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REVIEW ARTICLE

Emerging therapies for the treatment of relapsed or refractory diffuse large B cell lymphoma

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ABSTRACT

Diffuse large B cell lymphoma (DLBCL) is an aggressive non-Hodgkin lymphoma, accounting for approximately 30% of lymphoma cases in Canada. Although most patients will achieve a cure, up to 40% will experience refractory disease after initial treatment, or relapse after a period of remission. In eligible patients, salvage therapy followed by high-dose therapy and autologous stem-cell transplantation (ASCT) is the standard of care. However, many patients are transplant-ineligible, and more than half of those undergoing ASCT will subsequently relapse. For those patients, outcomes are dismal, and novel treatment approaches are a critical unmet need. In this paper, we present available data about emerging treatment approaches in the latter setting and provide a perspective about the potential use of those approaches in Canada.

Key Words Diffuse large B cell lymphoma, DLBCL, non-Hodgkin lymphoma, novel therapies

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INTRODUCTION

Non-Hodgkin lymphoma (NHL) is a malignancy of the lymphatic system that encompasses more than 60 subtypes of lymphoma[1]. In 2017, the projected incidence of NHL was 8300 cases annually, with an age-standardized incidence rate of 20.8 cases per 100,000 Canadians[2]. Diffuse large B cell lymphoma (DLBCL) is an aggressive form of NHL that constitutes approximately 30% of lymphoma cases in Canada[3,4]. Two molecular subtypes of DLBCL—germinal centre B cell (GCB) and activated B cell (ABC)—that differ in their cell of origin, oncogenic pathway, and clinical outcome have been identified[5], with the ABC subtype being associated with an inferior prognosis[3]. A highly aggressive lymphoma referred to as double- or triple-hit lymphoma, with concurrent translocations of *MYC* and either or both of *BCL2* and *BCL6,* is no longer categorized as DLBCL, but rather as high-grade B cell lymphoma[5,6]. Double-expressor lymphoma, which involves overexpression of Myc and Bcl2, is not considered a separate entity, but has also been associated with poorer prognosis[7].

In Canada, the long-term survival rate for patients with DLBCL is approximately 60% after immunochemotherapy with R-CHOP (rituximab with cyclophosphamide–doxorubicin–vincristine–prednisone)[5,8,9]. Canadian provincial guidelines[10–13] and guidelines from the United States[14] and Europe[15] indicate that R-CHOP is the standard first-line therapy for patients with DLBCL. Unfortunately, after an initial response to therapy, 30%–40% of patients will experience refractory disease or will relapse and require subsequent treatment[5,16,17]. Although optimal treatment for patients with double- or triple-hit lymphoma is unclear, some evidence suggests that, rather than R-CHOP, more-intensified induction therapy could be warranted in such patients[7,18].

For eligible patients who relapse or who are refractory to initial therapy, salvage chemotherapy followed by high-dose therapy and autologous stem-cell transplantation (ASCT) is the standard of care[5,10,12,14,15]. However, eligibility for that approach depends largely on response to salvage chemotherapy, performance status, age, and comorbidities[18,19]. Population-based studies in Canada and Denmark show that more than half the patients with relapsed or refractory (R/R) DLBCL are treated palliatively[20,21]. Further, eligibility for ASCT depends on demonstrated sensitivity to salvage chemotherapy, with 50% of patients being

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ineligible because of an inadequate response[22]. Of patients who proceed to ASCT, more than 50% will ultimately relapse[18,23]. Factors negatively affecting survival include prior treatment with rituximab, early relapse, and a high International Prognostic Index score at relapse[18].

Until recent evidence emerging from chimeric antigen receptor T cell (CAR-T) therapy[24–26], treatment for relapse after ASCT had been largely palliative, with median survival being approximately 6 months[27]. Although conventional chemotherapy can be given in the relapsed setting, clinical trials of novel agents are recommended because of poor prognosis with established therapies[15,28].

Patients for whom initial therapy fails have a poor prognosis and could benefit from more effective salvage therapies. Only 30% of patients treated in recent prospective trials involving salvage therapy and ASCT achieved long-term remission[22,29]. Furthermore, patients who are ineligible for salvage therapy or transplantation, and patients who have relapsed after ASCT, represent a critical unmet need for which novel treatment approaches are required. Here, we present available data about emerging treatment approaches, and we provide perspectives about the potential use of those approaches in Canada.

METHODS

A literature search in the U.S. Library of Medicine's PubMed database sought indexed papers published during January 2014–January 2019, using the search term "relapsed diffuse large B-cell lymphoma." Fourteen papers were included in the analysis based on the inclusion and exclusion criteria outlined in Figure 1. One additional published paper examining CAR-T therapy was included because of its potential impact in this setting, although the paper had not been identified in the original search, because the title used the term "large B-cell lymphoma" rather than "diffuse large B-cell lymphoma." In addition, eighteen relevant abstracts presented in 2018 at meetings of the American Society of Hematology, the American Society of Clinical Oncology, and the International Conference on Malignant Lymphoma were included (Tables I and II).

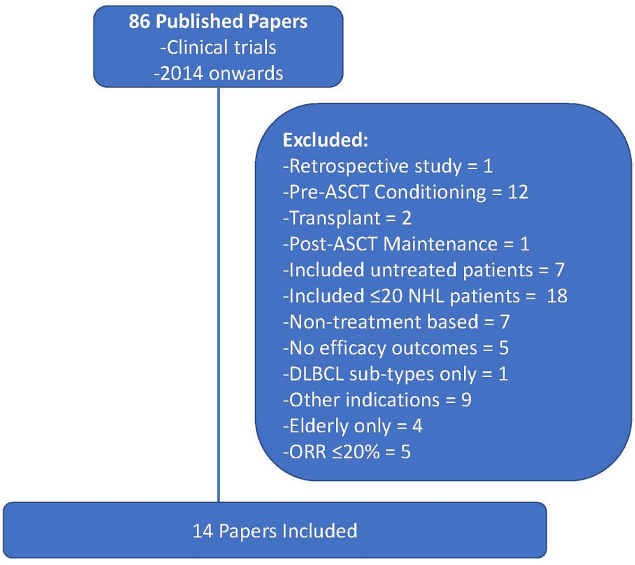

FIGURE 1 Selection of published papers in relapsed or refractory diffuse large B cell lymphoma. ASCT = autologous stem-cell transplantation; NHL = non-Hodgkin lymphoma; DLBCL = diffuse large B cell lymphoma; ORR = overall response rate.

EMERGING TREATMENTS FOR R/R DLBCL

Novel Agents

Table I summarizes the published papers and abstracts examining novel agents and combinations in R/R DLBCL. Most were nonrandomized phase I/II trials; the one randomized phase III trial was an ongoing study by Salles *et al.*[55] comparing pixantrone–rituximab with gemcitabine–rituximab in patients with R/R DLBCL. In addition, the search found four randomized phase II trials: one by Kuruvilla *et al.*[41] comparing ibrutinib plus rituximab and gemcitabine–dexamethasone–cisplatin (R-GDP) with R-GDP alone; one by Sehn *et al.*[60] comparing polatuzumab vedotin plus bendamustine–rituximab (BR) with BR alone; one by Czuczman *et al.*[38] comparing lenalidomide with investigator's choice; and one by Assouline *et al.*[33] comparing panobinostat with panobinostat–rituximab. In the subsections that follow, we discuss agents and regimens with the most promising evidence for further development in R/R DLBCL.

Ibrutinib

Activation of the B cell receptor is an integral part of B cell malignancies, controlling cellular functions such as proliferation, apoptosis, differentiation, and migration[61]. Nuclear factor κB, a transcription factor activated from the downstream pathway of the B cell receptor, is particularly important in the survival of ABC DLBCL lines[62]. Ibrutinib is an orally administered selective and covalent inhibitor of Bruton tyrosine kinase that reduces nuclear factor κB pathway signalling and might therefore be effective for patients with the ABC subtype of DLBCL[32]. A phase I/II trial by Wilson *et al.* examined the efficacy and safety of ibrutinib in 80 patients with R/R DLBCL, including 38 patients with ABC DLBCL and 20 patients with GCB DLBCL[32]. Two thirds of the patients were refractory to chemotherapy and had received a median of 3 (ABC DLBCL) or 3.5 (GCB DLBCL) prior regimens. An ASCT had been performed in 13% of the ABC DLBCL group and in 30% of the GCB DLBCL group. The overall response rate (ORR) was 25%, with a higher ORR in the ABC DLBCL group than in the GCB DLBCL group (37% vs. 5%, $p = 0.0106$). The duration of response (DOR) in patients with the ABC DLBCL subtype was 4.8 months. After a median follow-up of 11.5 months, median progression-free survival (PFS) and overall survival (OS) were, respectively, 1.6 and 6.4 months in all patients. The most frequent adverse events (AEs) were fatigue (40%), diarrhea (38%), and nausea (30%). Because the activity of ibrutinib monotherapy was only modest in R/R DLBCL, further trials examining combination therapy are ongoing.

A phase II study by Kedmi *et al.*[50] is examining the combination of ibrutinib and BR in patients with aggressive R/R NHL. The 32 patients evaluated had a median age of 69 years, with 75% being refractory to prior therapy and 19% having relapsed after ASCT. Preliminary results showed ORR and CR rates of 45% and 30% respectively. After a median

TABLE I Novel therapies for the treatment of relapsed or refractory diffuse large B cell lymphoma

Treatment	Mechanism of action	Reference	Phase	Patients	
				(n)	Details
Published papers					
Brentuximab	Antibody–drug conjugate	Jacobsen *et al.,* 2015[30]	II	68	■ 49 with CD30-positive DLBCL ■ Median 3 prior therapy lines
	Efficacy in DLBCL ■ Median follow-up: 4.6 months ■ Median progression-free survival: 4 months (all patients); overall response rate: 44%; complete response: 17%; median duration of response: 5.6 months (all patients) *Safety* ■ Grade 3 or greater adverse events: neutropenia, 37%; fatigue, 12%; nausea, 12%				
Polatuzumab vedotin	Antibody–drug conjugate	Palanca-Wessels *et al.,* 2015[31]	I	95	■ 40 with DLBCL ■ 3 or more prior therapy lines in 88%
	Efficacy in DLBCL ■ Median follow-up: 4.3 months ■ Median progression-free survival: 5.0 months; overall response rate: 14 of 25 (56%); complete response: 4 of 25 (16%); median duration of response: 5.2 months *Safety* ■ Grade 3 or greater adverse events: neutropenia, 40%; anemia, 11%; peripheral neuropathy, 9%				
Ibrutinib	Bruton tyrosine kinase inhibitor	Wilson *et al.,* 2015[32]	I/II	80	■ Median 3–3.5 prior therapy lines
	Efficacy in DLBCL ■ Median follow-up: 11.53 months ■ Median progression-free survival: 1.64 months; median overall survival: 6.41 months; overall response rate: 37% in activated B cell DLBCL, 5% in germinal centre B cell DLBCL; duration of response: 4.83 months in activated B cell DLBCL *Safety* ■ Fatigue, 40%; diarrhea, 38%; nausea, 30%				
Panobinostat vs. panobinostat–rituximab	Pan histone deacetylase inhibitor (panobinostat)	Assouline *et al.,* 2016[33]	II Randomized	40	■ Median 3 prior therapy lines
	Efficacy in DLBCL ■ Median progression-free survival: <3 months; overall response rate: 29% vs. 26%; complete response: 7 patients overall; median duration of response: 14.5 months *Safety* ■ Grade 3 or greater adverse events (single agent): thrombocytopenia, 71%; neutropenia, 24%; hyponatremia, 14%				
Coltuximab ravtansine	Antibody–drug conjugate	Coiffier *et al.,* 2016[34]	II	52	■ Median 2 prior therapy lines
	Efficacy in DLBCL ■ Median progression-free survival: 3.9 months; median overall survival: 9.0 months; overall response rate: 31.1%; median duration of response: 8.6 months *Safety* ■ Gastrointestinal adverse events: 52%; asthenia: 25%				
Tirabrutinib	Bruton tyrosine kinase inhibitor	Walter *et al.,* 2016[35]	I	90	■ 31 with non-germinal centre B cell DLBCL ■ Median 3 prior therapy lines
	Efficacy in DLBCL ■ Mean progression-free survival: 1.8 months; overall response rate: 35%; complete response: 2 of 31 patients *Safety* ■ Grade 3 or greater adverse events: neutropenia, 10%; anemia, 13.3%				

TABLE I Continued

Treatment	Mechanism of action	Reference	Phase	Patients	
				(n)	Details
Published papers continued					
Blinatumomab	Bi-specific T cell engager antibody	Viardot *et al.*, 2016[36]	II	25	■ Median 3 prior therapy lines
	Efficacy in DLBCL ■ Median follow-up: 15 months ■ Median progression-free survival: 3.7 months; median overall survival: 5.0 months; overall response rate: 43%; complete response: 19%; median duration of response: 11.6 months *Safety* ■ Tremor, 48%; pyrexia, 44%; fatigue, 26%				
Pinatuzumab vedotin with or without rituximab	Antibody–drug conjugate	Advani *et al.*, 2017[37]	I	91	■ 47 with DLBCL ■ 3 or more prior therapy lines in 62%
	Efficacy in DLBCL ■ Median follow-up: 3.8 months ■ Median progression-free survival: 4.0 months; overall response rate: 25% (single agent); complete response: 2 of 47 patients; median duration of response: 3.0 months *Safety* ■ Grade 3 or greater adverse events: 69%; neutropenia, fatigue, neuropathy most frequent				
Lenalidomide vs. investigator choice	Immunomodulator	Czuczman *et al.*, 2017[38]	II/III	102	■ 3 or more prior therapy lines in 49%
	Efficacy in DLBCL ■ Median progression-free survival: 13.6 vs. 7.9 weeks (3.1 vs. 1.8 months); median overall survival: 31.0 vs. 24.6 weeks (7.12 vs. 5.66 months); overall response rate: 27.5% vs. 11.8%; median duration of response: 73.9 vs. 29.2 weeks (17.0 vs. 6.72 months) *Safety* ■ Neutropenia: 42.6% vs. 36.4%; anemia: 33.3% vs. 47.3%; thrombocytopenia: 24.1% vs. 43.6%				
Selinexor	Selective inhibitor of nuclear export	Kuruvilla *et al.*, 2017[39]	I	79	■ 43 with DLBCL ■ Median 4 prior therapy lines
	Efficacy in DLBCL ■ Overall response rate: 32% (all patients); complete response: 4 of 70 patients *Safety* ■ Grade 3 or greater adverse events: thrombocytopenia, 47%; neutropenia, 32%; anemia, 27%				
CUDC-907 with or without rituximab	PI3K/pan histone deacetylase inhibitor Anti-CD20 antibody	Oki *et al.*, 2017[40]	I	37	■ Median 4 prior therapy lines
	Efficacy in DLBCL ■ Median progression-free survival: 2.9 months; overall response rate: 37%; complete response: 5 of 30 patients; overall response rate: 64% (*MYC*-altered disease); median duration of response: 11.2 months *Safety* ■ Most common adverse events: thrombocytopenia, diarrhea, fatigue				
MOR208	Anti-CD19 antibody	Jurczak *et al.*, 2018[49]	IIA	92	■ 35 with DLBCL ■ More than 3 prior therapy lines in 34%
	Efficacy in DLBCL ■ Median follow-up: 21 months ■ Median progression-free survival: 2.7 months (all patients); overall response rate: 26%; complete response: 6%; duration of response: 20.1 months (all patients) *Safety* ■ Infusion reactions, 12%; neutropenia, 12%				

TABLE I Continued

Treatment	Mechanism of action	Reference	Phase	Patients	
				(n)	Details
Abstracts					
Ibrutinib–R-GDP vs. R-GDP	Bruton tyrosine kinase inhibitor (ibrutinib)	Kuruvilla *et al.*, 2017[41]	II	30	■ After failure of rituximab–anthracycline ■ Prior therapy lines not given
	Efficacy in DLBCL ■ Median follow-up: 3.5 months ■ Overall response rate: 28.6% vs. 50.1% *Safety* ■ Ibrutinib–R–GDP: 8 serious adverse events (sepsis, pneumonia, infectious events)				
Polatuzumab vedotin–bendamustine–rituximab vs. bendamustine–rituximab	Antibody–drug conjugate (polatuzumab vedotin)	Sehn *et al.*, 2017[42] and Sehn *et al.*, 2018[43]	II Randomized	80	■ Median 2 prior therapy lines
	Efficacy in DLBCL ■ Median follow-up: 22.3 months ■ Median progression-free survival: 7.6 vs. 2.0 months (p<0.0001); median overall survival: 12.4 vs. 4.7 months (p=0.0023); overall response rate: 45% vs. 18%; PET complete response: 40% vs. 18% (p=0.026); duration of response: 10.3 vs. 4.1 months (p=0.032) *Safety* ■ Grade 3 or greater adverse events: higher rate of cytopenias with polatuzumab vedotin–bendamustine–rituximab than with bendamustine–rituximab; similar rates of infections and transfusions				
REGN1979	Bi-specific anti-CD20/CD3 antibody	Bannerji *et al.*, 2018[44]	I	54	■ 30 with DLBCL ■ Median 3 prior therapy lines
	Efficacy in DLBCL ■ Median follow-up: 12.29 weeks (2.8 months) ■ Overall response rate: 40%; median duration of response: 6.79 weeks (1.6 months) (all patients) *Safety* ■ Grade 3 or greater adverse events: cytokine release syndrome, 3 patients; lymphocytopenia, 8 patients; neutropenia, 7 patients				
Mosunetuzumab	Bi-specific anti-CD20/CD3 antibody	Budde *et al.*, 2018[45]	I	98	■ 55 with DLBCL ■ Median 3 prior therapy lines
	Efficacy in DLBCL ■ Median follow-up: 372 days (12.2 months) ■ Overall response rate: 33% *Safety* ■ Treatment-related adverse events: cytokine release syndrome, 21%; grade 3 or greater neutropenia, 13%				
Blinatumomab	Bi-specific T cell engager antibody	Coyle *et al.*, 2018[46]	II	41	■ Aggressive non-Hodgkin lymphoma
	Efficacy in DLBCL ■ Median follow-up: 8.8 months ■ Median overall survival: not reached; overall response rate: 37%; complete metabolic response: 22% *Safety* ■ Grade 3 or greater adverse events: 59%; 56% neurologic				
Acalabrutinib	Bruton tyrosine kinase inhibitor	Dyer *et al.*, 2018[47]	I	21	■ Median 3 prior therapy lines
	Efficacy in DLBCL ■ Overall response rate: 24%; complete response: 19% *Safety* ■ Grade 3 or greater adverse events: anemia, 24%; fatigue, 10%; abdominal pain, 10%				

TABLE I Continued

Treatment	Mechanism of action	Reference	Phase	Patients	
				(n)	Details
Abstracts continued					
RG6026	Bi-specific anti-CD20/CD3 antibody	Hutchings *et al.,* 2018[48]	I	64	■ 47 with DLBCL ■ Median 3 prior therapy lines
	Efficacy in DLBCL ■ Median follow-up: 3.2 months ■ Overall response rate: 33%; complete response: 21% *Safety* ■ Grade 3 or greater adverse events: neutropenia, 14 patients; all-grade cytokine release syndrome: 14 patients				
Ibrutinib–bendamustine–rituximab	Bruton tyrosine kinase inhibitor (ibrutinib)	Kedmi *et al.,* 2018[50]	II	32	■ 1 or more prior therapy lines
	Efficacy in DLBCL ■ Median follow-up: 14 months ■ Median progression-free survival: 2.7 months; median overall survival: 7.1 months; overall response rate: 45%; complete response: 30% *Safety* ■ Serious adverse events related to ibrutinib: atrial fibrillation, 1.6%; fatigue, 1.6%; thrombocytopenia, 1.6%				
Umbralisib–ublituximab–bendamustine	PI3K inhibitor, anti-CD20 antibody, alkylator	Lunning *et al.,* 2018[51]	I	39	■ 26 with DLBCL ■ Median 2 prior therapy lines
	Efficacy in DLBCL ■ Median follow-up for responders: 11.5 months ■ Overall response rate: 48%; complete response: 32%; median duration of response: 9.6 months (all patients) *Safety* ■ Grade 3 or greater adverse events: diarrhea, 15%; nausea, 5%; neutropenia, 33%				
Selinexor	Selective inhibitor of nuclear export	Maerevoet *et al.,* 2018[52]	IIb	110	■ Median 3 prior therapy lines
	Efficacy in DLBCL ■ Median overall survival: 9 months; overall response rate: 34.4%; median duration of response: 8.4 months *Safety* ■ Grade 3 or greater adverse events: nausea, 6%; fatigue, 10%; thrombocytopenia, 37%				
Ibrutinib–lenalidomide–rituximab	Bruton tyrosine kinase inhibitor, immunomodulator, anti-CD20 antibody	Ramchandren *et al.,* 2018[53]	Ib/II	55	■ Median 2 prior therapy lines
	Efficacy in DLBCL ■ Median progression-free survival: 5 months; median overall survival: 17 months; overall response rate: 55%; complete response: 30%; median duration of response in responders: 9 months *Safety* ■ Grade 3 or greater treatment-related adverse events: neutropenia, 33%; maculopapular rash, 15%; anemia, 11%				
MOR208–lenalidomide	Anti-CD19 antibody Immunomodulator	Salles *et al.,* 2017[54]	II	81	■ Median 2 prior therapy lines
	Efficacy in DLBCL ■ Median follow-up: 12 months ■ Median progression-free survival: 16.2 months; median overall survival: not reached; overall response rate: 58%; complete response: 33%; median duration of response: not reached *Safety* ■ Grade 3 or greater adverse events: neutropenia, 43%; thrombocytopenia, 17%; anemia, 9%				

TABLE I Continued

Treatment	Mechanism of action	Reference	Phase	Patients	
				(n)	Details
Abstracts continued					
Pixantrone–rituximab vs. gemcitabine–rituximab	Anthracenedione analog vs. nucleoside analog	Salles *et al.*, 2018[55]	III	312	■ 242 with *de novo* DLBCL ■ 1 prior therapy line in 62%
	Efficacy in DLBCL ■ All patients—median progression-free survival: 7.3 vs. 6.3 months; median overall survival: 13.3 vs. 19.6 months; overall response rate: 61.9% vs. 43.9% *Safety* ■ No new safety signals				

DLBCL = diffuse large B-cell lymphoma; PI3K = phosphoinositide 3-kinase; R-GDP = rituximab, gemcitabine–cisplatin–dexamethasone; PET = positron-emission tomography.

follow-up of 14 months, median PFS and OS were 2.7 months and 7.1 months respectively. Serious AEs with ibrutinib–BR included atrial fibrillation, fatigue, and thrombocytopenia. Another ongoing randomized phase II multi-arm trial added ibrutinib to R-GDP in 14 patients with R/R DLBCL and compared the combination with R-GDP alone[41]. Preliminary results suggested no advantage with the addition of ibrutinib to R-GDP (ORR: 28.6% vs. 50.1% in the control arm), and toxicity was increased because of serious infectious events with the addition of ibrutinib. Patient accrual to that treatment arm has been stopped.

Polatuzumab Vedotin

Polatuzumab vedotin is an antibody–drug conjugate consisting of an anti-CD79b monoclonal antibody and the microtubule-disrupting agent, monomethyl auristatin E[42,60]. A phase I study by Palanca-Wessels *et al.*[31] examined the safety and efficacy of polatuzumab vedotin in 40 patients with R/R DLBCL. Median age in those patients was 67 years, 88% had received 3 or more prior therapies, 78% were refractory to their last therapy, and 33% had undergone stem-cell transplantation. The ORR and CR rates were, respectively, 56% and 16%, with a median DOR of 5.2 months. After a median follow-up of 4.3 months, the median PFS was 5.0 months. The most frequent grade 3 or greater AEs in patients with NHL treated at the single-agent recommended dose ($n = 45$) were neutropenia (40%), anemia (11%), and peripheral neuropathy (9%).

The combination of polatuzumab vedotin and BR is being compared with BR alone in an ongoing phase II trial, which included a randomized portion of 80 transplantation-ineligible patients with R/R DLBCL[42,43,60]. Within the randomized portion, median age was 67 years, 73% had received 2 or more prior therapies, and 75% were refractory to their last treatment[43]. Rates of CR by positron-emission tomography were significantly higher in the polatuzumab vedotin–BR group than in the group receiving BR alone (40% vs. 18%, $p = 0.026$)[43]. The ORR and DOR—45% and 10.3 months respectively in the polatuzumab vedotin–BR group—were superior to those in the group receiving BR alone (18% and 4.1 months respectively). After a median follow-up of 22.3 months, the median PFS and OS were also superior in the polatuzumab vedotin–BR group (PFS: 7.6 months vs. 2.0 months with BR alone, $p < 0.0001$; OS: 12.4 months vs. 4.7 months with BR alone, $p = 0.0023$).

The addition of polatuzumab vedotin appeared to provide benefit regardless of molecular subtype or double-expressor status[43]. Grade 3 and 4 cytopenias were more frequent in patients receiving polatuzumab vedotin–BR than in those receiving BR alone; infection and transfusion rates were similar in the two arms[43]. Based on those results, polatuzumab vedotin in combination with BR is currently under priority review by the U.S. Food and Drug Administration[63] and has been granted orphan designation (medicine intended for use in a rare condition) by the European Medicines Agency[64] for the treatment of R/R DLBCL.

Lenalidomide

Lenalidomide is an immunomodulatory drug that is a structural and functional analog of thalidomide[65]. In a phase II randomized trial, lenalidomide was compared with investigator's choice of treatment (gemcitabine, rituximab, etoposide, or oxaliplatin) in 102 patients with R/R DLBCL[38]. Median age in the lenalidomide ($n = 51$) and investigator's choice ($n = 51$) groups was 69 years and 65 years respectively. In the lenalidomide and investigator's choice groups respectively, 49% and 62.7% of patients had received at least 3 prior lines of therapy, and 25% and 33.3% had undergone ASCT. The primary endpoint of the study was ORR, which was required to meet a minimum threshold for the study to proceed to a randomized phase III trial. The ORR was slightly greater with lenalidomide than with investigator's choice (27.5% vs. 11.8%), with a median DOR in the lenalidomide group of 17 months. Median PFS was marginally higher in the lenalidomide cohort (PFS: 3.1 months vs. 1.8 months, $p = 0.041$), with no difference in OS (7.13 months vs. 5.66 months, $p = 0.673$). Comparing the ABC with the GCB disease subtype, the ORR and median PFS appeared to be higher in patients with ABC DLBCL (45.5% vs. 21.4% and 18.87 months vs. 1.4 months respectively). The most frequent AEs of any grade in the lenalidomide group were neutropenia (42.6%), anemia (33.3%), and fatigue (33.3%). Infections were reported in 46.3% of patients in

the lenalidomide group. Because the randomized phase II results did not meet the protocol-specified threshold, the planned randomized phase III study was not performed. Given the modest activity of lenalidomide as a single agent, combinations are now being tested.

Ibrutinib and Lenalidomide

A phase I/II study is examining the combination of ibrutinib, lenalidomide, and rituximab in patients with non-GCB R/R DLBCL[53]. In 55 evaluable patients, median age is 63 years. The patients have received a median of 2 prior therapies, and 53% are refractory to their last therapy. Preliminary results include ORR and CR rates of 55% and 30% respectively, with a median DOR of 9 months. The median PFS and OS are 5 and 17 months respectively. The most frequent grade 3 or greater AEs include neutropenia (33%), rash (15%), and anemia (11%).

MOR208

The Fc-engineered humanized monoclonal MOR208 antibody is directed against the antigen CD19, which is broadly expressed on the surface of B cells[49]. A phase II trial examined the efficacy and safety of MOR208 in 35 patients with R/R DLBCL. Before administration of the study drug, patients who had previously received ASCT must have been at least 4 weeks post-transplant, with full hematologic recovery. Median age in the group was 71 years, 34% of patients had received 3 or more lines of therapy, 69% were refractory to rituximab, and 6% had previously undergone ASCT. The ORR and CR rates were 26% and 6% respectively, with a DOR of 20.1 months. After a median follow-up of 21 months, the median PFS was 2.7 months. The most frequent AEs of any grade in all patients with NHL (n = 92) included infusion-related reactions (12%) and neutropenia (12%).

MOR208 and Lenalidomide

An ongoing phase II study is examining the combination of MOR208 and lenalidomide in transplant-ineligible patients with R/R DLBCL[54]. Patients were ineligible for the trial if they had primary refractory disease or an Eastern Cooperative Oncology Group performance status greater than 2, or if they had received more than 3 prior therapies. In 81 evaluable patients, median age was 72 years, 49% had received 2 or more prior lines of therapy, 38% were refractory to rituximab, and 41% were refractory to their last line of therapy. The ORR and CR rates were 58% and 33% respectively. After a median follow-up of 12 months, the DOR and median OS were not reached, and the median PFS was 16.2 months. The most frequent grade 3 or greater AEs included neutropenia (43%), thrombocytopenia (17%), and anemia (9%).

Bi-specific Antibodies

Blinatumomab is a bi-specific T cell–engaging antibody that binds to CD3-positive T cells and CD19-positive B cells, resulting in T cell proliferation and T cell–mediated lysis of the B cells[36]. A phase II dose-escalation study examined the efficacy and safety of blinatumomab in 25 patients with R/R DLBCL[36] whose median age was 66 years. These patients had received a median of 3 prior lines of therapy, 65% had refractory disease, and 26% had undergone transplantation. The ORR in the group was 43%, and 19% of the patients achieved a CR, with a median DOR of 11.6 months. After a median follow-up of 15.0 months, the median PFS in the 21 patients evaluable for efficacy was 3.7 months. For all 25 patients, the median OS was 5.0 months, with a median follow-up of 11.7 months. The most frequent AEs included tremor (48%), pyrexia (44%), and fatigue (26%). Grade 3 neurologic events included encephalopathy and aphasia (9% each), and tremor, speech disorder, dizziness, somnolence, and disorientation (4% each).

An ongoing study is examining blinatumomab as second salvage therapy in patients with R/R NHL[46]. In 41 patients evaluated (68% with refractory disease), median age was 56 years. Preliminary results demonstrated an ORR of 37% and a complete metabolic response rate of 22%. After a median follow-up of 8.8 months, 8 of 9 patients achieving a complete metabolic response were alive without relapse. Grade 3 or greater AEs were reported in 59% of the patients, with 56% experiencing neurologic events of any grade. Although those results are encouraging, the rates of neurotoxicity and the prolonged continuous infusion required for this drug could limit its uptake.

Mosunetuzumab, REGN1979, and RG6026 are bi-specific CD20/CD3 antibodies that redirect cytotoxicity of endogenous T cells against malignant B cells by simultaneously binding to CD3 on T cells and to CD20 on B cells[44,45,48]. A phase I trial examining mosunetuzumab in patients with R/R transformed follicular lymphoma or DLBCL is ongoing[45]. In 55 patients evaluated in a preliminary analysis, median age is 64 years, patients have received a median of 3 prior lines of therapy, 71% are refractory to last therapy, and 24% have undergone ASCT. Preliminary results report ORR and CR rates of 33% and 21% respectively. All patients achieving a CR remained in remission after a median follow-up of 12.2 months. A second ongoing phase I trial is examining REGN1979 in patients with R/R DLBCL[44]. Of 30 patients treated with a median of 3 prior therapies, 76% are refractory to their last therapy, and 11% have received prior ASCT. Preliminary results in those patients demonstrated an ORR of 40%, all responses being partial. After a median follow-up of 2.8 months, the median DOR is 1.6 months. A third ongoing phase I trial is examining RG6026 in patients with R/R NHL[48]. In 64 evaluable patients, median age is 64 years, 61% are men, and patients have received a median of 3 prior lines of therapy. Preliminary results have demonstrated ORR and CR rates of 33% and 21% respectively in patients with R/R aggressive NHL. The most common treatment-related AE with all 3 of the foregoing agents is cytokine release syndrome, but importantly, the rate of neurologic complications is very low[44,45,48].

CAR-T Therapy

In CAR-T therapy, autologous genetically engineered T cells designed to express chimeric antigen receptors are used to target specific antigens[18]. Introduction of the new gene occurs through viral transfection, using either a retrovirus or a lentivirus[66]. The targeting domain of the CAR is a single-chain variable antibody fragment capable of targeting an antigen on a tumour cell. A number of CAR-T therapies targeting CD19, a cell-surface molecule present in most B cell leukemias and lymphomas, have been examined

in patients with R/R DLBCL (Table II). In pivotal trials, the CAR-T agents tisagenlecleucel, axicabtagene ciloleucel, and lisocabtagene maraleucel have demonstrated ORR and CR rates in the ranges 52%–83% and 40–58% respectively. Although long-term follow-up data are not yet available, the median DOR reported in the ZUMA-1 trial was 11.1 months, with 37% of patients remaining in CR at a follow-up of 27.1 months. The DOR was related to depth of response, with the DOR being longer in patients who obtained a CR than in those who had an objective or partial response.

The CAR-T therapies are associated with a number of unique toxicities: studies show rates of grade 3 or greater cytokine release syndrome and neurologic toxicity in the ranges of 1%–22% and 12%–32% respectively[24,25,56,59]. Two reports have examined the efficacy and safety of CAR-T therapy in the real-world setting, demonstrating promising results, with comparable rates of cytokine release syndrome and neurotoxicity[24,57,58]. Based on results from the pivotal trials, Health Canada has approved tisagenlecleucel[67] and axicabtagene ciloleucel[68] for the treatment of patients with R/R DLBCL after 2 or more lines of systemic therapy.

CANADIAN PERSPECTIVE

Patients with DLBCL for whom initial therapy fails have limited treatment options, ranging from supportive care to conventional salvage therapy and ASCT, with the choice of therapy depending on age and comorbidities. No national guidelines in this setting have been developed, and treatment is often individualized. However, the Alberta guideline provides a list of recommended salvage regimens, including DHAP (dexamethasone–cisplatin–cytarabine), ICE (ifosfamide–carboplatin–etoposide), GDP (gemcitabine–dexamethasone–cisplatin), CEPP (cyclophosphamide–etoposide–prednisone–procarbazine), and MEP (mitomycin C–etoposide–cisplatin)[12]. Of the salvage therapies, GDP is most commonly used[69] because it can be given on an outpatient basis; and in a randomized comparison, it demonstrated a favourable toxicity profile when compared with DHAP[12,29]. The addition of rituximab to salvage therapies has shown some benefit, and that agent can be given in this setting where provincial funding allows[70].

Patients who are not candidates for ASCT are usually treated with palliative intent and could receive sequential single- or multi-agent therapy depending on tolerance. Involved-field radiotherapy has a limited role in patients with R/R DLBCL, although it can be useful to treat symptomatic sites, depending on the location and burden of the disease. Notably, in patients who do not respond to standard salvage therapy or who relapse after high-dose therapy or ASCT, few treatment options are available. In such cases, clinical trials are highly recommended when feasible. Regardless of the approach, outcomes remain poor[27], and it is crucial that patients have access to effective novel therapeutic regimens.

The development of CAR-T therapy has opened up a novel and promising approach for R/R DLBCL. However, further follow-up is needed to determine its long-term potential and late toxicities. Moreover, in some studies, patients with rapid progression would likely not have been eligible, and therefore selection bias might exist[59]. Importantly, a number of logistical and practical barriers must be overcome before this costly therapy can be routinely offered in Canada. Currently, CAR-T therapy is manufactured in a centralized system in the United States, with production taking an average of 10–21 days[71]. Subsequently, the product has to be shipped through Canadian customs to reach infusion centres. Given the aggressive nature of R/R DLBCL, patients with uncontrollable disease might be unable to wait the required length of time. Such patients might need bridging therapy, the success of which might be limited in these highly refractory patients.

Access to CAR-T therapy in Canada currently remains limited, with some centres having access to clinical trials and small numbers of patients being treated in U.S. centres. For example, some patients have been referred for treatment in Seattle and Boston. In Alberta, a phase IB/II trial currently under development will examine the feasibility and cost of CAR-T therapy, with the manufacturing taking place in Edmonton and Calgary. A larger national trial with Canadian-developed products is also planned. Because of the infrastructure and expertise required for delivery of therapy and management of potential toxicities, CAR-T therapy will likely be available only at select academic centres. As a result, travel constraints, resource limitations, and provincial funding restrictions could limit the number of patients who ultimately have access. Finally, most patients currently receiving CAR-T therapy will experience disease progression and will require further treatment.

Given limited treatment options and overall dismal outcomes, R/R DLBCL remains a significant unmet medical need. The aggressive nature and chemotherapy refractoriness of the disease necessitates the development of novel therapies with unique mechanisms of action for major impact. A number of novel agents examined in phase I/II studies have shown promise and, compared with current palliative options, might prolong response (Table I). However, the efficacy of these agents as monotherapies remains limited and ongoing studies of combination therapy are underway. For example, ibrutinib[32] and lenalidomide[38] have both demonstrated some utility in patients with ABC DLBCL, but the associated DOR is short, and therefore novel combinations are being evaluated. Bi-specific antibodies harness the immune system and are showing significant promise similar to that with CAR-T therapy, but without the need for cellular manipulation. The continuous infusion route of administration for blinatumomab could limit its uptake, but novel constructs with easier administration such as mosunetuzumab, REGN1979, and RG6026 are under development.

Of the combination regimens, polatuzumab vedotin–BR; ibrutinib–lenalidomide plus rituximab; and MOR208–lenalidomide are furthest into development and have demonstrated promising efficacy[42,53,54,60]. Of those regimens, polatuzumab vedotin–BR might be the first to receive approval from the U.S. Food and Drug Administration based on impressive results showing a clinically meaningful improvement in OS[42,60]. On its own, BR has demonstrated modest activity in R/R DLBCL and is generally well tolerated; it might therefore provide a reasonable backbone for combination regimens[72,73]. Given the demonstrated OS benefit of adding polatuzumab vedotin to BR, a phase III trial using BR as a comparator is no longer feasible. Ultimately, head-to-head trials of novel combinations to assess their

TABLE II Pivotal studies of chimeric antigen receptor T cell therapy in relapsed or refractory diffuse large B cell lymphoma

Treatment	Reference (study name)	Phase	Patients	
			(n)	Details
Axicabtagene ciloleucel	Locke *et al.,* 2019[56] and Neelapu *et al.,* 2018[24] (ZUMA-1)	I/II	108	■ Median 3 prior therapy lines
	Efficacy in DLBCL ■ Median follow-up: 27.1 months ■ Median progression-free survival: 5.9 months; median overall survival: not reached; best overall response rate: 83%; best complete response: 58%; median duration of response: 11.1 months *Safety* ■ Grade 3 or greater adverse events: cytokine release syndrome, 11%; neurotoxicity, 32%; neutropenia, 39%; anemia, 45%; thrombocytopenia, 24%			
	Jacobson *et al.,* 2018[57]	Real-world setting	76	■ 36 with DLBCL ■ Prior therapy lines not given
	Efficacy in DLBCL ■ Median follow-up: 4 months; best overall response rate: 64%[a]; best complete response: 41%[a] *Safety* ■ Grade 3 or greater adverse events: cytokine release syndrome, 17%; neurotoxicity, 38%			
	Nastoupil *et al.,* 2018[58]	Real-world setting	211	■ 61% with DLBCL ■ Prior therapy lines not given
	Efficacy in DLBCL ■ Median follow-up: not given ■ 1-Month overall response rate: 79%; 1-month complete response: 50% *Safety* ■ Grade 3 or greater adverse events: cytokine release syndrome, 7%; neurotoxicity, 31%			
Lisocabtagene maraleucel	Abramson *et al.,* 2018[25] (TRANSCEND)	I	91	■ Median 3 prior therapy lines
	Efficacy in DLBCL ■ Median follow-up: not given ■ Best overall response rate: 74%[a]; best complete response: 52%[a] *Safety* ■ Grade 3 or greater adverse events: cytokine release syndrome, 1%; neurotoxicity, 12%			
Tisagenlecleucel	Schuster *et al.,* 2019[59] (JULIET)	II	93	■ More than 3 prior therapy lines in 21% ■ Median time from infusion to data cut-off: 14 months
	Efficacy in DLBCL ■ Median progression-free survival: not reported; median overall survival: 12 months; best overall response rate: 52%[a]; best complete response: 40%[a]; median duration of response: not reached *Safety* ■ Grade 3 or greater adverse events: cytokine release syndrome, 22%; neurotoxicity, 12%; cytopenias for more than 28 days: 32%; infections, 20%; febrile neutropenia, 14%			

[a] Recorded from study start to disease progression.
DLBCL = diffuse large B-cell lymphoma.

comparative effectiveness in R/R DLBCL would be helpful. Data related to quality of life will also be important to help guide selection of therapy for the purpose of palliation. However, the ultimate goal is to identify effective combinations that can extend survival and improve the chance of cure.

CONCLUSIONS

Patients with R/R DLBCL who are ineligible for ASCT or who relapse after transplantation have a poor prognosis and are in need of effective treatment approaches[27]. Outcomes with CAR-T therapy are encouraging and require further

follow-up to determine long-term benefit and toxicities. However, travel constraints, resource limitations, and provincial funding restrictions could limit accessibility. Novel agents that are well tolerated and that can extend survival are needed. However, the efficacy of novel therapies as single agents remains limited. Ongoing studies of novel combination regimens appear more promising and will likely lead to additional treatment options in the near future.

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