotic pathways, such as B cell lymphoma 2 (BCL2), or the enhancer of zeste homolog 2 (EZH2) methylation factor have been explored. In addition, non-specific reagents that enhance innate immune activation, such as immunomodulating drugs (IMiDs)—which may also have direct cytotoxic effects—and monoclonal antibodies targeting B cell-specific antigens have also been studied. We are beginning to see treatment combinations of several of these agents being explored.

Grading, Staging, Prognostic Indices, and Outcome

In the recently updated World Health Organization (WHO) classification of lymphomas, grading of FL is no longer considered mandatory because clinical outcomes among grades 1, 2, and 3A are not substantially different in the modern era.[2] Instead, these three are now referred to as "classic FL," whereas grade 3B is referred to as Follicular Large B Cell Lymphoma and is generally treated as diffuse large B cell lymphoma (DLBCL).

Given the prolonged survival of patients with FL, it is pertinent to identify patients at higher risk of progression following first-line therapy, histologic transformation, and early death. The Follicular Lymphoma International Prognostic Index (FLIPI) was developed in the pre-rituximab era to predict overall survival (OS), and incorporates age, stage, hemoglobin level, lactate dehydrogenase level, and the involvement of more than four nodal sites. It stratifies patients into low, intermediate, and high risk, characterized by an estimated 10-year OS of 71%, 51%, and 36%, respectively.[3] The FLIPI has been validated in a modern cohort of patients treated with chemoimmunotherapy (e.g. bendamustine and rituximab), even though current outcomes have numerically improved compared to this original model.[4] The newer FLIPI2 model was developed to predict progression-free survival (PFS) among a cohort of patients treated with rituximab and incorporates age, hemoglobin level, bone marrow involvement, longest diameter of the largest involved lymph node, and β2-microglobulin. By the FLIPI2, low, intermediate, and high-risk patients had a 5-year PFS of 79%, 51%, and 20%, respectively; and a 5-year OS of

Location	Target	Reagent	Health Canada approved	Funding
Cell surface	CD20	Rituximab	yes	Broad funding for induction and maintenance for IV and SC
		Obinutuzimab	yes	Chemotherapy obinutuzimab and obinutuzimab maintenance, Stage II bulky, Stage III and IV FL
		Radiolabelled mAbs	yes	Not funded for FL
	CD20xCD3	Mosunetuzumab, Glofitmab, Epcoritamab	Not approved for FL Glofitmab and Epcoritamab HC approved for R/R DLBCL	Not funded
	CD19	CAR-T	Axicel approved for R/R FL	Funding recommended in Ontario
Intracellular	*MYD88*	BTK inhibitors	Not approved for NHL	Not funded for FL
	PI3K	Idelalisib	Not approved for NHL	Not funded for FL
	EZH2	Tazemetostat	Not approved for FL	Not funded for FL
	Cereblon	Lenalidomide	Not approved for FL	Not funded for FL
	BCL2	Venetoclax	Not approved for FL	Not funded for FL
Microenvironment	Adaptive immune system	Lenalidomide	Not approved for FL	Not funded for FL
	T cells	Bispecific antibodies CAR-T cells	Axi-cel approved for R/R FL	Funding recommended in Ontario

Table 1. Biologic targets and associated treatments for FL; *courtesy of Samantha Hershenfeld, MD, FRCPC, Jennifer Teichman, MD, FRCPC, and Neil L. Berinstein, MD, FRCPC.*

Abbreviations: BTK: Bruton's tyrosine kinase; **CAR:** chimeric antigen receptor; **DLBCL:** diffuse large B cell lymphoma **FL:** follicular lymphoma; **HC:** Health Canada; **IV:** intravenous; **mAbs:** monoclonal antibodies; **R/R:** relapsed/refractory; **SC:** subcutaneous

98%, 88%, and 77%, respectively. Interestingly, β2-microglobulin, which is absent from the FLIPI model, was considered the covariate with the greatest prognostic weight in the FLIPI2 model.[5]

Recurrent genetic mutations cooperate with BCL2 translocations to drive lymphomagenesis in FL. The M7-FLIPI was therefore developed to integrate clinical and molecular risk factors to further improve prognostication among high-risk patients.[6] It was developed from a cohort of patients with advanced-stage disease who were treated with R-CHOP/R-CVP (cyclophosphamide, doxorubicin, prednisone, rituximab, and vincristine/ rituximab, cyclophosphamide, vincristine, and prednisone). The M7-FLIPI includes the FLIPI score, Eastern cooperative oncology group (ECOG) performance status, and seven recurrently mutated genes (*EZH2, ARID1A, MEF2B, EP300, FOXO1, CREBBP,* and *CARD11*). The model identified a high-risk and a low-risk group, with a five-year failure-free survival of 38% versus 77%, respectively. The M7-FLIPI reclassified about half of patients with a high-risk FLIPI score into the low-risk M7-FLIPI category due to the presence of favourable risk mutations, particularly in *EZH2*. However, in a separate analysis of the GALLIUM trial, the M7-FLIPI was not prognostic in patients treated with bendamustine-based therapy, likely due to a reversal of the prognostic impact of *EZH2* mutations in that setting.[7] In light of this and limitations in access to DNA sequencing, the M7-FLIPI is not currently used in routine clinical practice in Canada.

None of these models have been validated as tools to select or adapt treatment in FL. Furthermore, they are not used dynamically throughout a patient's disease course. Disease progression within 24 months following front-line chemoimmunotherapy (POD24) is a poor prognostic factor that predicts inferior OS.[8] Currently, the FLIPI and FLIPI-2 are commonly used to prognosticate in real-world clinical settings, but newer dynamic and treatment-adaptable models are needed.

Treatment Approach-Overall

a. Localized Disease:

The rare patient presenting with localized follicular lymphoma may be treated with curative intent involved-field radiation therapy (IFRT). However, long-term follow-up of these patients has demonstrated late relapses (≥10 years) in up to 50% of patients. Recurrences typically occur outside of radiation fields, in patients with larger initial tumours, and are more likely to occur in those with stage 2 versus stage 1 disease.[9] Positron emission tomography (PET) staging prior to treatment upstages some patients and better identifies those with localized disease. High response rates and durable remissions can be achieved with low dose IFRT (4 Gy in two fractions); however, randomised data suggests that 24 Gy in 12 fractions may be more effective for preventing relapse.[10,11] Alternatives include observation for asymptomatic patients, particularly for older patients, or initiation of chemotherapy for patients with bulky or non-contiguous and symptomatic early-stage disease.

b. Low Volume Advanced:

These patients may be monitored without treatment. Three randomised controlled trials have shown no survival advantage for early versus delayed initiation of therapy in asymptomatic patients.[12-14] Watchful waiting was compared to rituximab monotherapy with or without maintenance rituximab.[15] Time to initiation of new therapy (chemotherapy or radiation) was delayed in the two arms that received rituximab and quality of life was improved in the rituximab maintenance arm. In a Canadian context, rituximab induction in asymptomatic patients is more cost-effective than watchful waiting or rituximab induction plus maintenance[16]; however, whether delaying time to next treatment is clinically meaningful is questionable. The Resort trial showed that retreatment with rituximab in patients with low volume, advanced-stage disease previously treated with rituximab is as effective as maintenance rituximab in delaying the time to chemotherapy, but required considerably less rituximab use.[17]

c. High Volume Advanced:

Treatment for high-volume advanced disease is often delayed until one of the groupe d'etude des lymphomes folliculaires (GELF) criteria is met.[13] The standard of care chemotherapy in most geographical locations for patients with symptomatic advanced disease is bendamustine and rituximab (BR). In the StiL and BRIGHT trials, BR outperformed R-CHOP with a more favourable toxicity profile.[18,19] Lymphopenia and susceptibility to infections are increased with BR. The PRIMA trial demonstrated a PFS benefit

Stage	Recommended treatment	Alternative treatments	Comments
Stage 1 or 2 contiguous and low volume	IFRT	Observation rituximab	24 Gy in 12 fractions has higher cure rate[10], but 4 Gy in 2 fractions is effective palliation.[11]
Stage 2 non-contiguous or high volume (>3 cm)	Observation	IFRT palliation, Rituximab monotherapy	Maintenance rituximab can be added.
Stage 3, 4-asymptomatic	Observation[14]	Rituximab monotherapy[15]	Maintenance can be added but retreatment at relapse is acceptable.[17]
Stage 3, 4-symptomatic (GELF criteria)	BR[18]	R-CHOP, R-CVP O-chemo and O maintenance are more active but more toxic.[23]	Lenalidomide + rituximab is a non-funded, equally effective option.[27]
	Maintenance Rituximab[20]	Maintenance Obinutuzumab	In patients with higher risk of infections or CR to front-line, or in pandemic maintenance call be shortened or eliminated Obinutuzumab is a non-funded option that cannot be given subcutaneously.

Table 2. Acceptable front-line therapies in Canada; *courtesy of Samantha Hershenfeld, MD, FRCPC, Jennifer Teichman, MD, FRCPC, and Neil L. Berinstein, MD, FRCPC.*

Abbreviations: BR: bendamustine + rituximab; **CR:** complete response; **IFRT:** involved-field radiation therapy; **GELF:** groupe d'etude des lymphomes folliculaires; **R-CHOP:** rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; **R-CVP:** rituximab, cyclophosphamide, doxorubicin, prednisone

of maintenance rituximab after CVP or CHOP, with 51% of patients who received maintenance alive without progression at 10 years .[20,21] It is not known whether rituximab maintenance improves PFS after BR treatment. Rituximab monotherapy followed by four maintenance infusions every two months can produce durable remissions in a subset of chemo-naïve patients with non-rapidly progressing disease.[22]

Obinutuzumab, the glycol-engineered anti-CD20 monoclonal antibody, was compared to rituximab in combination with either bendamustine, CVP, or CHOP as front-line therapy in the Phase III GALLIUM trial.[23] Obinutuzumab demonstrated modestly improved PFS (3 year-PFS of 80% versus 73.3%, p=0.66), higher rates of minimal residual disease (MRD), and PET negativity, as well as decreased POD 24, as compared to rituximab. The OS was not different between the arms in this trial. Obinutuzumab was associated with more frequent grade ≥3 adverse events (76% versus 67.8%), serious adverse events (46.1 % versus 39.9), and infusion reactions (59% versus 48.9%, p=.001). Given these modest incremental benefits and higher toxicity profile, obinutuzumab was not recommended for funding to use in the front-line management of FL in Canada.

There are comparable pharmacokinetic and clinical efficacy results with intravenous versus

subcutaneous rituximab[24] but a subcutaneous formulation of obinutuzimab is not available.

Rituximab has also been used as monotherapy in patients with advanced stage symptomatic FL. In the SAKK trial, 64 chemotherapy-naïve patients were randomly assigned to four doses of rituximab monotherapy with or without four additional doses given at two-month intervals.[22] The event-free survival was longer in the prolonged rituximab arm with 45% of patients showing no disease progression at 8 years, suggesting that this therapy could be offered to advanced stage FL in cases where a rapid response to therapy was not required.

Radioimmunotherapy has been studied as front-line therapy for FL both as monotherapy or as adjuvant therapy after initial chemotherapy for advanced symptomatic disease. Bexxar (^{131}I-tositumomab) did not show improved PFS when compared to rituximab after R-CHOP chemotherapy. Zevalin (^{90}Y-ibritumomab tiuxetan) resulted in a 36-month improvement in PFS compared to placebo after combination chemotherapy, but most patients did not receive initial R-chemotherapy. Given the limitations with the above results, radioimmunotherapy has not been widely used.[25]

Although a long PFS has been observed after front-line high-dose therapy and autologous stem cell transplant with 50% of patients being disease-free at 10 years, no plateau in the survival curve has been documented.[26] In addition, a relatively high incidence of second malignancies, including myelodysplastic syndromes (MDS), acute myeloid leukemia (AML), and solid tumours, has dampened the enthusiasm for this approach.

d. Chemotherapy-Free Options-Targeted Therapies:

The RELEVANCE trial compared rituximab and lenalidomide (R2) to R-chemotherapy (investigator's choice of either CHOP (72%), bendamustine (23%) or CVP (5%).[27] PFS at 6 years was 60% for R2 and 59% for R-chemotherapy, and OS at 6 years was identical at 59% in both groups. There were more cytopenias, fatigue, nausea, vomiting, and peripheral neuropathy in the R-chemotherapy group, while the R2 group had more diarrhea, rash, and cutaneous reactions. These results suggest R2 is a chemotherapy-free option with similar results to chemotherapy and may be well-suited for patients who are more frail or older. The combination of lenalidomide and rituximab has also been compared to rituximab monotherapy in the SAKK35/10 trial for symptomatic advanced-stage patients.[28] The most recent update from the American Society of Hematology (ASH) 2023 Annual Meeting showed a median PFS of 9.3 years in the lenalidomide rituximab group compared to 2.3 years with rituximab monotherapy.[29] Although not studied in a randomised trial, treatment with lenalidomide and obinutuzimab in the Phase Ib/II GALEN trial demonstrated impressive results with a 92% ORR and a CR at 30 months of 63% compared to 48% in the RELEVANCE trial.[30]

Although BTKi have had limited activity as monotherapy in recurrent disease, they have been studied in combination with anti-CD20 monoclonal antibodies in the front-line setting. In the Phase II PCYC-1125-CA trial, concurrent ibrutinib and rituximab was compared to a two-month lead-in of ibrutinib followed by ibrutinib and rituximab.[31] In the concurrent arm, the objective response rate (ORR) was 85% (40% complete response [CR]); however, the PFS at 30 months was 67%, which is inferior to the PFS seen in the RELEVANCE trial with R2. BTKi adverse events included bleeding in 40% of patients, although grade 3–4 bleeding occurred in only 2.5% , and cardiac events in 14% of patients.

Trials with different durations of treatment with rituximab and ibrutinib and with obinutuzumab combined with venetoclax are underway.

e. Novel Targeted Therapies in the Front-Line:

There has been an attempt to intensify treatment with targeted therapies in high-risk patients in the front line. Tazemetostat has shown activity in relapsed and refractory FL-particularly in patients with *EZH2*-mutated disease.[32] A recent abstract presented at the ASH 2023 Annual Meeting examined R-CHOP and tazemetostat (an *EZH2* inhibitor), followed by maintenance with tazemetostat and rituximab in the front-line for higher-risk FL. Seventy-nine percent of patients achieved a complete metabolic response after induction therapy, and 18-month PFS and OS rates were 89.3% and 98.3%, respectively.[33]

Early Phase I and II trials are currently examining novel immunotherapies such as BiTEs in the first line. Subcutaneous mosunetuzumab was given as monotherapy for 8 cycles in patients with stage II-IV FL and indications for treatment based on GELF criteria. Of the 26 patients thus far evaluable for response, the best ORR was 96% and CR was 81%.[34] A similar ongoing study

is examining mosunetuzumab in combination with lenalidomide for 12 cycles in first-line FL. In 27 patients evaluable thus far, the ORR was 88.9% and CR rate 81.5%.[35] About half of patients developed cytokine release syndrome in both trials, but all cases were low-grade. Despite the promising results, current follow-up is short, and BiTEs are not currently approved in the front-line setting by Health Canada. A summary of ongoing and completed clinical trials for novel agents in the front-line setting, as well as promising treatments in the relapsed/refractory setting, are summarized in **Table 3**.

f. Maintenance Therapy:

Because advanced-stage FL is incurable, strategies to delay relapse have been pursued, predominantly with anti-CD20 monoclonal antibodies. Several trials showed that rituximab maintenance improved outcomes in patients with symptomatic high-volume FL after various R-chemotherapy combinations. Longer-term follow-up of the PRIMA trial showed a median PFS of 10.5 years versus 4.1 years in favour of maintenance rituximab. OS was not improved. A meta-analysis of 2,315 patients from 11 randomised trials showed an OS benefit to maintenance therapy.[36] The OS benefit was greatest in patients receiving maintenance rituximab after second-line therapy. However, there are toxicities associated with rituximab maintenance, including B cell depletion, hypogammaglobulinemia, and rarely neutropenia and immune-related pneumonitis. The B cell depletion reduces immune reactivity to active vaccination, and only 10% of patients were found to have primary responses to vaccination against COVID-19 or influenza.[37]

Risk-adapted maintenance therapy was evaluated in the FOLL12 trial.[38] Over 800 patients with high tumour burden FL who received either R-CHOP or BR were assessed by PET. Those with complete metabolic responses were randomised to four doses of rituximab maintenance if MRD positive by molecular testing for BCL2/IGH, or no further treatment if MRD negative. Those without a complete metabolic response were treated with radio-immunotherapy and then rituximab maintenance. PFS was inferior in those who did not receive maintenance rituximab.

g. Management of Hypogammaglobulinemia:

Exposure to anti-CD20-based therapy increases the risk of hypogammaglobulinemia and infections, and this risk is further increased by maintenance therapy.[39] This is particularly relevant in the COVID-19 era, where recent anti-CD20 use and hypogammaglobulinemia have been associated with poorer outcomes after COVID-19 infection.[40,41] Low levels of all immunoglobulins may be observed following therapy; however, treatment with intravenous or subcutaneous immunoglobulin (IVIg/SCIg) is only available for low IgG levels and will not impact IgA or IgM. Asymptomatic hypogammaglobulinemia does not require treatment. Immunoglobulin replacement therapy is recommended in symptomatic hypogammaglobulinemia, defined as patients having two or more severe infections within a year.[42] The typical starting dose is 400–600 mg/kg monthly for IVIG, or 100–200mg/kg weekly for SCIg. There is little evidence regarding the duration of treatment, with some sources suggesting that immunoglobulin replacement therapy may be paused 9-12 months following discontinuation of anti-CD20 therapy, with re-evaluation of IgG and clinical status 3–4 months later.[43]

h. Vaccine Responsiveness After B Cell Depleting Therapy:

Impaired vaccine responsiveness is a key consideration and should be discussed with patients when offering anti-CD20 therapy. A meta-analysis of 905 patients receiving anti-CD20 therapy demonstrated poor seroconversion rates ranging from 0–25% across all vaccinations studied, including seasonal influenza and pneumococcal vaccinations.[44] Perry *et al*. demonstrated that patients with lymphoma who had received anti-CD20 therapy within the prior 6 months had a response rate to mRNA COVID-19 vaccines (as measured by antibody titres) of only 7%. In contrast, those who had anti-CD20 therapy >6 months prior had a response rate of 67%, with increasing time from the last anti-CD20 treatment being associated with improved response. Although the B-cell response is impaired, it is possible that COVID-19 vaccination may induce a T-cell responses.[45] Thus, while anti-CD20 maintenance therapy is generally given in advanced-stage symptomatic FL to prolong PFS, poor vaccine response and subsequent risk of infections must be discussed with the patient, and the patient's individual risk profile should be considered, particularly in the COVID-19 era.

Drug Class	Regimen (trial name)	Setting	Type of Study
Immunomodulators			
• Lenalidomide	**Lenalidomide + rituximab (RELEVANCE)**	**Front-line**	**Phase III**
	Lenalidomide + obinutuzumab	Frontline	Phase II
BTK inhibitors			
• Ibrutinib	**Ibrutinib + rituximab (PERSPECTIVE)**	**Front-line**	**Phase III**
• Acalabrutinib	Acalabrutinib +/- rituximab	zR/R≥1 prior tx	Phase Ib
• Zanubrutinib	Zanubrutinib	R/R≥1 prior tx	Phase I/II
PI3K inhibitors		R/R≥1 prior tx	Phase II
• Idelalisib	Idelalisib	R/R≥1 prior tx	Phase II
• Duvelisib	Duvelisib (DYNAMO)	R/R≥2 prior tx	Phase II
• Copanlisib	Copanlisib (CHRONOS-I)	R/R ≥1 prior tx	Phase III
	Copanlisib + rituximab (CHRONOS-3)		
• Umbralisib	Umbralisib (UNITY-NHL)	R/R ≥2 prior tx	Phase IIb
BCL2 inhibitors			
• Venetoclax	**Venetoclax + BO (PrECOG-0403)**	**Front-line**	**Phase II**
	Venetoclax + obinutuzumab (LEVERAGE)	**Front-line**	**Phase I/II**
	Venetoclax + R-CHOP or G-CHOP (CAVALLI)	**Front-line or 1 prior tx**	**Phase Ib**
	Venetoclax + BR (CONTRALTO)	R/R≥1 prior tx	Phase II
	Venetoclax	R/R	Phase I
EZH2 inhibitors			
• Tazemetostat	Tazemetostat	R/R≥2 prior tx	Phase II
	Tazemetostat + rituximab (SYMPHONY-1)	R/R ≥1 prior tx	Phase III
Monoclonal antibodies			
• Tafasitamab (anti-CD19)	Tafasitamab + lenalidomide + rituximab	R/R ≥1 prior tx	Phase III
• Magrolimab (anti-CD47)	Magrolimab + rituximab	R/R	Phase 1b/II
	Magrolimab + venetoclax + obinutuzumab (VENOM)	R/R ≥2 prior tx	Phase I
Antibody-drug conjugates			
• Polatuzumab vedotin (anti-CD79b)	Polatuzumab vedotin + rituximab	R/R	Phase II
	Polatuzumab vedotin + lenalidomide + obinutuzumab	R/R ≥1 prior tx	Phase Ib/II
• Loncastuximab tesirine (anti-CD19)	Loncastuximab tesirine	R/R	Phase I
	Loncastuximab tesirine + rituximab	R/R	Phase II
Bispecific antibodies			
• CD19targeted	Blinatumomab	R/R ≥1 prior tx	Phase I
• CD20-targeted	**Mosunetuzumab + polatuzumab vedotin**	**Front-line**	**Phase II**
	Mosunetuzumab	R/R ≥2 prior tx	Phase II
	Glofitamab +/- obinutuzumab	R/R≥1 prior tx	Phase I
	Epcoritamab + rituximab +/- lenalidomide (EPCORE NHL-2)	**Front-line**	**Phase Ib/II**
	Odronextamab (ELM-1)	R/R≥1 prior tx	Phase I
CAR-T cell therapy	Axicabtagene citoleucel (ZUMA-5)	R/R ≥2 prior tx	Phase II
	Tisagenlecleucel (ELARA)	R/R ≥2 prior tx	Phase II
	Lisocabtagene maraleucel (TRANSCEND)	R/R	Phase II
Immune checkpoint inhibitors	Pembrolizumab + rituximab	R/R≥1 prior tx	Phase II

Table 3. Promising future treatments; clinical trials either completed or ongoing in the front-line setting, and selected studies in the relapsed/refractory setting; *courtesy of Samantha Hershenfeld, MD, FRCPC, Jennifer Teichman, MD, FRCPC, and Neil L. Berinstein, MD, FRCPC.*
Abbreviations: BO: bendamustine + obinutuzumab; **BR:** bendamustine + rituximab; **BTK:** Bruton's tyrosine kinase; **G-CHOP:** obinutuzumab, cyclophosphamide, doxorubicin, vincristine, prednisone; **PI3K:** phosphoinositide 3-kinase; **R-CHOP:** rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; **R/R:** relapsed/refractory; tx treatments.[42, 43]

Conclusion

While follicular lymphoma is an indolent lymphoma with excellent long-term survival, the majority of patients will require multiple lines of treatment in their disease course. Prognostic models such as the FLIPI or FLIPI-2 may identify those with favourable or unfavourable prognosis and those with very unfavourable outcome are identified by POD24. BR with maintenance rituximab is the standard of care for symptomatic patients with advanced stage disease, but an individualized treatment approach should include an assessment of infection risk. For frail patients unable to tolerate bendamustine, rituximab with or without lenalidomide is an option. Novel agents including *EZH2* inhibitors and BiTEs may have a front-line role in the future, but randomized phase III data are currently lacking. Long-term follow up of patients treated with frontline therapy should include monitoring for signs and symptoms of histologic transformation and for the complications of hypogammaglobulinemia. Patients on treatment with anti-CD20 monoclonals are unlikely to mount protective immune responses to antimicrobial vaccines for at least 6 months after the last treatment dose.

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