CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Obinutuzumab (Gazyva) for Follicular Lymphoma

June 2, 2017

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1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding obinutuzumab for follicular lymphoma. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding obinutuzumab for follicular lymphoma conducted by the Lymphoma/ Myeloma Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on obinutuzumab for follicular lymphoma, a summary of submitted Provincial Advisory Group Input on obinutuzumab for follicular lymphoma, and a summary of submitted Registered Clinician Input on obinutuzumab for follicular lymphoma, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

As per the Health Canada Product Monograph and reimbursement criteria requested, the objective of this review is to evaluate the safety and efficacy of obinutuzumab in combination with chemotherapy, followed by obinutuzumab monotherapy, in the treatment of adults with follicular lymphoma who relapsed after, or are refractory to, a rituximab containing regimen.

Notice of Compliance was issued December 29, 2016. Of note, the Health Canada Product Monograph for obinutuzumab includes the following serious warnings and precautions:

- Infusion reactions (IRs)
- Hepatitis B virus (HBV) reactivation
- Progressive multifocal leukoencephalopathy (PML)
- Tumour lysis syndrome (TLS)
- Cardiovascular (serious cardiac events, including worsening of existing underlying cardiac disease and fatal cases, such as fatal myocardial infarctions)

Obinutuzumab should be administered as an intravenous infusion through a dedicated line in an environment where full resuscitation facilities are immediately available and under the close supervision of an experienced physician. For induction obinutuzumab treatment, the recommended dosage is 1000 mg administered on Day 1, Day 8 and Day 15 of the first 28 day treatment cycle followed by 1000 mg administered on Day 1 only for each subsequent 28 day treatment cycle (Cycles 2 to 6). Patients who respond to induction treatment (i.e. the initial 6 treatment cycles) or have stable disease should continue to maintenance. For maintenance obinutuzumab treatment, the recommended dose is 1000

mg alone once every 2 months until disease progression or for up to two years (whichever occurs first).[1]

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included one open-label, randomized Phase III study in patients with indolent non-Hodgkin's lymphoma (NHL; N=413). The GADOLIN study included patients who had no response to, or who progressed within 6 months of treatment with rituximab or a rituximab-containing regimen. In the GADOLIN trial, rituximab refractory was defined as no response to, or progression within 6 months of completion of the last dose of rituximab therapy (either as monotherapy or in combination with chemotherapy, see 6.3.2.1a for detailed definitions). Of the 413 patients enrolled in the GADOLIN study, 335(81%) had follicular non-Hodgkin's lymphoma.

Patients were assigned to one of two treatment arms:

1) Obinutuzumab plus bendamustine group: obinutuzumab 1000 mg intravenously on days 1, 8, and 15 of cycle 1 and day 1 of cycles 2–6, plus bendamustine 90 mg/m^2 per day intravenously on days 1 and 2 of cycles 1–6 or

2) Bendamustine monotherapy group: 120 mg/m^2 per day intravenously on days 1 and 2 of each cycle for up to six cycles; each cycle was 28 days.

The patients were relatively healthy, with most ECOG scores 0 or 1; approximately 15% of the entire study population had B symptoms (fever, night sweats, weight loss) at baseline.[2] More than half of the study patients had been exposed to at least 2 treatment regimens for indolent NHL and the mean time since the last treatment was approximately 8 months. Of the 327(79%) patients whose lymphoma was refractory to a previous rituximab chemotherapy combination, 152(46%) had progressive disease during or within 6 months after the last rituximab maintenance dose.

Patient enrollment occurred between 2010 and 2015 and included 86 patients (24%) in Canada. At least three interim efficacy analyses were performed (data cutoffs September 1, 2014, May 1, 2015 and April 1, 2016). Not all results were available for the 2016 data cutoff, therefore, data from earlier data cutoff dates are also included in this report. Median follow up time was approximately 24 months at the May 1, 2015 data cutoff and approximately 32 months at the April 1, 2016 data cutoff.

Table 1. Highlights of Selected Efficacy Outcomes from GADOLIN, data cut-off May 1, 2015[1,3,4]

	iNHL Overall Study Population		Follicular Lymphoma Subgroup	
	B N=209	GB N=204	B N=171	GB N=164
Deaths, n(%)	56(27)	42(21)	48(28)	30(18)
Median OS(95%CI), months	NE(NE)	NE(NE)	NE(42.2,NE)	NE(NE)
HR(95%CI)	0.72(0.48,1.08); p=0.11		0.62(0.39,0.98); p=0.038	
Patients with PFS event, n(%)*	125(60)	87(43)	108(63)	67(41)
Median PFS(95%CI), months	14.1(11.7,16.6)	29.2(20.5,NE)	13.8(11.5,15.8)	29.2(20.5,NE)
HR(95%CI)	0.53(0.40,0.70) p<0.0001		0.47(0.34,0.64); p<0.0001	

	iNHL Overall Study Population		Follicular Lymphoma Subgroup	
	B N=209	GB N=204	B N=171	GB N=164
Overall best response (CR/PR), n(%)†	162(78)	154(76)	135(79)	125(76)
ARR(95%CI)	-2.02-10.46,6.42); p=0.52		-2.73(-11.99,6.54); p=0.51	
Best response (CR), n(%)†	36(17)	33(16)	33(19)	25(15)
ARR(95%CI)	-1.05(-8.50,6.41); p=0.93		-4.05(-12.46,4.35); p=0.50	
Patients with EOI Response, n(%)	134(64)	136(67)	111(65)	111(67)
ARR(95%CI)	2.24(-7.20,11.69); p=0.83		2.39(-8.07,12.85); p=0.79	

ARR= absolute risk reduction; CR= complete response; EFS = Event Free Survival (time from randomization to progression or relapse, death or start of new anti-lymphoma treatment); EOI= end of induction; HR= hazard ratio; iNHL= indolent non-Hodgkin's lymphoma; NE= not estimable; OS= overall survival; PFS= progression free survival; PR= partial response;

*PFS assessment by independent review committee; †during treatment and within 12 months of starting treatment

Efficacy

The primary outcome was progression-free survival as assessed by an independent review committee. Other outcomes included overall survival, overall response, duration of response and quality of life. In the subgroup of patients with follicular lymphoma, there were statistically significant differences observed in the progression-free survival analyses at the first, second and third interim analyses. The most recent analysis (April 1, 2016) estimated the median progression free survival was 14.0 months in patients taking bendamustine alone versus 25.3 months in patients taking obinutuzumab plus bendamustine (HR[95%CI]: 0.52[0.39,0.69]; p<0.0001). The overall survival estimates in the follicular lymphoma patients at the April 1, 2016 data cutoff also favoured the obinutuzumab plus bendamustine group compared to the bendamustine alone group (HR[95%CI: 0.58[0.39,0.86]; p=0.0061). There were no statistically significant differences in overall response between the two treatment arms for overall response (complete response plus partial response) at end of induction, or best responds within 12 months of treatment initiation. There were no notable differences between the bendamustine and obinutuzumab plus bendamustine groups in any of the average scores on a quality of life questionnaire (FACT-Lym) in the follicular lymphoma subgroup.

Harms

Interpretation of the adverse event data in the induction phase is complicated by the fact that the bendamustine dose was not the same in both arms and interpreting the adverse event data beyond the induction phase is complicated by the fact that there was no maintenance treatment in the bendamustine-only treatment group. In the induction phase, the study group with bendamustine plus obinutuzumab had a higher rate of serious adverse events (28%) compared to bendamustine (22%). Of note, the treatment arm had a lower planned dose of bendamustine than the comparator arm which had a higher planned dose of bendamustine. Grade 3-5 thrombocytopenia and grade 3-5 infusion reactions were more common during the induction phase in the group that received obinutuzumab. Grade 3-5 infections were more common in the group receiving bendamustine alone, during the induction phase.

Key Limitations

There was little observable separation in the survival curves for overall survival or progression-free survival at 6 months, which corresponds to the end of the induction period (see Figures 2 and 3). The overall response (complete response+PR) and complete response rates were not different between the two study arms after 12 months on study. Because there was no maintenance therapy in the

bendamustine arm of GADOLIN, these observations make assignment of responsibility for the improvement in progression free and overall survival to any particular phase of the experimental treatment challenging. It is not clear if the improvements in these survival endpoints noted in the obinutuzumab plus bendamustine arm were attributable to the induction treatment with obinutuzumab plus bendamustine, or from the addition of obinutuzumab as maintenance.

The bendamustine doses differed between treatment groups (90 vs 120 mg/m^2 /day for GB and B, respectively) during the induction phase. Therefore it is not certain that any observed differences in adverse event rates or efficacy during the induction phase may be attributable to the addition of obinutuzumab. Higher doses of bendamustine may increase risk of myelosuppression (e.g. neutropenia, infectious complications).

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively. One supplemental issue was identified during the development of the review process, a critical appraisal of Propensity Score Analyses used to inform the economic evaluation.

Patient Advocacy Group Input

From a patient's perspective, LC stated that patients with early stage FL who participated in the survey experienced minimal symptoms with their disease and tended to have a good quality of life. However, it was noted that for those with relapsed disease, quality of life was impacted more significantly. LC described that patients commonly reported fatigue, loss of appetite, fever, night sweats, stomach problems, itchy skin, muscle and joint pain, as well as difficulties with memory, concentration, anxiety, depression, insomnia and intimacy. Furthermore, LC also expressed that additional complications were reported, which included frequent infections (due to compromised immunity), shortness of breath (attributed to anemia) and easy bruising (caused by low platelet counts). LC stated that all of these symptoms can interfere with a patient's performance, ability to work, travel and day-to-day activities. Among the patients who responded to the LC survey, they reported that treatment options for relapsed FL included: single agent or combination chemotherapy, rituximab (alone or in combination), or radiation therapy. LC indicated that these treatment options tend to be associated with increased toxicity, reduced anti-tumour activity and unpleasant side effects. In terms of expectations for a new therapy, LC survey respondents reported that they were seeking treatments that will prolong their life, offer disease control, bring about a remission and improve quality of life. Furthermore, LC stated that patients who had experience with obinutuzumab had fewer and more manageable side effects as compared to other therapies, as well as improvements in their disease symptoms and in quality of life. LC added that patients who are refractory to rituximab could also benefit from an effective immunotherapy that can be combined with available chemotherapy agents. Finally, LC noted that there are very few effective treatment options for FL patients who have relapsed after initial therapy and that obinutuzumab in combination with chemotherapy followed by obinutuzumab maintenance may potentially improve remissions.

Provincial Advisory Group (PAG) Input

Input was obtained from all the provinces participating in pCODR. PAG identified the following as factors that could impact the implementation of obinutuzumab for follicular lymphoma (FL):

Clinical factors:

- Clarity on the use of obinutuzumab plus bendamustine after rituximab plus bendamustine
- Evidence on use of obinutuzumab plus chemotherapy
- The long-term safety and benefits of obinutuzumab maintenance
- Sequencing of treatments – first-line, second-line and downstream treatments

Economic factors:

- Potentially large prevalent patient population
- Unknown duration of treatment until disease progression or unacceptable toxicities

Registered Clinician Input

Registered clinician input was not received on the review for obinutuzumab for follicular lymphoma.

Summary of Supplemental Questions

The manufacturer performed a systematic literature review to identify studies that would allow comparisons between obinutuzumab and other treatments via a network meta-analysis. Insufficient data were available to populate such a network, therefore, the manufacturer compared data from the GADOLIN trial to data from a registry using a propensity score approach. Their results suggested that a regimen with obinutuzumab plus bendamustine (N=139) had statistically significant improvements in progression-free survival, relative to chemotherapy (N=21). However, there were significant limitations in their analysis and reporting of their results that cast doubt on the reliability of their conclusions. These include lack of detail in reporting of statistical methods, generalizability of the patient population in the registry, potential prognostic confounding factors unaccounted for in the analysis and very small sample size. Given the limitations of internal validity and external validity, no conclusions can be drawn with regards to the relative efficacy of obinutuzumab relative to other treatments.

See section 7.1 for more information.

Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for Obinutuzumab

Domain	Factor	Evidence from the GADOLIN trial	Generalizability Question	CGP Assessment of Generalizability
Population	Stage of disease	≥50% of study patients were Ann Arbor Stage IV at study entry. ≥40% of follicular lymphoma patients were FLIPI High (≥3). 35% of patients had bulky disease at baseline. 15% of patients had B symptoms at baseline. Patients must have had life expectancy >5 years to be included in the trial.	Does disease stage in GADOLIN limit the interpretation of the trial results with respect to Canadian clinical practice?	As expected in trial recruitment, the GADOLIN population has baseline characteristics representative of a healthier, selected patient population compared to refractory patients seen in clinical practice; however, because there was randomized treatment assignment and the trial results favoured obinutuzumab the CGP is confident that the superiority of the obinutuzumab arm can be generalized to the Canadian clinical practice.
	Performance Status	>95% of patients were ECOG 0 or 1 at baseline.	Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect Canadian clinical practice?	About 40% of patients in clinical practice have ECOG of 2 or greater. There are no safety data for using this regimen in this group. This limits the generalizability of the safety/toxicity results from the trial for such

Domain	Factor	Evidence from the GADOLIN trial	Generalizability Question	CGP Assessment of Generalizability
				patients and this limitation will need to be considered by Canadian oncologists using obinutuzumab. The relative efficacy results should not be affected.
	Age	Mean age of patients was 62 years and approximately 45% of patients in the trial were older than 65 years. There was no restriction on age in the trial.	Does the age in the trial limit the interpretation of the trial results with respect to the target population?	The results are generalizable to target patients in clinical practice. There were no subgroup analyses performed by age in the GADOLIN trial. There are no data in this trial or elsewhere to suggest efficacy would be different in patients, for instance, older than 65 years.
	Organ dysfunction	Patients with active infections, existing cardiovascular or pulmonary disease, elevated creatinine or elevated liver enzymes were excluded from the trial.	Does the exclusion of these patients limit the interpretation of the trial results with respect to Canadian clinical practice?	Renal, hepatic, and cardiac organ dysfunctions are important predictors of worse prognosis. Exclusion of patients with these dysfunctions limits generalizability of the results; however, such exclusion clarifies attribution of toxicity to treatment and is necessary for conduct of trials such as this. On balance the trial results should still be interpretable

Domain	Factor	Evidence from the GADOLIN trial	Generalizability Question	CGP Assessment of Generalizability
				in the Canadian context.
	Metastatic Sites	Patients with central nervous system lymphoma or evidence of histological transformation to a higer grade lymphoma were excluded.	Did the exclusion of these patients limit the interpretation of the trial results with respect to Canadian clinical practice?	Yes, these trial results are not relevant to management of patients with CNS or transformed lymphoma. This was intended and does not limit the trial results' usefulness.
	Ethnicity or Demographics	More than 85% of patients were white.	Is there a known difference in effect based on ethnicity that might yield a different result in a Canadian setting?	There are no data on differences based on ethnicity.
	Biomarkers	N/A	Is the biomarker an effect modifier (i.e., differences in effect based on biomarker status)? Are the results of the trial applicable to all subgroups equally? Is there a substantial group of patients excluded from the trial to whom the results could be generalized?	Biomarkers such as *BCL2*/*IgH* translocation and FcγR polymorphisms are not routinely checked for in clinical practice. Such biomarkers are not known to be effect modifiers, as there are no data on the correlation of biomarkers with treatment or survival endpoints.
	Other related lymphoma	Most patients had follicular non-Hodgkin's lymphoma (n=335, 81%). Non-follicular subtypes included extranodal marginal zone lymphoma	Can the results from the follicular lymphoma subgroup be extrapolated to patients with marginal zone lymphoma and small	Patients with non-FL iNHLs represented less than 20% of study participants preventing an evaluation of treatment efficacy in these smaller cohorts. The CGP also

Domain	Factor	Evidence from the GADOLIN trial	Generalizability Question	CGP Assessment of Generalizability
		(n=26, 6%), nodal marginal zone lymphoma (n=17, 4%), small lymphocytic lymphoma (n=30, 7%), splenic marginal zone (n=4,1%) and other (n=1). Results for the cancer subtypes were not presented individually. Subgroup analyses on IRC-assessed PFS (May 2015 cutoff) were: Non-FL (n=75): HR= 0.94(95% CI: 0.46,1.90) FL (n=321): HR= 0.49 (95% CI: 0.35 to 0.68)	lymphocytic lymphoma?	acknowledged that it is unlikely that phase 3 studies will be carried out among the non-FL subtypes given small sample sizes. Although rigorous proof that the effects of the use of anti-CD20 monoclonal antibodies can be extrapolated from follicular lymphoma to the other indolent small B cell lymphomas is lacking, available indirect comparisons have been consistent with that interpretation and remain reasonably extended to obinutuzumab, until such rigorous evidence becomes available.
Intervention	Line of therapy	GADOLIN excluded patients who received treatment with bendamustine within two years of trial start.	Are the results of the trial generalizable to patients who have received bendamustine plus rituximab in the front-line setting?	The treatment effect size results can only be generalized to bendamustine-naïve patients, who may represent perhaps 5% to 10% of today's patient population. However, while the treatment effect size cannot be generalized to patients who were not eligible for the trial, the

Domain	Factor	Evidence from the GADOLIN trial	Generalizability Question	CGP Assessment of Generalizability
				treatment effect itself can be reasonably generalized. Thus, addition of obinutuzumab appears to have enhanced the efficacy of cytotoxic chemotherapy even in a population of patients whose lymphoma had become refractory to rituximab.
	Administration of intervention	Bendamustine 90mg/m2/day was used in combination with obinutuzumab during induction.	Are the results of a trial using concomitant bendamustine generalizable to obinutuzumab in combination with chemotherapy?	Probably. Another alkylator chemotherapy can likely substitute bendamustine. This type of generalization is frequently seen. For example, when rituximab works well with cyclophosphamide in a patient, it is probable that chlorambucil, a different alkylator, would also work well.
Comparator	Dose and Schedule	Comparator in GADOLIN was bendamustine during the induction phase.	Is bendamustine an appropriate comparator for the Canadian context given that treatment approaches in Canada have changed since GADOLIN was started in 2010?	Bendamustine was the most reasonable comparator at the time of trial execution. However, bendamustine is now the primary therapy choice in Canada therefore, this limits the direct generalizability of the results of

Domain	Factor	Evidence from the GADOLIN trial	Generalizability Question	CGP Assessment of Generalizability
				GADOLIN, which are only directly relevant for "legacy patients", i.e. patients who are rituximab-refractory but are naïve to bendamustine. Because of this change in primary treatment the GADOLIN results are best viewed as a proxy for obinutuzumab + cytotoxic chemotherapy.
		Bendamustine 120 mg/m^2/day was given in the comparator treatment group, for induction.	If the dose and/or schedule is not standard, are the results of the trial relevant in the Canadian setting?	While the dose is considered high, it is the opinion of the CGP that the trial results are relevant.
Outcomes	Appropriateness of Primary and Secondary Outcomes	Primary outcome: progression-free survival.	Were the primary and secondary outcomes appropriate for the trial design?	Yes. PFS and OS were analyzed in the trial.
Setting	Countries participating in the Trial	There were 82 study sites in 14 countries. Countries with highest recruitment were Canada (24.0%), France (19.7%), USA (17.4%), Czech Republic (7.6%), and the United Kingdom (7.3%). Subgroup analyses by geographical region for the	Would difference in clinical practice in other regions influence the generalizability of the results to the Canadian clinical context?	It is the opinion of the CGP that trial results are generalizable to Canada, which had the highest recruitment (24%).

Domain	Factor	Evidence from the GADOLIN trial	Generalizability Question	CGP Assessment of Generalizability
		primary outcome (PFS) were: Eastern Europe (n=86): HR= 0.89(95%CI: 0.43,1.82) North America (n=248) HR=0.38(95%CI: 0.24,0.60) Western Europe (n=283): HR=0.69(95%CI: 0.46,1.01)		
	Supportive medications, procedures, or care	Premedications included acetaminophen, antihistamines, and corticosteroids prior to obinutuzumab infusions. Antiemetics were used prior to bendamustine infusions	Are these premedications similar to those used in the Canadian treatment context?	Yes.

1.2.4 Interpretation

Burden of Illness and Need

Follicular lymphoma (FL) is the 2nd most common type of non-Hodgkin lymphoma (NHL) diagnosed newly in 2800 Canadians per year.[5] Despite advances in treatment with chemotherapy and immunotherapy, FL is incurable with the average age of diagnosis being 59 years. Standard front line therapy has traditionally included an alkylator based chemotherapy and rituximab, a chimeric type 1 anti-CD20 monoclonal antibody. To date, the most efficacious front line chemo-immunotherapy combination is bendamustine and rituximab (BR) therapy with an overall progression free survival of 69.5 months.[6]

Patients whose lymphoma is refractory to or relapsed after a rituximab containing regimen have limited treatment options. Obinutuzumab is a glycoengineered type II anti-CD20 monoclonal antibody that has shown in vitro superiority to rituximab, including improved antibody-dependent cellular cytotoxicity.

Effectiveness

The GADOLIN trial was initiated 2010, when the standard front line chemotherapy for indolent NHL did not include BR. This open-label front line phase 3 clinical trial aimed to assess the efficacy and safety of bendamustine with obinutuzumab (GB) therapy followed by obinutuzumab maintenance therapy compared to bendamustine (B) monotherapy in a rituximab-refractory indolent non-Hodgkin's lymphoma population (including follicular lymphoma grades 1 – 3a, marginal zone lymphoma, small lymphocytic lymphoma, and lymphoplasmacytic lymphoma). Rituximab refractory disease was defined as a failure to respond to, or progression during a previous rituximab containing regimen, or progression within 6 months of the last rituximab dose. The definition is used by public drug plans as well. Importantly, patients who were treated with bendamustine within two years of starting GB were excluded from this clinical trial. 81% of patients in this trial had follicular lymphoma, with 79% of them being refractory to a previous rituximab-chemotherapy combination.

Data from the GADOLIN study demonstrates that treatment with obinutuzumab plus bendamustine results in progression-free survival (PFS) for a median of 29.2 months (95% CI 20.2 – not estimable) compared to bendamustine alone with a median of 14.1 months (based on independent central review PFS; hazard ratio 0.53 (95% CI: 0.40 to 0.70).[3] At time of the primary publication of the trial results, there were no significant differences in overall survival, complete and overall response rates between treatment groups, nor was there any evaluation of health-related quality of life (HRQOL) data with this trial publication. However, after publication of the trial, an updated analysis in April 2016 showed a median OS for B was 53.9(40.9,NE) and median OS for GB was NE(NE) (HR = 0.58(0.39,0.86); p=0.0061). Further, there were no notable differences between obinutuzumab plus bendamustine versus bendamustine in any of the average scores on a quality of life questionnaire (FACT-Lym) among follicular lymphoma patients.

Safety

Toxicity:

Grade 3 to 5 adverse events (AE) were reported in 68% and 62% of the GB and B arms respectively. Myelotoxicity was the most common subtype of AEs, with grade 3 neutropenia occurring in the 33% of the GB versus 26% in the B arm and thrombocytopenia occurring in 11% versus 16% respectively. The rates of febrile neutropenia and infection were less than 5% in each treatment arm. Of note, Health Canada had issued black box warnings for infusion reactions, hepatitis B virus reactivation, progressive multifocal leukoencephalopathy, tumour lysis syndrome, and cardiovascular adverse events. Infusion reactions, for example, can be safely managed with proper supervision and pre-medication.

Death:

After a median follow up of 21.9 months, of the 34 patients (18%) who died in the GB arm, 22 (65%) of deaths were due to disease progression. Of the 41 (21%) of deaths in the single agent bendamustine arm, 29 (71%) died due to disease progression.

Other considerations:

This is an open label clinical trial wherein prior response rates to single agent bendamustine ranged between 7 to 9 months in the iNHL patient population.[7] Patients receiving GB, received doses of obinutuzumab similar to other trials in iNHL (1000 mg intravenously on days 1, 8, 15 of cycle 1 and day 1 of cycles 2-6) followed by maintenance of 1000 mg every 2 months. It is unclear whether omission of obinutuzumab maintenance would have yielded similar results in

the GB arm, as omission of maintenance anti-CD20 antibody is not consistent with the standard of care for iNHL when an anti-CD20 monoclonal agent was included in the preceding primary treatment. The GB trial arm also dosed bendamustine at 90 mg/m^2 compared to the single agent dose of 120 mg/ m^2 with no data comparing the efficacy of both bendamustine treatment strategies available. However, the experimental arm of obinutuzumab + bendamustine, and maintenance obinutuzumab was shown in the clinical trial to produce statistically significant improvement in progression-free and overall survival in comparison to bendamustine alone. Since patients on both arms of the trial received bendamustine, it is the opinion of the CGP to attribute most or even all of the improved survival to the obinutuzumab.

The treatment of indolent non-Hodgkin lymphoma, including follicular lymphoma, has evolved quite substantially in the 6 years since the clinical trial was initiated. Presently the standard regimen used across Canada since approximately 2014 includes bendamustine in primary treatment, usually in combination with rituximab. Thus, in 2017 and going forward there will be very few patients, perhaps 5%, matching those enrolled in the clinical trial, who, by definition, were bendamustine naïve. For this reason, it is quite unlikely that clinicians wishing to select treatment based on this clinical trial will choose to use the experimental arm because that would mean employing an agent to which the patient's lymphoma had, by definition, recently demonstrated resistance. Thus, at first glance the clinical trial results might be seen to have little current relevance. No one would adopt the experimental arm. However, that interpretation would miss the core observation available from the trial: addition of obinutuzumab to chemotherapy led to improved progression-free and overall survival. Surprisingly, a second anti-CD20 antibody, obinutuzumab, caused improved survival in patients with lymphoma demonstrably resistant to a first anti-CD20 antibody, rituximab.

The reimbursement criteria request obinutuzumab in combination with any chemotherapy, while the GADOLIN trial used obinutuzumab in combination with bendamustine. It is the opinion of the CGP that bendamustine employed on the experimental arm simply served as a proxy for chemotherapy in general. It is a very reasonable extrapolation from that observation that obinutuzumab could and would add to the effectiveness of agents other than bendamustine, agents likely to be chosen by clinicians seeking sensible treatment for patients whose lymphoma has progressed despite recent use of rituximab. If improvements in survival endpoints noted in the obinutuzumab plus bendamustine arm could be attributable to the addition of obinutuzumab as maintenance, this would add weight to the argument that obinutuzumab could be offered in combination with chemotherapy, rather than only in combination with bendamustine. However, the design of the GADOLIN trial design which did not include maintenance therapy in the bendamustine arm makes assignment of responsibility for the improvement to either the induction phase or maintenance phase challenging.

In feedback on pERC's Initial Recommendation, the PAG asked for clarity that the use of obinutuzumab plus bendamustine when patients are deemed rituximab-refractory is not recommended for patients who are rituximab-refractory after prior therapy with rituximab plus bendamustine and whether this would be obinutuzumab with chemotherapy or with bendamustine. The CGP noted that, in broad terms, there will be two distinct populations eligible for the proposed use of obinutuzumab in Canada: (1) patients whose follicular lymphoma was previously treated with rituximab plus chemotherapy other than bendamustine whose lymphoma progresses within six months of the last exposure of rituximab and (2) patients who were previously treated with rituximab plus bendamustine whose follicular lymphoma progresses within six months of the last exposure to rituximab. Canadian patients in the first group will usually be treated with bendamustine plus obinutuzumab, due to the ability of bendamustine to overcome treatment resistance to other cytotoxic chemotherapy agents and of obinutuzumab to overcome rituximab resistance. However, the combination of bendamustine plus obinutuzumab would not be used by Canadian specialists for the second group of patients because all such patients would have previously received bendamustine, most likely quite recently prior to the

lymphoma progression now requiring treatment, making bendamustine a strongly unattractive choice. The CGP's expert opinion is that, since the GADOLIN trial conceptually demonstrated that the addition of obinutuzumab to cytotoxic chemotherapy overcomes demonstrated resistance to rituximab, Canadian specialists will choose to combine the obinutuzumab with a lymphocytotoxic chemotherapy agent but they will choose an agent or agents different from bendamustine. Of note, the combination of bendamustine plus rituximab has become the overwhelmingly most frequently chosen primary chemotherapy regimen for follicular lymphoma in all Canadian provinces during the past five years. Thus, most patients addressed by the Initial Recommendation by pERC will fall into this second group described above.

Patients with non-FL iNHLs represented less than 20% of study participants preventing an evaluation of treatment efficacy in these smaller cohorts. The CGP also acknowledged that it is unlikely that phase 3 studies will be carried out among the non-FL subtypes given their small numbers and the difficulty of recruiting sufficient sample sizes.

1.3 Conclusions

The Clinical Guidance Panel concluded that **there is a net clinical benefit** of bendamustine with obinutuzumab in the rituximab relapsed-refractory follicular lymphoma patient population as defined in the GADOLIN trial. The CGP felt the extrapolation of net clinical benefit to chemotherapy in general with obinutuzumab was reasonable. The generalizability to extend this benefit to other iNHL subtypes is plausible due to the limited cohort numbers of these increasingly rare tumor types. This conclusion was based on the results of the open label phase III study of GB verses B single agent with primary end points of PFS most recently reported at 29.2 months versus 13.7 months. The adverse event profiles were manageable with the most common grade 3 or higher toxicity being neutropenia. One third of such patients in each arm required granulocyte colony stimulating factor support.

The Clinical Panel also considered that:

- At the time of trial initiation, few patients with FL had ever had previous exposure to bendamustine outside of clinical trial. Since 2014, bendamustine with rituximab has become the standard of care for front line patients with iNHL. The GADOLIN trial indicates that 79% of patients were refractory to both rituximab and alkylator agents and almost no patients were exposed to bendamustine two year prior to trial inclusion.
- Appreciating both the change in treatment for front line iNHL, few patients may in fact match the entry criteria outlined in the GADOLIN trial. That is, the GADOLIN compromised of bendamustine naïve patients whereas practices have changed since trial initiation such that first line therapy for FL patients is includes bendamustine in primary treatment, usually in combination with rituximab. Despite this, it is clear that obinutuzumab has efficacy in the rituximab refractory patient and this type II antibody was the clear defining variable that led to a much improved PFS compared to single agent bendamustine. The CGP appreciates, based on the GADOLIN data, that chemotherapy + obinutuzumab is a reasonable option for treatment of the relapsed-refractory iNHL patient population. The CGP acknowledges the extent of improvement (effect size) noted in the trial can only be applicable to bendamustine naïve patients, who may represent perhaps 5% of today's patient population. While the treatment effect size cannot be generalized to patients who were not eligible for the trial, the treatment effect itself can be reasonably generalized. In other words, addition of obinutuzumab appears to have enhanced the efficacy of cytotoxic

chemotherapy even in a population of patients whose lymphoma had become refractory to rituximab.

- Specific patient populations were excluded in this trial including patients with a previous treatment with obinutuzumab, previous treatment with bendamustine within 2 years of starting cycle 1, CNS lymphoma, transformed lymphoma, existing cardiovascular or pulmonary disease, creatinine clearance of < 40 ml/min, or significant cytopenias unless due to bone marrow infiltration of disease itself. These trial results are not relevant to management of patients with CNS or transformed lymphoma. The exclusion of patients with organ dysfunctions also limits generalizability of the results. However, such exclusion clarifies attribution of toxicity to treatment and is necessary for conduct of trials such as this.
- If patients have an ECOG that is more than 2 due to the burden or nature of their disease, they should be optimized and treatment should be left to the discretion of the treating physician. There are no safety data for using this regimen in patients with an ECOG of 2 or more.
- Infusion reactions occur in up to 11% of patients with GB and can be safely managed with proper supervision and pre-medication (i.e. corticosteroids) for patients
- At the time of published analysis, overall survival was not significant between treatment arms.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Lymphoma/ Myeloma Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Follicular lymphoma (FL) is the most common type of indolent non-Hodgkin lymphoma (NHL), and the second most common NHL, accounting for approximately 35% of cases. Non-Hodgkin lymphoma made up 4.3% of all new cancers in Canada in 2016, and it is estimated that more than 2800 Canadians are newly diagnosed with follicular lymphoma every year.[5] It is usually diagnosed in patients, over the age of 50 and it is uncommon in young people. Prognosis is estimated by the Follicular Lymphoma-specific International Prognostic Index (FLIPI) which incorporates patient-specific, and disease-specific features at the time of diagnosis. Based on this model, prognosis varies from a 10 year survival of 84% in the low risk group, to 42% in the high risk group. [8]

The diagnosis of follicular lymphoma is typically made on an excisional lymph node biopsy. The lymphoma is classified according to the World Health Organization based on histologic features of the lymph node. Grade 1, 2, and 3a lymphoma is determined based on the number of blast cells seen under high power microscopy. Regardless of the grading, these subtypes are all considered indolent lymphoma and are managed identically. The majority of clinical opinion classifies grade 3b follicular lymphoma, with characteristic sheets of blast cells, as an aggressive lymphoma, and as a result, is managed differently than the indolent subtypes. Initial investigations for staging of the disease include a CT scan of the chest, abdomen and pelvis as well as a bone marrow biopsy. Stage I and II disease, as defined by the Ann Arbour staging system, has disease confined to the same side of the diaphragm. Stage III disease is defined as widespread adenopathy above and below the diaphragm, and stage IV disease includes patients with bone marrow or diffuse extralymphatic organ involvement. Non-bulky stage I or II disease may be eligible for radiation as a potentially curable option. Advanced stage follicular lymphoma, defined as bulky disease, or stage III or IV disease are considered incurable. Indication for treatment is for symptomatic disease, and typically involves chemoimmunotherapy to treat the widespread burden of illness.

2.2 Accepted Clinical Practice

There is significant heterogeneity with respect to the clinical course of advanced stage lymphoma. Given the incurable nature of the disease, and its indolent clinical course, treatment is typically initiated at onset of symptomatic disease. This includes B-symptoms such as fevers, unexplained weight loss, and drenching sweats at night, or bulky adenopathy causing symptoms. Marked cytopenias due to bone marrow involvement may also be an indication for therapy if severe and/or progressive. Early chemoimmunotherapy intervention for patients with asymptomatic disease has not been associated with an improvement in survival compared to a “watch and wait” strategy. [9] However, early intervention in asymptomatic patients using single agent rituximab immunotherapy resulted in improved progression-free survival (PFS).[10] Long-term outcomes of such therapy remains uncertain.

When a patient develops symptomatic disease, chemoimmunotherapy is the treatment of choice. Several studies have been done confirming the addition of rituximab to chemotherapy significantly improves response rate, duration of response and overall survival.[11] Although many chemotherapies have been combined with rituximab, the use of an alkylator combined with rituximab has emerged as the standard of care. Historically, the most commonly used alkylator was cyclophosphamide. In an attempt to determine

optimal first-line therapy, a phase III study compared R-CVP (rituximab, cyclophosphamide, vincristine, prednisone), R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), and R-FM (rituximab, fludarabine, mitoxantrone) chemotherapy.[12] The results confirmed R-CHOP as the regimen of choice with a longer remission compared to R-CVP, and less toxicity compared to R-FM. More recently, bendamustine, a cytotoxic bifunctional alkylating agent combined with rituximab has become the standard first-line therapy for follicular lymphoma across Canada.[11] When compared to R-CHOP, bendamustine and rituximab (BR) had an improvement in PFS (not reached (NR), vs. 40.9 months for R-CHOP, HR 0.61, $p<0.0072$), and improved time to next treatment (NR vs. 42.3 months, HR=0.52, $p<0.001$).[6] Bendamustine and rituximab also had an improved toxicity profile, making this the preferred regimen for first-line therapy in follicular lymphoma.

Eventually, patients with advanced disease at initial presentation will develop progressive disease. Asymptomatic progression can be observed, with chemotherapy reserved for patients with symptoms as outlined above. There is no standard of care for treating relapsed disease. Numerous regimens have been tried but never compared against each other. Cytotoxic drugs in combination with rituximab is recommended if the duration of remission is greater than 6 months after receiving a rituximab containing regimen. Many of the same chemoimmunotherapy protocols used in first line therapy have demonstrated activity in second line phase II studies with response rates varying from 65-90%. Such examples include BR,[13] CVPR,[14] and R-CHOP.[15] Consequently, the choice of treatment may be based on what was given in the past, incorporating a drug with a different mechanism of action. Purine analogues have also shown activity in relapsed follicular lymphoma with complete response rates as high as 74% using FCR (fludarabine, cyclophosphamide, rituximab), and could also be used in the relapsed setting.[16]

The role of stem cell transplantation in follicular lymphoma is controversial. For select patients, it may provide prolonged PFS, and potentially cure the disease if an allogeneic stem cell transplant is considered. However, there is no consensus regarding which patients might benefit from this approach and the utilization of high dose chemotherapy is decreasing since the introduction of rituximab in the treatment paradigm.[17] Based on consensus opinion, autologous stem cell transplant may be considered in first or second chemo-sensitive relapse for young, healthy patients, with high risk disease. This patient group is defined as under the age of 70, with high risk disease based on the FLIPI score, or relapsed disease within 3 years after first-line chemoimmunotherapy. However, the benefits of this approach in the rituximab era are less certain, and the risks of high dose chemotherapy need to be balanced against the benefit. Consensus opinion also suggests the use of allogeneic stem cell transplant for healthy patients under the age of 40, with progressive disease post-autologous stem cell transplant.[17] The number of patients eligible for such a procedure would be small, and the magnitude of benefit is uncertain.

Although follicular lymphoma is considered a chemotherapy-sensitive disease, it remains an incurable disease for patients not eligible for allogeneic stem cell transplant, and resistance occurs with re-treatment, and multiple lines of therapy. New treatments with a novel mechanism of action are necessary for patients with refractory disease. Radioimmunotherapy using a radiolabeled monoclonal antibody, such as Yttrium-90 (90Y)-labelled ibritumomab, has some evidence of activity in patients with relapsed disease.[18] However, concerns regarding long-term hematologic toxicity, and a restricted indication for patients with low burden of disease in the marrow have limited its utilization. Other drugs with novel mechanisms of action, such as bortezomib and lenalidomide look promising, but there is insufficient data to consider these agents as standard care. Idelalisib is a phosphoinositide-3 kinase (PI3K) inhibitor, but is not publicly funded for in Canada.

Standard therapy for transplant-ineligible patients with follicular lymphoma:

Line of Therapy	Standard chemotherapy options
1st-Line	Bendamustine-Rituximab
Maintenance	Rituximab
2nd-Line	Alkylator + Rituximab (ie. Cyclophosphamide or chlorambucil)

Evidence-Based Considerations for a Funding Population

The population under consideration here includes patients with refractory to or relapsed after rituximab, defined as no response to, or progression within 6 months of completion of the last dose of rituximab therapy (either as monotherapy or in combination with chemotherapy).

2.3 Other Patient Populations in Whom the Drug May Be Used

None identified.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The Lymphoma Canada (LC) patient advocacy group provided input on obinutuzumab in combination with chemotherapy followed by obinutuzumab monotherapy for patients with relapsed and/or refractory follicular lymphoma (FL). LC conducted online surveys and interviews with FL patients and caregivers to provide more insight into how FL impacts patient's lives and how different therapies influence their lymphoma.

Patients and caregivers registered on the LC database were sent links to surveys via email. These links were also made available via LC Twitter and Facebook accounts, as well as through FL patient forums and the Lymphoma Association (UK).

The surveys had a combination of multiple choice, rating and open-ended questions. Skipping logic was built into surveys so respondents were asked questions only relevant to them. Open-ended responses to surveys and quotes obtained from interviews that reflected the sentiment of a majority are included verbatim to provide a deeper understanding of patient and caregiver perspectives.

The following table shows the responders who participated in the surveys and interviews conducted by LC stratified by country:

Participants by Country		**Canada**	**USA**	**UK**	**Italy**	**South Africa**	**Did Not Specify**	**N**
Surveys	Patients without obinutuzumab experience	81	14	16	1	1	24	**137**
	Patients with obinutuzumab experience	3	2	1	-	-	1	**7**
	Caregivers	12	2	3	-	-	2	**19**
Interviews	Patients with obinutuzumab experience	1	1	-	-	-	-	**2***
	TOTAL ***The two (2) patients interviewed also completed a survey**							**163***

From a patient's perspective, LC stated that patients with early stage FL who participated in the survey experienced minimal symptoms with their disease and tended to have a good quality of life. However, it was noted that for those with relapsed disease, quality of life was impacted more significantly. LC described that patients commonly reported fatigue, loss of appetite, fever, night sweats, stomach problems, itchy skin, muscle and joint pain, as well as difficulties with memory, concentration, anxiety, depression, insomnia and intimacy. Furthermore, LC also expressed that additional complications were reported, which included frequent infections (due to compromised immunity), shortness of breath (attributed to anemia) and easy bruising (caused by low platelet counts). LC stated that all of these symptoms can interfere with a patient's performance, ability to work, travel and day-to-day activities. Among the patients who responded to the LC survey, they reported that treatment options for relapsed FL included: single agent or combination chemotherapy, rituximab (alone or in combination), or radiation therapy. LC indicated that these treatment options tend to be associated with increased toxicity, reduced anti-tumour activity and unpleasant side effects. In terms of expectations for a new therapy, LC survey respondents reported that they were seeking treatments that will prolong their life, offer disease control, bring about a remission and improve quality of life. Furthermore, LC stated that patients who had experience with obinutuzumab had fewer and more manageable side effects as compared to other therapies, as well as improvements in their disease symptoms and in quality of life. LC added that patients who are refractory to rituximab could also benefit from an effective immunotherapy that can be combined with available chemotherapy agents. Finally, LC noted that there are very few effective treatment options for FL patients who have relapsed after initial therapy and that obinutuzumab in combination with chemotherapy followed by obinutuzumab maintenance may potentially improve remissions.

Please see below for a summary of specific input received from the patient advocacy groups. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that was reported have also been reproduced as is according to the submission, without modification.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Follicular Lymphoma

LC reported that patients with early stage FL had minimal symptoms associated with their disease and tended to report a good quality of life. However, for patients with relapsed disease, quality of life was impacted more significantly. These patients commonly reported fatigue, loss of appetite, fever, night sweats, stomach problems, itchy skin, muscle and joint pain. Some patients with FL expressed difficulties with memory, concentration, anxiety, depression, insomnia and intimacy. Additional complications reported included frequent infections (due to compromised immunity), shortness of breath (attributed to anemia) and easy bruising (caused by low platelet counts).

LC asked patient respondents how FL impacts their day-to-day life. Specifically, respondents were asked to rate on a scale of 1 (No Impact) to 10 (Very Significant Impact), how much the symptoms associated with FL have impacted or limited their day-to-day activities and quality of life.

The following table provides information on how FL impacted a patient's day-to-day life. LC reported that for factors with a rating average of ≥5, there was a greater than neutral impact on day-to-day life.

Impact on Day-to-Day Life of R/R FL Patient Participants (N= 32)	**Rating of ≥7 n (%)**	**Rating Average**	**Impact on Day-to-Day Life of all other FL Patient Participants (N=93)**	**Rating of ≥7 n (%)**	**Rating Average**
Ability to work	15 (46.9%)	6.2	Ability to work (*N=92)	33 (35.9%)*	5.1
Ability to travel	15 (46.9%)	5.6	Ability to travel	25 (26.9%)	4.6
Ability to exercise	12 (37.5%)	5.6	Ability to concentrate	26 (28.0%)	4.5
Ability to attend to household chores	11 (34.4%)	5.3	Ability to exercise	25 (26.9%)	4.5
Ability to fulfill family obligations	13 (40.6%)	5.1	Ability to contribute financially to household expenses	25 (26.9%)	4.2
Ability to spend time with family & friends	11 (34.4%)	5.1	Ability to volunteer *(N=90)	27 (30.0%)*	4.2
Ability to contribute financially to household expenses (*N=31) (* 1 skipped)	11 (35.5%)*	5.0	Ability to attend to household chores	16 (17.2%)	4.1

Ability to concentrate	11 (34.4%)	4.9	Ability to spend time with family & friends	21 (22.6%)	3.9
Ability to volunteer	13 (40.6%)	4.8	Ability to fulfill family obligations	15 (16.1%)	3.8

*Respondents skipped the question

To help illustrate the impact of this cancer, the following responses were submitted by three respondents who described their experiences with FL:

- "*Critical reduction in oxygen absorption rate. Movement from chair rest to bathroom and back left me breathless and starving for oxygen. Was placed on oxygen supply at home with some improvement. Second round of chemo seems to have resolved the issue for the most part. Having just completed six months of treatment (monthly infusions and biweekly pill regimen), I do not know what will happen when the swelling may return to limit the exchange of oxygen.*"(Male; 65-74; Canada)
- "*The second time I relapsed it was after birthing my third child and it was a nightmare. Mental Health is definitely impacted even after being in remission for 10 years. I could not attend to my children for two years due to the side effects of chemo and everything associated to having lymphoma.*"(Female; 35-44; Canada)
- *"When symptoms were at their worst, before treatments began, I had chronic bladder/kidney infections, a build up of fluids due to difficulty urinating, and discomfort wherever the tumours happened to be pressing, night sweats, heaviness and weakness in legs which made walking and stairs difficult, as well as cracked and bleeding feet. I stopped working, cut back on commitments to family and friends as I was able.*" (Female; 55-64; Canada)

3.1.2 Patients' Experiences with Current Therapy for Follicular Lymphoma

LC stated that while current treatment options can work initially, patients with FL usually relapse after treatment, and in most cases each period of remission becomes shorter. Treatment options for relapsed FL include: single agent or combination chemotherapy, rituximab (alone or in combination), or radiation therapy. Thirty-three (33) respondents indicated they had relapsed FL of which 29 respondents (87.9%) provided the names of the treatment(s) received.

The table below shows prior treatments that the 29 respondents may have received:

Treatments Received (N= 29)	n	Treatments Received	n
R-CHOP; ASCT	2	Bendamustine-Rituximab	1
R-CHOP; Rituximab maintenance	2	R-CVP; Bendamustine-	1
CVP; R-CHOP	2	CVP; FCM; Rituximab maintenance	1
Bendamustine-Rituximab; R-CHOP; R-GDP	1	R-CHOP; Radiation	1
Ritxumab; R-CHOP; R-CVP; Bendamustine; ASCT	1	CHOP; R-CHOP	1
CHOP; DHAP; Fludarbine; Interferon; B-R	1	CHOP; Rituximab	1
R-CHOP; DHAP; FCR; SCT (with total body irradiation)	1	R-CVP; Rituximab maintenance	1
Rituximab alone; CVP; GA-101; Bendamustine	1	R-CHOP; Radiation	1
CHOP; R-Galiximab; Radiation	1	R; Chlorambucil	1
CHOP; Zevalin; Bendamustine-Ritxuimab	1	R-GDP	1

CHOP; R-CVP; Rituximab Maintenance	1	Rituximab alone	1
Radiation; CVP; CHOP	1	Rituximab maintenance	1
Rituximab; Bendamustine-Rituximab	1	R-CHOP	1
Please note: ASCT = Autologous Stem Cell Transplant; SCT = Stem Cell Transplant.			

LC indicated that respondents listed both positive (disease control) and negative side effects (disease progression; adverse events; discontinue treatment due to side effects) of their treatment. The following responses were submitted by five (5) respondents with relapsed FL who described their experiences with current therapies:

- "*I feel like I'm wading through water. Dry mouth. Fatigue. My body injures and bruises easily. It takes a long time to recover. Just in case no one asks it has ruined my sex life because of the above symptoms". (Female; 45-54; UK; R-CHOP; Radiation)*
- *"GDP-R was my last therapy. I found it becoming more difficult to rebound after each cycle. My hemoglobin and platelets were so low I had to have a few blood transfusions. At the end of it all my cancer was larger*." (Male; 55-64; Canada; Bendamustine-Rituximab, CHOP-R, GDP-R)
- "*The cancer never went away it just shrunk. Radiation had no effect whatsoever on the tumours. Of the different drugs I was given prednisone was the most difficult drug. I was unable to sleep or relax for five days. I can't imagine ever having to take that truck again. I lost my hair but I really didn't find that such a big deal. I found being hooked up to an IV line for 3 to 4 hours very difficult*." (Female; 55- 64; Canada; CHOP; R-CVP; Rituximab Maintenance)
- "*Bendamustine/rituximab was not so toxic as the CHOP regime, 12 years ago, although it seems I have had a reaction to Rituximab and was not allowed to continue with maintenance treatment as I developed numerous chest infections and bronchiectasis. My lymphocyte level is still very low. (0.02) and I take antibiotics and antivirals on a daily basis*." (Female; 65-74; UK; CHOP; Zevalin; B-R)
- "*It is potentially life threatening. So being denied treatment due to criteria funding is distressing*." (Female; 55-64; Canada; CHOP; DHAP; Fludarabine, Interferon; Bendamustine-Rituximab)

In terms of current therapy symptom management, LC stated that there are very few effective treatment options for Canadian FL patients who were refractory to rituximab or who have relapsed after chemo-immunotherapy with rituximab. LC asked patients to rate their level of agreement with how much their current therapy(ies) are (or most recent therapy(ies) was able to manage symptoms associated with their FL with 1 (Strongly Disagree) to 10 (Strongly Agree). LC reported that 20 patient respondents living in Canada who identified as having relapsed FL who answered this question rated much lower (rating average 6.15) than the 38 patient respondents living in Canada who identified as not having relapsed FL (rating average 8.0).

Furthermore, when considering treatment, LC asked respondents on how important is it for them and their physician to have choice in deciding which drug to take based on known side effects and expected outcomes using a rating scale of 1 (Not Important As Long There Is At Least One Treatment Choice) to 10 (Extremely Important To Have Choice of Treatment). It was reported that 86/117 respondents (73.5%) who answered this question gave this a rating of 8 or higher. The rating average was 8.6, which according to LC means a large proportion of respondents felt that choice was very important based on known side effects and expected outcomes of a drug. LC also asked patients if they feel that there is currently a need for more choice in drug therapy(ies) for patients with FL. The vast majority of the 117 respondents (n=112, 95.7%) who answered this question felt there is a definitive need for more therapies. One respondent expressed: "*I am running out of options*." (Male; 55-64; Canada; Bendamustine- Rituximab; R-CHOP; R-GDP).

LC also asked respondents how difficult it was to access their current or most recent therapy(ies). LC reported that 16/78 (20.5%) of Canadian patient respondents who answered this question experienced difficulties with access. Difficulties expressed by these respondents included the need to: travel great distances to receive treatments in Canada; meet specific provincial drug funding criteria; pay out-of-pocket costs for treatments and associated travel. The following responses were provided by four (4) Canadian respondents:

- "*I have 3 days in hospital instead of 2, I used to do bloodwork, see the Dr & have chemo in one day then chemo the next day, so only 2 days of travel & time spent in hospital. Now it's one day for bloodwork & Dr & then back 2 more days for chemo. Extra wear & tear on us, our car & our pocketbook for parking*." (Female; 55-64; Canada)
- "*Not difficult to get to London Regional Cancer Clinic and oncologists outstanding, the only challenge was the government's refusal to fund my maintenance Rituxin. That has been distressing*."(Female; 55-64; Canada)
- "*There were not volunteer drives that were accessible. I had to stay 3-5 hours past their return departure time. My therapy caused huge reactions so I had to stay overnight after treatment. We couldn't afford the lodge or motel bills. I had no one else willing to drive me to appointments. There were so many cancer patients at the cancer centre that I had to always make sure the times they scheduled me actually worked for bloodwork deadlines before treatment and giving enough time for slowed-down infusions before closing. If I didn't alert staff immediately that the booked times did not work out, I could lose my place for treatment that day or that week and would have to prolong my treatment cycle. My world revolved totally around my medical appointments and chemotherapy and that was not helpful. Staff were overworked*." (Female; 45-54; Canada)
- "*Having to go to Toronto for the best part of the day is very tiring when you are having chemo and therefore it is not advisable to drive yourself. Therefore, I had to have someone take me. I did not feel well enough to use public transit as I never knew how sick I would be on the way home*."(Female;65-74; Canada)

3.1.3 Impact of Follicular Lymphoma and Current Therapy on Caregivers

Overall, there were 19 caregivers who participated in the LC survey. Among these participants, seven (36.8%) respondents were retired and 12 (63.2%) respondents were still working at the time of completing the survey. LC asked caregivers to rate how much caring for a person with FL has impacted their day-to-day life using a scale of 1 (No Impact) to 10 (Very Significant Impact).

The following table provides information on how much caring for a person with FL has an impact on the day-to-day life of caregivers who were retired and not retired. LC noted that for factors with a rating average of ≥5 means that there was a greater than neutral impact on day-to-day life.

Impact on Day-to-Day Life of Retired Caregivers (N= 7)	**Rating of ≥7 n (%)**	**Rating Average**	**Impact on Day-to-Day Life of <u>Not</u> Retired Caregivers (N=12)**	**Rating of ≥7 n (%)**	**Rating Average**
Ability to volunteer	3 (42.9%)	7.4	Ability to travel	5 (41.7%)	5.8
Ability to travel *1 skipped	4 (66.7%)*	6.8*	Ability to Work	4 (33.3%)	5.4
Ability to concentrate	2 (28.6%)	4.6	Ability to concentrate	4 (33.3%)	5.3

Ability to fulfill family obligations	2 (28.6%)	4.3	Ability to volunteer	3 (25.0%)	5.0
Ability to spend time with family & friends	2 (28.6%)	4.1	Ability to exercise	5 (41.7%)	4.9
Ability to exercise	2 (28.6%)	4.0	Ability to fulfill family obligations	4 (33.3%)	4.8
Ability to attend to household chores	1 (14.3%)	3.6	Ability to spend time with family & friends	3 (25.0%)	4.7
Ability to contribute financially to household expenses	1 (14.3%)	2.1	Ability to contribute financially to household expenses	2 (16.7%)	3.6
Ability to work	Not asked		Ability to attend to household chores	2 (16.7%)	3.5

Other common challenges were described by three (3) caregivers:

- "*Self employed family business, husband on treatment and unable to take sick leave. Caring for husband attending hospital plus running company/staff/clients - friends and family mean well but are emotionally needy asking and worrying and constantly calling/telephoning... Hospitals and appointments are very slow and not time efficient...Communication between different hospitals, GP and clinicians not good due to being different areas/foundation trusts etc…Travel and parking is an additional burden on time and most hospitals have limited spaces so drive round and round constantly seeking parking...Cancer isn't 9-5 and many people still need to work to survive in addition to being treated and struggling to stay alive*." (Wife; Not Retired; 45-54; UK)
- "*The biggest impact for me as a spouse has been the emotional/psychological impact...There has been nothing offered support wise to help us cope with the reality that his life has been shortened by decades*." (Wife; Not Retired; 35-44; Canada)
- "*When my husband was first diagnosed the life we knew ended. Period. Everything changed. Our children were greatly affected also. We live in a rural area so we had to travel 30 min (family doctor) to 3 hours (oncologist - Cancer Center) for every doctor appointment/treatment so time & cost is a huge factor. My responsibilities doubled as I took on everything my husband used to do. Which wasn't easy as I was also a 24/7 caregiver….I cannot imagine a person with cancer going thru treatments without someone to keep track of medications, appointments, driving the patient around & insuring there is proper food always available…Now that my husband is in remission things have gotten a lot better, but when he was first diagnosed "the not knowing" almost killed us both!!... The worst thing with fNHL is there is no cure... Do I think more funding is needed for this disease? Absolutely!! With all my heart!!*" (Wife; Not Retired; 55-64; Canada)

Caregivers also reported difficulties managing "side effects" of treatment. Here, three (2) caregivers described their experiences,

- "*The nausea at the time of treatment was a huge factor. He had to eat "as soon as" he felt hungry or he would loose his appetite. I would pre make meals that could be quickly heated. The "chemo brain" has made it frustrating for both of us because he couldn't remember things. The neuropathy in his feet has just made it uncomfortable for him*." (Female; Spouse/Partner; Not Retired; 55-64; Canada)

- "*My dad got really sick at his first treatment and had an incredibly bad reaction to the drugs. As his daughter it was pretty scary to see my dad at his most vulnerable and so helpless*."(Female; Daughter; Not Retired 25-24; Canada)

LC also reported that caregivers discussed difficulties with accessing treatments, where financial burden and ability to travel in order to receive treatment were the most common factors. Some caregivers had to take time off work to assist with taking care of the patient (loss of income), while others reported that the drug was difficult to access because they had to travel to a cancer centre which was far from home. To help illustrate the challenges, four (4) caregivers reported the following experiences:

- "*It was a long drive. We had to be there for hours so we had to be there early in the morning. I had to take at least one day off work and sometimes two days*." (Spouse /Partner; Not Retired; Male; 45-54; Canada)
- "*We had to apply for income support and a drug card for my child as they had no coverage. I am currently off work on LTD while treatment is occurring*."(Parent; Not Retired; Female; 45-54; Canada)
- "*Can't concentrate on work, 1-hour and fifteen minutes to cancer treatments, health care needs improvements, finances a struggle, the process is not easy. There should be financial help for people*." (Spouse /Partner; Not Retired; Male; 45-54; Canada)
- "*It is potentially life threatening. So being denied treatment due to criteria funding is distressing*." (Female; 55-64; Canada)

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Obinutuzumab

Patient Expectations with Obinutuzumab

For those who do not have experience with obinutuzumab, LC asked respondents to rate on a scale of 1 (Will Not Tolerate Any Side Effects) to 10 (Will Tolerate Significant Side Effects) the extent to which they would be willing to tolerate side effects if they were to consider having treatment with a new drug approved by Health Canada for the treatment of their FL. LC stated that among the 81 Canadian respondents, the majority gave a rating of 8 or higher (rating average 6.9). LC noted that many respondents were willing to tolerate side effects if they could live longer, achieve a remission, have control of their disease and have an improved quality of life. Four (4) respondents described the following:

- "*I would hope they were only short term and that side effects from treatment would be less debilitating than the symptoms of the disease. The best of the two evils I suppose!*" (Female; 65-74; Canada)
- "*If it will make you sicker than a dog then all of a sudden you are not going to get better, then I probably would not want to tolerate that too much. I will take side effects, but not massive side effects. I would not want to be laid up in bed*." (Male; 58; Canada)
- "*If the drugs give me more time to live I will certainly strongly consider putting up with side effects*." (Female; 65-74; Canada)
- "*My quality of life was drastically reduced during my treatment. I had complications which impacted my health*." (Female; 45-54; Canada)

LC also asked patient respondents to rate, on a scale of 1 (Not Important) to 10 (Very Important), how important it is for a new drug to be able to control specific aspects associated

with their FL. LC reported that the vast majority of respondents who answered this question assigned a rating of '10' to all aspects listed in the table below.

Factors Associated with Long-term Health and Well-being	Rating of 10 n (%)	Rating Average
Allow me to live longer (N=119)	109 (91.6%)	9.66
Bring about a remission (N=119)	105 (88.2%)	9.59
Control disease and symptoms associated with the disease (N=119)	102 (85.7%)	9.56
Improve Quality of Life (N =119)	96 (80.7%)	9.46
Improve blood counts (N = 117)	83 (70.9%)	8.90

One respondent interviewed by LC stated: "*Well if it's going to help patients with lymphoma and put them into a remission and gives them more time and improves their overall health. I can understand why someone would be willing to say they would be willing to have side effects. As long as it is not detrimental to their health and it is not on-going.*" (Male, 70 years; USA)

Respondents who have experiences with obinutuzumab

LC reported that seven (7) patient respondents had experience with obinutuzumab, and that their ages ranged from 35 to ≥75 years. According to the LC, six (6) respondents had received other treatments prior to taking obinutuzumab and the mean number of lines of therapy prior to obinutuzumab treatment was two lines of therapy (range: 0-3). Furthermore, five (5) respondents had received (or were receiving) obinutuzumab in combination with chemotherapy and one (1) respondent received obinutuzumab monotherapy as first-line treatment. In addition, LC stated that one (1) respondent skipped the question.

LC also asked six (6) respondents how obinutuzumab compared in terms of side effects, with other treatments they had taken for FL, on a scale of 1 - 10, with 1 being (Far Less Side Effects) and 10 being (Many More Side Effects). LC reported that the average rating was 3.3 and 67% of respondents provided a rating of ≤ 4. According to LC, this indicated that most respondents had experienced fewer side effects with obinutuzumab than they had with other lymphoma therapies. LC also asked respondents to rate the quantity of side effects they had experienced due to obinutuzumab, on a scale of 1 - 10, with 1 being (No Side Effects) and 10 being (Many Side Effects), 100% of respondents gave a rating of ≤ 3. LC noted that the following side effects were attributed to obinutuzumab by at least one respondent: infusion reaction, nausea, neutropenia, diarrhea, constipation and infections. Two (2) respondents stated that:

- "*My bowel habits were changed with some constipation and I also developed some skin sensitivity, which was easily resolved with spray Calamine lotion. But overall I felt fine the whole time. It really didn't feel like I was getting treated for cancer*." (Male, age 70, USA)
- "*The side effects were a breeze…compared to the chemo I had before…*" (Female, age 45-54, Ontario, Canada)

In terms of improvement in symptoms, LC asked respondents on a scale from 1 (No Improvement) to 10 (Very Significant Improvement) for each of the following symptoms associated with FL, how much each symptom has improved with obinutuzumab. The respondents provided the following ratings in the table below.

Symptoms	Average Rating	No. of respondents	Symptoms	Average Rating	No. of respondents
Aches and/or pains	7	4	Low platelet counts (thrombocytopenia)	9	2
Enlarged lymph node(s)	8	5	Low red blood cell counts (anemia)	9	3
Enlarged spleen	Not Applicable	Not Applicable	Night sweats	Not Applicable	Not Applicable
Fatigue	8	4	Reduced appetite	Not Applicable	Not Applicable
Fever	Not Applicable	Not Applicable	Weight loss	Not Applicable	Not Applicable
High white blood cell counts (leukocytosis)	9	4			

LC also asked five (5) respondents about quality of life and most respondents (80%) reported that obinutuzumab brought their disease under control and made them feel similar to the way they did before their diagnosis. The following experiences were described by two (2)respondents:

- "*I feel great…after 1 year, I've never felt better. It didn't interfere with my life at all*." (Female, age 55-64, British Columbia, Canada)
- "*No side effects at all with this treatment. I was really worried…but it has gone really well and I'm almost finished with the treatments so fingers crossed…*" (Female, age 65-74, UK)

When asked by LC, based on their personal experience, if they would recommend obinutuzumab to other patients with FL, 5 of the 7 respondents replied "yes" and 2 respondents replied "no". Two (2) respondents reported the following experiences:

- "*It worked for me providing complete remission for now 1 year*." (Male, age 70, USA)
- "*If you are rituxan resistant as I am this is one of the only good options*." (Male, age 35-44, USA)

3.3 Additional Information

None.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all the provinces participating in pCODR. PAG identified the following as factors that could impact the implementation of obinutuzumab for follicular lymphoma (FL):

Clinical factors:

- Clarity on the use of obinutuzumab plus bendamustine after rituximab plus bendamustine
- Evidence on use of obinutuzumab plus chemotherapy
- The long-term safety and benefits of obinutuzumab maintenance
- Sequencing of treatments – first-line, second-line and downstream treatments

Economic factors:

- Potentially large prevalent patient population
- Unknown duration of treatment until disease progression or unacceptable toxicities

Please see below for more details.

4.1 Factors Related to Comparators

For previously treated FL patients who are refractory to rituximab, treatment varies across the jurisdictions and there is no standard of care. Treatments available include fludarabine, bendamustine, cyclophosphamide/vincristine/prednisone (CVP) or cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP). For patients who have relapsed on rituximab therapy, rituximab re-treatment is an option depending on time to relapse from last dose of rituximab. PAG is seeking data on the comparison of obinutuzumab to rituximab re-treatment.

PAG noted that in the GADOLIN trial, induction therapy of both treatment arms appear to produce similar benefits and the difference between the two arms occur in the obinutuzumab maintenance phase suggesting that bendamustine monotherapy is an effective induction therapy. PAG also noted that although there are meaningful progression-free survival data, there are no overall survival data given the short follow-up and this may be similar to treatment with rituximab where prolonged progression-free survival occurs but no overall survival benefit.

4.2 Factors Related to Patient Population

PAG noted that a large prevalent number of patients with refractory FL may be eligible to receive treatment with obinutuzumab plus bendamustine/chemotherapy followed by obinutuzumab maintenance. This would provide a treatment option for patients who are refractory to rituximab. PAG noted the funding request includes patients who have relapsed on rituximab but the GADOLIN trial enrolled patients who are rituximab refractory. PAG is seeking clarity on the group of patients who would be eligible for

treatment with obinutuzumab and the definition of refractory and relapsed, including time period from last treatment.

PAG noted that the GADOLIN trial excluded patients who have received treatment with bendamustine within two years of trial start. PAG is seeking guidance on the use of obinutuzumab plus bendamustine in patients who have received bendamustine plus rituximab in the front-line setting.

PAG noted that the submitted indication to Health Canada is obinutuzumab in combination with bendamustine but the funding request under review is obinutuzumab in combination with chemotherapy. PAG is seeking clarity on the generalizability of the GADOLIN trial results to treatment with obinutuzumab in combination with chemotherapy and whether there are data to support use of obinutuzumab with chemotherapy as the GADOLIN trial is for obinutuzumab with bendamustine.

PAG also noted that the GADOLIN trial included a small number of patients with marginal zone lymphoma (MZL) and small lymphocytic lymphoma (SLL). Although only results for FL were reported, PAG is seeking information on whether these results on FL can be extrapolated to MZL and SLL or whether the results for MZL and SLL are available. PAG noted that there may be requests to use obinutuzumab in patients with MZL and SLL.

4.3 Factors Related to Dosing

Obinutuzumab dose is flat dosing, regardless of patient's weight or body surface area. PAG noted that the vial sizes available provide these doses without drug wastage. These are enablers to implementation.

4.4 Factors Related to Implementation Costs

Obinutuzumab is administered by intravenous infusion over 4 hours and in cycle 1, three doses are required, followed by monthly doses for cycles 2 to 6 and maintenance dose of every 2 months until disease progression or for two years. These are barriers as there would be chemotherapy chair utilization and increased nursing resources. PAG also recognized that there may be additional costs associated with obinutuzumab treatment, such as monitoring for infusion related reactions and other adverse reactions.

In addition, treatment duration with maintenance phase is until disease progression or up to two years, whichever occurs first. The number of patients eligible for treatment is unknown and PAG noted that there could be a large incremental budget impact.

4.5 Factors Related to Health System

PAG identified that first dose of obinutuzumab in cycle 1 can be given divided over day 1 and 2 to reduce risk of infusion reaction. This coincides with bendamustine administration. This may necessitate greater chemotherapy chair-time for those days. However it does not require an additional visit for the patients, as they would be returning for day 2 of bendamustine.

PAG noted that there is a higher number of infusion-related reactions in cycle 1 of obinutuzumab compared to rituximab, based on experience with obinutuzumab in chronic lymphocytic leukemia. Thus, in some jurisdictions, the administration of obinutuzumab is restricted to treatment centres with the experience and resources to manage infusion related reactions.

4.6 Factors Related to Manufacturer

PAG noted the high cost of obinutuzumab would also be a barrier to implementation.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Registered clinician input was not received on the review for obinutuzumab for follicular lymphoma.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the safety and efficacy of obinutuzumab in combination with chemotherapy, followed by obinutuzumab monotherapy, on patient outcomes in the treatment of adults with follicular lymphoma who relapsed after, or are refractory to, a rituximab containing regimen.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 3. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCTs. In the absence of RCT data, fully published clinical trials investigating the efficacy of obinutuzumab should be included. Reports of trials with a dose escalation design should be excluded.	Adults with follicular (grade 1, 2, or 3a) lymphoma who relapsed after, or are refractory to, a rituximab containing regimen.	Induction: obinutuzumab IV plus chemotherapy Maintenance: obinutuzumab	No current consensus exists for standard of care. Treatment strategies include: • CHOP • CVP • FCM • Single agent bendamustine • Single agent fludarabine • Gemcitabine • No active therapy/symptom management • Rituximab retreatment • Idelalisib • Observation	• **OS** • **PFS** • **Response rate** • **Time to next treatment** • **Time to symptomatic disease** • **Duration of Response** • **Quality of Life** • **SAEs** • **AEs** • WDAEs

AE= adverse event; CHOP= cyclophosphamide + doxorubicin + vincristine + prednisone; CVP= cyclophosphamide + vincristine + prednisone; DFS=disease-free survival; FCM = bendamustine or fludarabine + cyclophosphamide; IV= intravenous PFS= progression free survival; OS= overall survival; RCT= randomized controlled trial; SAE=serious adverse event; WDAE= withdrawal due to adverse event;

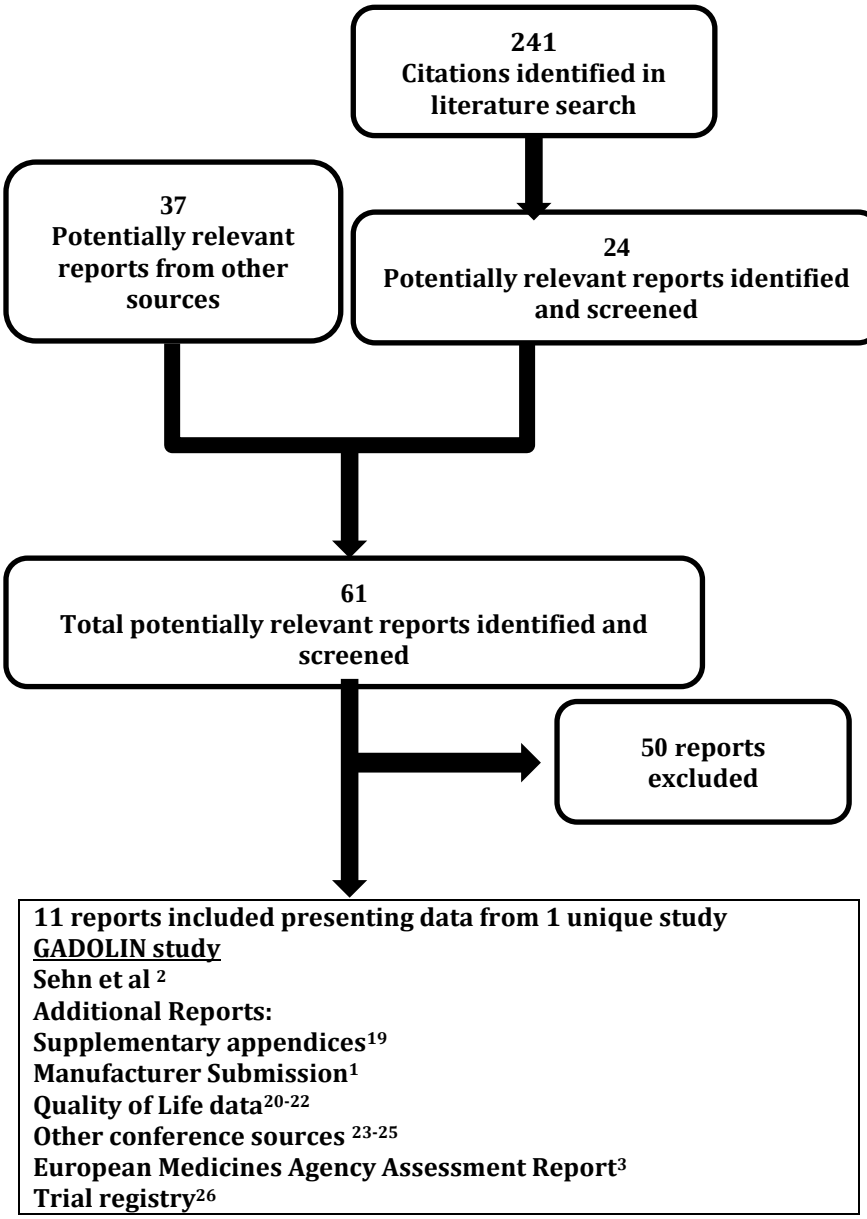
** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.3 Results

6.3.1 Literature Search Results

Of the 61 potentially relevant reports identified, 1 study was included in the pCODR systematic review (GADOLIN)[2] and 50 reports were excluded.

Figure 1: QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to the GADOLIN study were also obtained through requests to the Submitter by pCODR[27]

6.3.2 Summary of Included Studies

One randomized, open label, Phase III study (GADOLIN) met the inclusion criteria for this review. The study is ongoing, but not recruiting patients.

6.3.2.1 Detailed Trial Characteristics

Table 4: Summary of Trial Characteristics of the Included Study

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
GADOLIN (NCT01059630) Two group, parallel, open-label Phase III study, randomized 1:1 Patient Enrolment Dates: April 15, 2010 to January 7, 2015 Randomized iNHL patients: N=396 for September 1, 2014 cut-off N=413 for May 1, 2015 cut-off Randomized FL patients: N= 321 for September 1, 2014 cut-off N= 335 for May 1, 2015 cut-off Data cut-off dates: September 1, 2014 (N= 396) analysis date for main publication by Sehn et al)[2] May 1, 2015 (N=413)[3] April 1, 2016 (N=413)[24] 82 sites in 14 countries (Europe, Asia, North and Central America) Funding: Hoffman-La Roche	Key Inclusion Criteria: • Histologically documented, CD20-positive iNHL (FL grades 1–3a, MZL, SLL and WM) refractory to rituximab. • ≥1 bidimensionally measurable lesion (>1.5 cm) • ECOG 0,1 or 2 • Life expectancy of 5 years • Previous anti-lymphoma treatment (up to four chemo regimens permitted) Exclusion Criteria • monoclonal antibody (other than rituximab) within 3 months of trial start • chemotherapy within 28 days of trial start • bendamustine within 2 years of trial start • Existing CV or pulmonary disease • Active infections • CNS lymphoma • Evidence of histological transformation to a higher grade lymphoma	Intervention: Obinutuzumab 1000 mg IV, days 1, 8, and 15 of cycle 1 and day 1 of cycles 2–6, plus bendamustine 90 mg/m^2/day IV days 1 and 2 of cycles 1–6. If no evidence of progression following induction, obinutuzumab 1000 mg IV was continued every 2 months for 2 years, or until disease progression. Comparator: Bendamustine monotherapy 120 mg/m^2/day IV, days 1 and 2 of each cycle for up to six cycles; each cycle was 28 days No patient crossover was allowed prior to primary analysis	<u>Primary:</u> PFS as assessed by an IRC <u>Secondary:</u> • PFS assessed by investigator • OS • Overall response (complete + partial response) at end of induction • Best overall response within 12 month of treatment start (by IRC and investigator) • Duration of response • Disease-free Survival • Event-free Survival • Minimal residual disease • FACT-lymphoma • EQ-5D <u>Post-hoc analyses:</u> • Time to new anti-lymphoma treatment Adverse Events
Abbreviations: CNS= central nervous system; CV= cardiovascular; ECOG= Eastern Cooperative Oncology Group; EQ-5D= EuroQol 5 dimension health index scale; FACT=functional assessment of cancer treatment; FL= follicular lymphoma; iNHL= indolent non Hodgkin's lymphoma; IRC= independent review committee; IV=intravenous; MZL= marginal zone lymphoma; OS= overall survival; PFS= progression-free survival; QoL= quality of life; SLL= small lymphocytic lymphoma; WM= Waldenstrom's macroglobulinemia;			

Table 5: Select quality characteristics of included studies of obinutuzumab in patients with follicular lymphoma

Study	Treatment vs. Comparator	Primary outcome	Required sample size	Sample size	Randomization method	Allocation concealment	Blinding	ITT Analysis	Final analysis	Early termination	Ethics Approval
GADOLIN	Obinutuzumab + bendamustine for induction, followed by obinutuzumab maintenance versus bendamustine monotherapy induction	PFS	410 (260 PFS events)	413 iNHL 335 with FL	Centrally administered	Yes	No	Yes	No	No	Yes
iNHL= indolent non-Hodgkin's lymphoma; FL= follicular lymphoma; PFS= progression free survival;											

a) Trials

GADOLIN is an ongoing, open-label, phase III, randomized, parallel group study with a superiority design. Randomization was stratified by four factors: 1) Indolent NHL subtype (follicular versus other); 2) Refractory type (rituximab monotherapy vs. rituximab + chemotherapy); 3) Number of prior therapies (≤2 vs. >2); 4) Geographic region.[3]

The primary outcome was progression-free survival as assessed by an independent review committee. The study was funded by Hoffman La Roche and there were 82 study sites in 14 countries (N=413). Countries with highest recruitment were Canada (24.0%), France (19.7%), USA (17.4%), Czech Republic (7.6%), and the United Kingdom (7.3%).[3] There were 10 sites in Canada that recruited 86 patients.[19]

GADOLIN included patients with indolent NHL who had no response to, or who progressed within 6 months of treatment with rituximab or a rituximab-containing regimen. In the GADOLIN trial, rituximab refractory was defined as no response to, or progression within 6 months of completion of the last dose of rituximab therapy (either as monotherapy or in combination with chemotherapy), including:[3]

- Patients with progressive disease while receiving rituximab monotherapy (after at least one full cycle), rituximab + chemotherapy (after at least one full cycle), or rituximab maintenance treatment (after having received at least one full dose [375 mg/m^2] of rituximab)
- Patients with no clinical response (partial response or better) to a rituximab-containing regimen consisting of at least four weekly doses of rituximab monotherapy or at least four cycles of rituximab + chemotherapy
- Patients with disease relapse (after having achieved a clinical response) within 6 months of completion of the last dose of rituximab therapy in a regimen consisting of at least four weekly doses of rituximab monotherapy or at least four cycles of rituximab + chemotherapy
- Rituximab-refractory as defined included patients who were refractory to any prior rituximab containing regimen, not just the most recent regimen containing rituximab. [3]

Efficacy assessments were performed on the intention-to-treat population. The first interim analysis for efficacy was performed when approximately 65% of the total PFS events had occurred and used a one-sided critical p-value of ≤0.0075.[3] The publication by Sehn et al summarizes the results of this analysis, which was based on the data cut-off date of September 1, 2014.[2] This analysis excluded 17

patients who enrolled after September 1, 2014. Two other interim analyses were performed with data cut-offs of May 1, 2015[3] and April 1, 2016;[1,23,24] the May 1, 2015 analysis was not part of the protocol-planned analyses.[27] A final analysis of overall survival is planned at 96 months (e.g. 4 years after the last patient enrollment, or approximately 264 deaths).[27]

Key exclusion criteria for GADOLIN included the following abnormal laboratory test results: creatinine concentration more than 1.5× the upper limit of normal, or creatinine clearance less than 40 mL/min; aspartate aminotransferase or alanine aminotransferase concentration more than 2.5 × upper limit of normal; total bilirubin 3 or more × upper limit of normal; and any of the following results unless they were due to underlying disease, as established by extensive bone marrow involvement: platelet count less than 100×10^9 cells per L; neutrophil count less than 1.5×10^9 cells per L; or haemoglobin less than 9 g/dL.[2]

b) Populations

Most patients had follicular non-Hodgkin's lymphoma (n=335, 81%). Non-follicular subtypes included extranodal marginal zone lymphoma (n=26, 6%), nodal marginal zone lymphoma (n=17, 4%), small lymphocytic lymphoma (n=30, 7%), splenic marginal zone (n=4,1%) and other (n=1). The focus of this review will be the subpopulation of patients with follicular lymphoma. Subgroup analyses were preplanned for patients with follicular lymphoma in the statistical analysis plan for the GADOLIN study.[27]

The baseline characteristics and disease status of the entire study population and the subgroup with follicular lymphoma are presented in Tables 6 and 7. The patients were relatively healthy, with low ECOG scores; approximately 15% of the entire study population had B symptoms (fever, night sweats, weight loss) at baseline.[2] More than half of the study patients had been exposed to at least 2 treatment regimens for indolent NHL and the mean time since the last treatment was approximately 8 months. The mean time from diagnosis to study entry was approximately 4 years. 77% of patients in the bendamustine group and 81% of patients in the obinutuzumab plus bendamustine group were refractory to rituximab and chemotherapy at baseline.[3] Of the 327(79%) patients who were refractory to a previous rituximab chemotherapy combination, 152(46%) had progressive disease during or within 6 months after the last rituximab maintenance dose.[3] Most patients (92%) were refractory to their last treatment regimen, irrespective of whether it contained rituximab.[4]

Table 6: Baseline characteristics in GADOLIN (ITT population)

	All Patients[1,3,4]		Follicular Lymphoma patients[2-4]	
	B N=209	GB N=204	B N=171	GB N=164
Mean age (SD), years	62(12)	62(11)	62(11)	62(11)
Male, n(%)	122(58)	116(57)	98(57)	91(56)
White race, n(%)	181(86)	180(88)	148(86)	144(88)
Mean weight , kg	81	80	82(20)	80(18)
ECOG 0-1, n(%)	196(95)	195(96)	*157(96)*	*147(95)*
ECOG 2, n(%)	10(5)	9(4)	*7(4)*	*8(5)*
FL Grade at initial diagnosis, n/N(%)				
1			*54/150(36)*	*51/160(32)*
2			*68/160(43)*	*69/150(46)*
3			*5/160(3)*	*0/150*
3a			*35/160(22)*	*24/150(16)*
Unclassified			*1/160(1)*	*3/150(2)*
FLIPI				
Low (0-1)			*34/159(21)*	*42/149(28)*
Intermediate (2)			*58/159(36)*	*47/149(32)*
High (≥3)			*67/159(42)*	*60/149(40)*
Ann Arbor Stage, n(%)				
I	12(6)	10(5)	9/170(5)	9/164(6)
II	20(10)	17(8)	20/170(12)	16/164(10)
III	53(26)	40(20)	45/170(27)	33/164(20)
IV	112(54)	124(61)	86/170(51)	96/164(59)
Unknown	11(5)	13(6)	10/170(6)	10/164(6)
Bone marrow involvement, n(%)	70/195(36)	65/197(32)	50(32)	42(28)
Extranodal involvement, n(%)	103/208(50)	113/204(55)	76(46)	82(53)
Bulky disease (>6cm), n(%)	74/206(36)	70/204(34)	*58(35)*	*49(32)*
Mean time from initial diagnosis to randomization (range), years	4.2 (0.3–29.9)	4.2 (0.3–32.1)	4.3 (0.3–29.9)	4.3 (0.3–32.1)
Median total prior regimens, (range)	2.0 (1.0–7.0)	2.0 (1.0–10.0)		
Median time since last regimen (maximum), months	3.89 (64)	3.94 (128)		
Refractory to last regimen, n(%)	193(92)	188(92)		
B Symptoms at baseline, n(%)[1,4]	29 (14)	32(16)	28(16)	21(13)

ECOG= Eastern Cooperative Oncology Group; FL= follicular lymphoma; FLIPI= follicular lymphoma international prognostic index; iNHL=indolent non-Hodgkin's lymphoma; NR=not reported; SD=standard deviation;

Note: Data in this table are from the May 2015 data cut-off, except the figures in *italics*, which are from the September 2014 data cut-off.

Table 7: Rituximab refractory status at baseline in GADOLIN, all patients data cut-off May 1, 2015[3]

	B N=209	GB N=204
Refractory to rituximab monotherapy	48(23)	38(19)
PD prior to last rituximab dose	4(8)	3(8)
Best response of SD	16(33)	8(21)
PD within 6 months of last rituximab dose	28(58)	27(71)
Refractory to rituximab and chemotherapy	161(77)	166(81)
PD prior to last rituximab induction dose	2(1)	5(3)
Best response of SD	27(17)	39(24)
PD within 6 months after last rituximab induction dose	60(37)	33(20)
PD during or within 6 months after last rituximab maintenance dose	70(43)	82(49)
PD within 6 months of last maintenance dose (no induction rituximab or last rituximab induction dose unknown)	1(<1)	3(2)
PD more than 6 months after last rituximab dose but within 6 months after best response	1(<1)	1(<1)
Not refractory	0	3(2)

B= bendamustine; GB= obinutuzumab plus bendamustine; PD= progressive disease

c) Interventions

According to the pivotal trial, "patients assigned to obinutuzumab plus bendamustine received obinutuzumab 1000 mg intravenously on days 1, 8, and 15 of cycle 1 and day 1 of cycles 2–6, plus bendamustine 90 mg/m^{2}per day intravenously on days 1 and 2 of cycles 1–6. Patients assigned to bendamustine monotherapy received 120 mg/m^2 per day intravenously on days 1 and 2 of each cycle for up to six cycles; each cycle was 28 days. Patients in the obinutuzumab plus bendamustine group without evidence of progression following induction received obinutuzumab maintenance therapy given as 1000 mg intravenously every 2 months for 2 years, or until disease progression. No patient crossover was allowed before primary analysis".[2]

"Acetaminophen and an antihistamine were administered 30–60 min before obinutuzumab infusions. Other recommended premedications included corticosteroids (before the first obinutuzumab dose in cycle 1) and antiemetics (before bendamustine infusions). Dosing of obinutuzumab and bendamustine was delayed for up to 4 weeks in the event of grade 3 or 4 neutropenia or anaemia, grade 2–4 thrombocytopenia or grade 2–4 non-haematological toxicity; if the toxicity resolved within the 4-week period, dosing was resumed, but the bendamustine dose was reduced to 90 mg/m^2 per day or 60 mg/ m^2 per day for subsequent cycles depending on the number of previous episodes of that toxicity. If toxicity did not resolve, the patient was withdrawn from study treatment. Dose reductions were allowed for bendamustine but not for obinutuzumab".[2] Dose interruption, delays, discontinuations and infusion rate reduction were allowed.

The Provincial Advisory Group was seeking data on the comparison of obinutuzumab to rituximab re-treatment, but there were no studies that evaluated this comparison.

d) Patient Disposition

In the 335 patients with follicular lymphoma, the overall median follow up time was 24.5 months as of the May 1, 2015 data cut-off.[1] 75 patients (48[29%] of 168 in the bendamustine group and 27[16%] of 164 patients in the obinutuzumab plus bendamustine group) withdrew from induction treatment before

receiving all scheduled doses. There was one ongoing patient on bendamustine induction and there were 21 ongoing patients on obinutuzumab maintenance out of the 125 patients who started the maintenance phase.

Table 8: Patient disposition in subgroup with follicular lymphoma (N=335), data cut-off May 1, 2015[1]

	B	GB
Screened	NR	
Met eligibility	171	164
Randomized (ITT population)	171	164
Did not start induction	3	0
Started induction	168	164
Withdrew from induction	48	27
Adverse event	29(17)	11(7)
Death	0	1(<1)
Other	1(<1)	0
Physician decision	1(<1)	3(2)
Progressive disease	12(7)	10(6)
Withdrawal by subject	5(3)	3(2)
Still on bendamustine induction	1	N/A
Did not start maintenance	N/A	12
Started maintenance with obinutuzumab	N/A	125
Withdrew from maintenance with obinutuzumab	N/A	64
Adverse event	N/A	10(6)
Death	N/A	1(<1)
Other	N/A	5(3)
Physician decision	N/A	2(1)
Progressive disease	N/A	43(26)
Withdrawal by subject	N/A	3(2)
Still on obinutuzumab	N/A	21
Completed maintenance	N/A	40
Patients who started follow up at the 2 year timepoint	157	134
Withdrawn from initial 2 year follow up	105	66
Follow up ongoing	102	95

B= bendamustine; GB= obinutuzumab plus bendamustine; ITT= intention-to-treat; N/A= not applicable; NR= not reported;

Table 9: Exposure to study medications (as of May 1, 2015)[3]

	Induction			Maintenance
Treatment group	Bendamustine N=205	Bendamustine/Obinutuzumab N=204		Bendamustine/ Obinutuzumab N=204
	N=205	N=203	N=204	N=154
Drug	Bendamustine	Bendamustine	Obinutuzumab	Obinutuzumab
Patients who received all cycles*,n(%)	147(72)	159(78)	167(82)	50(33)

Median number of doses received (range)	12(2-12)	12(1-12)	8(1-8)	7(1-12)
Median duration of treatment (range), days	170(25-243)	170(1-233)	169(1-264)	394(15-729)

* For induction, 6 cycles, each of 28 days (†bendamustine: 2 infusions in each cycle of Cycles 1-6[Day 1 and 2], total 12 infusions); obinutuzumab: 3 infusions in Cycle 1 [Day 1,2, 8 and 15], and one infusion in each cycle of Cycles 2-6 (Day 1), total of 8 infusions). For the Maintenance phase, up to 12 cycles (or disease progression) each of 2 months (one obinutuzumab infusion per cycle (up to total 12 infusions).

The exposure data for the May 1, 2015 cutoff in Table 9 indicate that approximately 72% of patients in the bendamustine only group received all planned cycles during the induction phase. The proportion of patients was slightly higher in the bendamustine and obinutuzumab group during induction, with 78% and 82% of patients receiving all planned cycles, respectively.

Table 10 summarizes the observation time in GADOLIN and at the most recent data cut-off (April 1, 2016), the median observation times for the bendamustine and bendamustine plus obinutuzumab groups were 30 and 34 months, respectively.

Table 10: Observation time in overall GADOLIN study population

Data cut-off	**September 1, 2014[2]**		**May 1, 2015[1]**		**April 1, 2016[1,24]**	
	B N=202	GB N=194	B N=209	GB N=204	B N=209	GB N=204
Total observation time for entire cohort, years	NR	NR	424	446	529	565
Median observation time, months	NR	NR	24	25	30	34

B= bendamustine; GB= obinutuzumab plus bendamustine; NR= not reported;

e) Limitations/Sources of Bias

- At baseline, prognostic risk factors such as demographic characteristics and previous treatment history were well balanced between the treatment groups, with the exception of a slightly higher proportion of patients in the obinutuzumab plus bendamustine group with extranodal involvement, indicating more advanced disease.
- Investigators and patients were aware of treatment assignment in GADOLIN. The independent review committee also performed unblinded assessments of data.[2] Reviewers acknowledge that incorporating blinded treatment groups in GADOLIN would have been difficult, however, the open-label nature of the trial could have introduced assessment and reporting biases in the efficacy and adverse events analyses. Investigator assessments of overall survival and progression-free survival were generally congruent with the findings of the independent review committee.
- There was little observable separation in the survival curves for overall survival or progression-free survival at 6 months, which corresponds to the end of the induction period (see Figures 2 and 3). The overall response (complete response+PR) and complete response rates were not different between the two study arms after 12 months on study. Because there was no maintenance therapy in the bendamustine arm of GADOLIN, these observations make assignment of responsibility for the improvement in progression free and overall survival to any particular phase of the experimental treatment challenging. It is not clear if the improvements in these survival endpoints noted in the obinutuzumab plus bendamustine arm were attributable to the induction treatment with obinutuzumab plus bendamustine, or from the addition of obinutuzumab as maintenance.
- While there was some evidence of improvements in overall survival for the patients taking obinutuzumab plus bendamustine, relative to bendamustine monotherapy, the magnitude of difference in median survival is unclear based on the most recent data cut-off(April 1,2016).

- The bendamustine doses differed between treatment groups (90 vs 120 mg/m^2 /day) during the induction phase. Therefore it is not certain that any observed differences in adverse event rates or efficacy during the induction phase may be attributable to the addition of obinutuzumab. Higher doses of bendamustine may increase risk of myelosuppression (e.g. neutropenia, infectious complications).
- The GADOLIN study began enrolling patients in 2010. Since that time, bendamustine has moved to an earlier treatment line than is reflected by the GADOLIN study. This limits generalizability (see section 1.2.3).
- There were statistical analyses performed at multiple time points for outcomes such as overall survival and progression-free survival (e.g. 2014, 2015, 2016). The May 1, 2015 analysis was not preplanned in the protocol.[27] In many cases, there was no reference to the alpha level used to assess statistical significance. For example, it is not clear what the critical p-value is for the most recent overall survival data (April 1, 2016). With multiple analyses at multiple time points, there is an increased chance of demonstrating a statistically significant effect by chance.
- Several of the Kaplan-Meier plots for progression free survival and overall survival have lines that cross each other (e.g. Figures 2 and 3, below). In response to a pCODR request, the manufacturer tested the proportional hazards assumption for ICR-assessed PFS using the May 2015 data cut and for OS using the May 10 2015 and April 2016 data cuts.[27] Testing revealed some evidence to suggest that the proportional hazards assumption was not met for the progression free survival analysis and the overall survival analyses. NICE also assessed the proportional hazards assumption using Schoenfeld residuals for PFS from the GADOLIN trial.[4] They concluded strong evidence (spline regression fit, p = 0.0188) that the assumption was not valid. [4] This increases uncertainty in the effect estimates and the 95% confidence intervals around the hazard ratios. An option for addressing this issue is stratification—that is, fitting different Cox regressions for different time frames to obtain different hazard ratios. However, these methods reduce the sample size, and increase the likelihood of type 2 error. Currently, the hazard ratio can be interpreted as an "average" of the curves over time (or the average of the different hazard ratios after stratifying by different time frames). Qualitatively, the PFS and OS analyses favour obinutuzumab plus bendamustine over bendamustine monotherapy, but there is uncertainty associated with the actual effect size.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Table 11. GADOLIN results, data cut-off May 1, 2015[1,3,4]

	iNHL Overall Study Population		Follicular Lymphoma Subgroup	
	B N=209	GB N=204	B N=171	GB N=164
Deaths, n(%)	56(27)	42(21)	48(28)	30(18)
Median OS(95%CI), months	NE(NE)	NE(NE)	NE(42.2,NE)	NE(NE)
HR(95%CI)	0.72(0.48,1.08); p=0.11		0.62(0.39,0.98); p=0.038	
Patients with PFS event, n(%)*	125(60)	87(43)	108(63)	67(41)
Median PFS(95%CI), months	14.1(11.7,16.6)	29.2(20.5,NE)	13.8(11.5,15.8)	29.2(20.5,NE)
HR(95%CI)	0.53(0.40,0.70) p<0.0001		0.47(0.34,0.64); p<0.0001	
Overall best response (CR/PR), n(%)†	162(78)	154(76)	135(79)	125(76)
ARR(95%CI)	-2.02(-10.46,6.42); p=0.52		-2.73(-11.99,6.54); p=0.51	
Best response (CR), n(%)†	36(17)	33(16)	33(19)	25(15)
ARR(95%CI)	-1.05(-8.50,6.41); p=0.93		-4.05(-12.46,4.35); p=0.50	
Patients with EOI Response, n(%)	134(64)	136(67)	111(65)	111(67)
ARR(95%CI)	2.24(-7.20,11.69); p=0.83		2.39(-8.07,12.85); p=0.70	
DoR after CR or PR, patients with event, n/N(%)	100/165(61)	61/158(39)	88/137(64)	47/126(37)
Median DoR(95%CI), months	12.7(10.4,14.1)	38.5(25.4,NE)	11.6(8.8,13.6)	NE(22.8,NE)
HR(95%CI)	0.43(0.31,0.61); p=NR		0.39(0.27,0.55); p=NR	
DFS after CR, patients with event, n/N%	17/37(46)	4/46(9)	16/33(49)	3/35(9)
Median DFS(95%CI), months	13.2(8.5,NE)	NE(NE)	13.0(8.2,NE)	NE(NE)
HR(95%CI)	0.13(0.04,0.45); p=NR		0.14(0.04,0.48); p=NR	

ARR= absolute risk reduction; CR= complete response; DoR= Duration of Response (time from CR or PR to progression, relapse or death); DFS= Disease Free Survival (time from CR until relapse or death); EFS = Event Free Survival (time from randomization to progression or relapse, death or start of new anti-lymphoma treatment); EOI= end of induction; HR= hazard ratio; iNHL= indolent non-Hodgkin's lymphoma; NE= not estimable; NR= not reported; OS= overall survival; PFS= progression free survival; PR= partial response;

*PFS assessment by independent review committee; †during treatment and within 12 months of starting treatment

Note: Patient Advocacy Group Input indicated that patients consider the following outcomes as important: overall survival, remission of disease, symptom control and quality of life.

a) Efficacy Outcomes

Overall Survival

Overall survival was a secondary endpoint in the GADOLIN study. There was no statistically significant difference in overall survival in the overall study population at the first and second interim efficacy analyses (data cut-off September 1, 2014, May 1, 2015). A recent abstract reported a statistically significant difference in overall survival, favouring the obinutuzumab plus bendamustine group, in a third interim analysis (April 1, 2016; HR[95%CI]: 0.67[0.47,0.96]).[1,23,24]

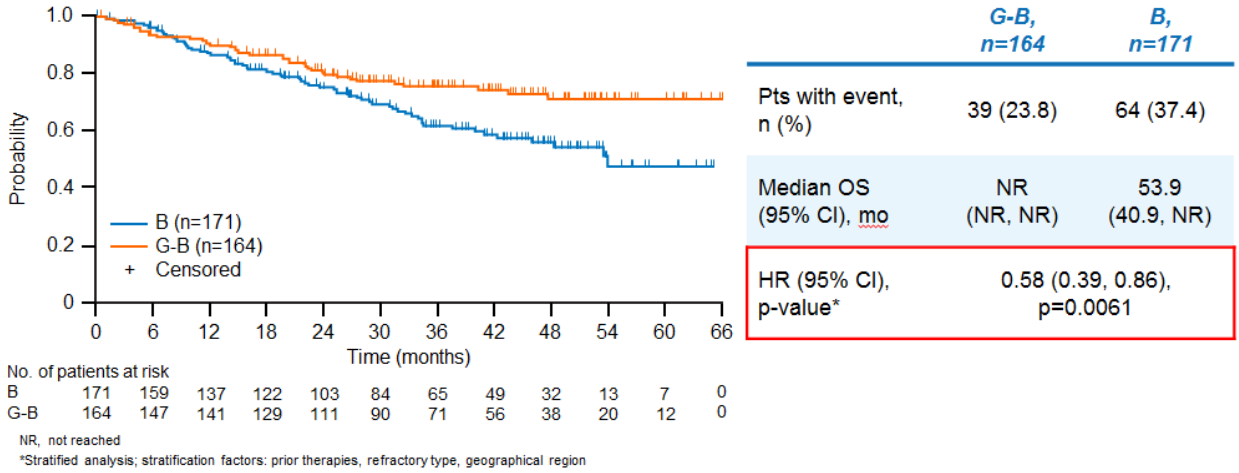
In the subgroup of patients with follicular lymphoma, there were statistically significant differences observed in the overall survival analyses at the second and third efficacy analyses, as shown in Table 12.

Table 12: Overall Survival in Follicular Lymphoma Patients

Data Cut-off	Deaths, n/N(%)		Median OS (95%CI)		HR(95%CI)
	B	GB	B	GB	
September 1, 2014[2]	36/166(22)	25/155(16)	NE(39.8, NE)	NE(NE)	0.71(0.43,1.19); p=0.20
May 1, 2015[3]	48/171(28)	30/164(18)	NE(42.2,NE)	NE(NE)	0.62(0.39,0.98); p=0.038
April 1, 2016[1,24]	64/171(37)	39/164(24)	53.9(40.9,NE)	NE(NE)	0.58(0.39,0.86); p=0.0061

B= bendamustine; GB= obinutuzumab plus bendamustine; NE=not estimable; OS=overall survival;

Figure 2: GADOLIN follicular lymphoma patients, overall survival (data cut-off April 1, 2016)[23]



Adapted with permission from: Cheson BD, Trneny M, Bouabdallah K, Dueck G, Gribben J. Obinutuzumab plus bendamustine followed by obinutuzumab maintenance prolongs overall survival compared with bendamustine alone in patients with rituximab-refractory indolent non-Hodgkin lymphoma: updated results of the GADOLIN study [slide deck]. Abstract presented at: Presented at ASH 58th Annual Meeting and Exposition; 2016 Dec 3-6; San Diego, CA. 2016.

Progression-Free Survival

Progression-free survival as assessed by the independent review committee was the primary end point for the GADOLIN study. There was a statistically significant difference in progression-free survival in the overall study population at the first efficacy analysis favouring the obinutuzumab plus bendamustine group (data cut-off September 1, 2014; HR[95%CI]: 0.55[0.40,0.74], p=0.0001).[2] There were statistically significant differences favouring the obinutuzumab plus bendamustine group for progression free survival in the second and third efficacy analyses (data cut-off May 1, 2015 and April 1, 2016).[1,3,24]

In the subgroup of patients with follicular lymphoma, there were statistically significant differences observed in the progression-free survival analyses at the first, second and third interim analyses, as shown in Table 13.

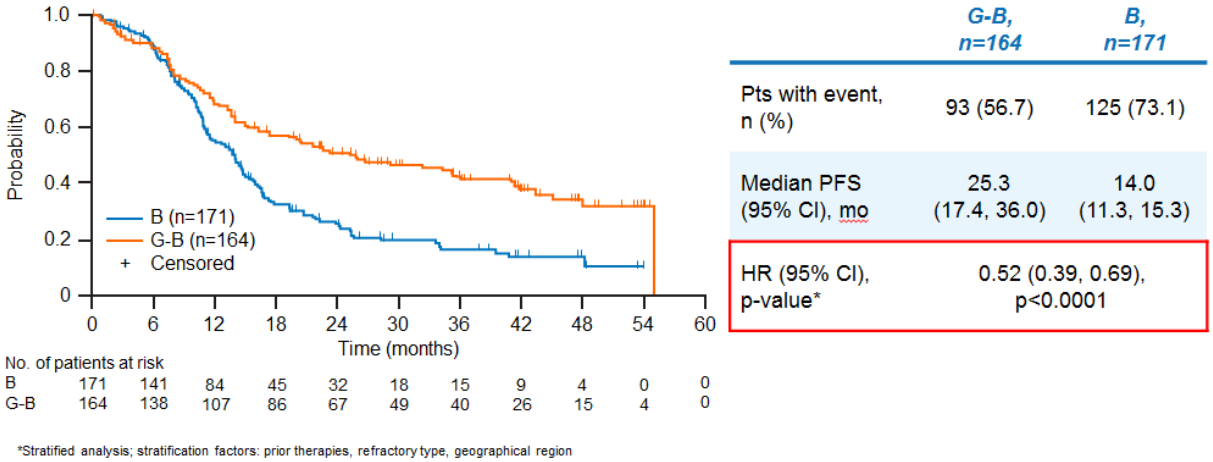
Table 13: Progression-Free Survival in Follicular Lymphoma Patients*

Data Cut-off	PFS Events, n/N(%)		Median PFS (95%CI)		HR(95%CI)
	B	GB	B	GB	
September 1, 2014[2,3]	90/166(54)	54/155(35)	13.8(11.4,16.2)	NE(22.5,NE)	0.48(0.34,0.68); p<0.0001
May 1, 2015[3]	108/171(63)	67/164(41)	13.8(11.5,15.8)	29.2(20.5,NE)	0.47(0.34,0.64); p<0.0001
April 1, 2016[1,24]	125/171(73)	93/164(57)	14.0(11.3,15.3)	25.3(17.4,36.0)	0.52(0.39,0.69); p<0.0001

B= bendamustine; GB= obinutuzumab plus bendamustine; NE=not estimable; PFS=progression-free survival;

*Data were assessed by the independent review committee except for data from April 1, 2016, which were investigator assessed

Figure 3: GADOLIN follicular lymphoma patients, PFS (data cut-off April 1, 2016)[23]



Adapted with permission from: Cheson BD, Trneny M, Bouabdallah K, Dueck G, Gribben J. Obinutuzumab plus bendamustine followed by obinutuzumab maintenance prolongs overall survival compared with bendamustine alone in patients with rituximab-refractory indolent non-Hodgkin lymphoma: updated results of the GADOLIN study [slide deck]. Abstract presented at: Presented at ASH 58th Annual Meeting and Exposition; 2016 Dec 3-6; San Diego, CA. 2016.

Response Rate

GADOLIN measured overall response (complete response+partial response) at the end of induction, and best overall response within 12 months of treatment initiation. There were no statistically significant differences in overall response between the two treatment arms at any of the data cut-offs for these outcomes (Table 11). As of the May 1, 2015 data cut-off, the rates of best response during treatment and within 12 months of starting treatment in patients with follicular lymphoma were 79% in the bendamustine group and 76% in the obinutuzumab plus bendamustine group (absolute risk reduction[95%CI]: -2.73[-11.99,6.54]; p=0.51).[3]

Time to Next Treatment

Time to next anti-lymphoma treatment was reported at the September 1, 2014 timepoint.[2] This event occurred in 97/202 (48%) patients in the bendamustine group and 69/194 (36%) patients in the obinutuzumab plus bendamustine group (HR[95%CI]: 0.65[0.47,0.88]).

There was also a statistically significant difference in time to next anti-lymphoma treatment in the analysis of April 1, 2016. In the overall study population, the median time to event was 19.4 months in the bendamustine group vs 40.8 months in the obinutuzumab plus bendamustine group (HR [95%CI]: 0.59; [0.45, 0.77]). In the follicular lymphoma subgroup, the median time to event was 18.0 months in the bendamustine group vs 33.6 months in the obinutuzumab plus bendamustine group (HR [95%CI]: 0.57; [0.43, 0.75]).[24]

Time to Symptomatic Disease

This outcome was not reported in the GADOLIN trial.

Duration of Response

Duration of response was assessed in the group of patients who achieved complete response or partial response, and it was also assessed in the group of patients who achieved a complete response.

In the overall trial population, there were statistically significant differences in duration of response at two assessment time points (September 1, 2014, May 1, 2015). Median duration of response for patients with complete response or partial response as of May 1, 2015 was 12.7 months (95%CI: 10.4, 14.1) for patients taking bendamustine and 38.5 months (95%CI: 25.4, not estimable) for patients taking obinutuzumab plus bendamustine (HR[95%CI] 0.43[0.31,0.61]).[1,4]

In patients with follicular lymphoma, the results for duration of response were similar to the results in the overall trial population. Median duration of response for patients with complete response or partial response as of May 1, 2015 was 11.6 months (95%CI: 8.8,13.6) for patients taking bendamustine and not estimable for patients taking obinutuzumab plus bendamustine (HR[95%CI]: 0.39[0.27,0.55]).[1,4]

Duration of response was not reported for the most recent interim analysis (April 1, 2016 data cut-off).

Quality of Life

FACT-Lym

Patient-reported health-related quality of life (HRQoL) was measured using the FACT-Lym. It measures 5 sub-scales which includes 42 items; responses to each item range from 0, "Not at all" to 4, "Very much". Total score ranges from 0-168. Physical Well-being sub-scale includes 7 items measured on 0-4 point scale. The total score for physical well-being sub-scale is sum of each 7 items (range: 0-28). Higher scores indicate a better participant-reported outcome (PRO)/quality of life (QoL).[26] The authors of the publication summarizing the HRQoL data stated that the analyses were considered exploratory and statistical comparisons were not performed for many of the comparisons. Relative to the range of the FACT-Lym Total scale (range: 0-168), the differences observed between the two treatment groups were small and no statistical testing was performed.[20] A major limitation of the FACT-Lym data is that questionnaire completion rates decreased substantively over time. Completion rates for all scales of the FACT-Lym for the bendamustine group and the bendamustine plus obinutuzumab group declined over time from end of induction (76% vs 77%) to 18 months after end of induction (58% vs 76%). The published data on the FACT-Lym did not clearly explain the methods used for data imputation where data were missing.

In the follicular lymphoma subgroup, median time to deterioration of FACT-Lym Trial Outcome Index (TOI) score, defined as ≥ 6-point worsening from baseline, was 5.6 months in the bendamustine group compared to 7.8 months in the bendamustine plus obinutuzumab group (HR[95%CI]: 0.83[0.60,1.13]).[20] Data were censored at the time of randomization if patients did not have a post-baseline FACT-Lym assessment and patients who did not reach ≥6-point worsening were censored at their last completed PRO questionnaire.[20] The authors of the QoL publication cite a validation study in mantle-cell lymphoma to support their selection of a 6 point cut-off for the TOI results for GADOLIN.[28] The validation study is available in abstract format only and therefore the methods for deriving the minimal clinically important differences could not be adequately appraised.

EQ-5D

Health status was measured by the EQ-5D and the EQ-5D visual analog scale in GADOLIN. The Health State Profile component assesses level of current health for 5 domains: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression; 1 indicates better health state (no problems); 3 indicates worst health state ("confined to bed"). The scoring formula assigns a utility value for each domain in the profile. The score is transformed and results in a total score range -0.594 to 1.000; a higher score indicates a better health state.[26] The available EQ-5D allowed comparisons of the two treatment groups at various times throughout the induction phase, but the data for the maintenance phase were only recorded for the obinutuzumab plus bendamustine arm. There were no statistical analyses available for the EQ-5D data.[26]

Harms Outcomes[1,3,27]

Selected adverse event data are summarized in Table 14. Interpretation of the adverse event data in the induction phase is complicated by the fact that the bendamustine dose was not the same in both arms and interpreting the adverse event data beyond the induction phase is complicated by the fact that there was no maintenance treatment in the bendamustine-only treatment group. In the induction phase, the study group with a lower bendamustine dose plus obinutuzumab had a higher rate of serious adverse events (28%) compared to bendamustine at a higher dose (22%). Grade 3-5 thrombocytopenia and grade 3-5 infusion reactions were more common during the induction phase in the group that received obinutuzumab. Grade 3-5 infections were more common in the group receiving bendamustine alone, during the induction phase.

Table 14: Adverse Events of interest by treatment arm and treatment phase, n(%) (Cut-off April 1, 2016) [3,23,27]

	Induction		Maintenance	Overall	
	B, n=205[¥]	G-B, n=204	G-B, n=158*	B, n=203*#	G-B, n=204#
SAE	45(22)	58(28)	26(16)	75(36.9)	89(43.6)
Grade 3-5 AE	108(53)	113(55)	53(34)	133(65.5)	148(72.5)
AE leading to withdrawal from any study treatment	35(17)	29(14)	5(3)	35(17.2)	41(20.1)
AE leading to dose modification†	87(42)	86(42)	27(17)	86(42.2)	102(50)
Gr 3-5 Neutropenia‡	55(26.8)	56(27.5)	17(10.8)	55(27.1)	71(34.8)
Gr 3-5 Thrombocytopenia‡	32(16)	21(10.3)	2(1.3)	32(15.8)	22(10.8)
Gr 3-5 Infections and infestations	25(12.2)	16(7.8)	16(10.1)	39(19.2)	46(22.5)
Gr 3-5 Infusion-related reactions‡	7(3.4)	18(8.8)	1(0.6)	7(3.4)	19(9.3)
Gr 3-5 Neoplasms§¶	2(1.0)	2(1.0)	4(2.5)	11(5.4)	12(5.9)
Gr 3-5 Cardiac disorders§**	2(1.0)	5(2.5)	3(1.9)	3(1.5)	9(4.4)
Gr 3-5 GI perforation	0	1(<1)	0	0	1(0.5)
Gr 3-5 Hepatitis Reactivation	1(<1)	0	0 (one event happened during follow-up)	1(0.5)	1(0.5)#

*2 patients who crossed over from the B arm to the G-B arm during maintenance are excluded;

†decrease or delay;

[¥] patients who crossed over from the B arm to the G-B arm during maintenance are included;

‡by preferred term;

§ by SOC;

¶benign, malignant and unspecified (including cysts and polyps);

**8 of 12 patients with a history of cardiac disease; # includes follow up patients and AE were counted once trough the treatment per patient.

6.4 Ongoing Trials

There were no ongoing or unreported trials identified that would meet the inclusion criteria for the pCODR systematic review.

7 SUPPLEMENTAL QUESTIONS

The following supplemental question was identified during development of the review protocol as relevant to the pCODR review of Obinutuzumab (Gazyva) for the treatment of adults with follicular lymphoma who relapsed after, or are refractory to, a rituximab containing regimen. Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Critical Appraisal of Propensity Score Analyses of GADOLIN Data and Registry Data: Obinutuzumab versus Chemotherapy Regimens for Patients With Follicular Lymphoma

7.1.1 Objective

The GADOLIN pivotal trial compared the efficacy of obinutuzumab and bendamustine followed by obinutuzumab maintenance (hereafter referred to as GB) to bendamustine alone. Other FL treatment options were not examined in the trial. Based on a systematic literature review and feasibility assessment, the submitter conducted propensity score analyses to address the following question:

What is the comparative efficacy of GB versus relevant treatment options in progression-free survival (PFS) for patients with FL who are relapsed or refractory to treatment with a rituximab-containing regimen?

Comparative efficacy was measured in terms of progression-free survival (PFS), defined as the time from start of treatment line to progression or death.

7.1.2 Methodology

Systematic literature review

In a systematic literature review, the submitter searched MEDLINE, MEDLINE In-Process, EMBASE, NHS EED, and the Cochrane Library from 1998 which corresponds to when rituximab was first approved on the market, to 2016. Languages included English, French, and German. Hand searches of conference proceedings, clinical trial registries, and regulatory body websites supplemented the systematic database search. The purpose of the search was to identify comparative trials for generating comparisons between GB and other available treatment options for FL in patients relapsed or refractory to a rituximab-containing regimen in Canada.

Based on the comparator groups, patient characteristics, study characteristics, and network diagram of the identified comparative trials, the submitter deemed propensity score (PS) analyses as the most appropriate method for synthesizing the evidence. PS techniques may approximate a randomized trial, balancing measured baseline characteristics between treatment groups and reducing the impact of confounding. This is done by combining baseline characteristics into a single summary score called a PS for each patient. Overall, propensity scores represent the probability of a patient receiving the particular treatment, conditional on the observed characteristics. Scores are then used for adjustment by weighting or matching to create balance between treatment groups. Such techniques use individual patient data as opposed to aggregate data from the literature.

Data sources

To compare GB to other relevant FL treatment options, the submitter used two data sources:

1. GADOLIN trial (enrollment from 2010; unplanned analysis using May 2015 data cut off) to inform the GB group
2. A registry to inform the other FL treatment groups (comparator)

The LymphoCare registry contains individual patient data maintained by Hoffmann-La Roche. Patients with FL (n = 2,728) from 265 sites in the United States were enrolled between 2004 and 2007, and followed until 2014 or until death, withdrawal of consent, or lost to follow up. The submitter identified and included registry patients who were refractory to rituximab monotherapy or rituximab-containing regimens (n = 322 of the 2,728 individuals in the registry) using the refractory definition as per the GADOLIN protocol: "No response to or progression within six months of completion of the last dose of rituximab (either as monotherapy with a minimum of 4 doses or in combination with chemotherapy with a minimum treatment duration of 4 cycles)".[1] Data on patient characteristics, treatment options, and treatment outcomes were captured in the registry. Of note, the submitter's report did not define progression, and it was not possible to compare the definition used in the registry with the one used in the GADOLIN trial. Further, the submitter's report did not specify when baseline characteristics were collected (i.e., when patients first entered the registry, or when patients started the treatment of interest).

Comparators

To identify the relevant comparators to Canadian patients in the PS analyses, the submitter conducted a chart audit in 2014-2015 of 1,000 charts from 30 to 40 Canadian hematologists. From the chart audit, treatments that were in at least 1% of rituximab-refractory patients with FL were included in the analyses. Further, a systematic literature review of single-arm studies on FL patients informed other treatment options not captured in the registry, such as idelalisib. Among the treatment options identified by the submitter, the pCODR Clinical Guidance Panel felt one comparator— chemotherapy, was relevant to current Canadian clinical practice. The category, "Relevant Chemotherapies in Canada" defined by the submitter, comprised of bendamustine, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), CVP (cyclophosphamide, vincristine, prednisone), GDP (gemcitabine, dexamethasone, cisplatin), FC (fludarabine, cyclophosphamide), F (fludarabine), and G (gemcitabine).

Propensity score estimation

The submitter sought the expert opinion of three hematologists from Ontario, Quebec, and Saskatchewan, who identified the following factors a priori as important predictors of treatment response: (1) Follicular Lymphoma International Prognostic Index (FLIPI), which includes age 60 and older, Ann Arbor stage III-IV, hemoglobin level <120 g/L, serum lactate dehydrogenase (LDH) level > upper limit normal, number of nodal sites; (2) refractoriness to previous therapy; (3) median number of prior therapies; and (4) bone marrow involvement. Among the recommendations, the following five factors were captured in the registry and consequently used in the PS estimation:

1. number of prior therapies
2. age

3. Ann Arbor stage
4. bone marrow involvement
5. elevated serum LDH

The PS estimation involved fitting a multivariate logistic regression model with treatment option (GB versus chemotherapy) as the dependent variable and the five factors above as independent variables. Propensity scores of all patients were logit transformed for subsequent weighting and matching.

The CGP felt that the Ann Arbor stage was not an important prognostic factor because the patient population was refractory, and already at an advanced stage. The CGP noted that other factors, listed in order of importance, were not included in the PS model: major organ dysfunction (renal, hepatic, and cardiac), and performance status.

Primary analyses: Inverse probability of treatment weighting

The submitter used inverse probability of treatment weighting (IPTW) in the primary analysis to compare patients treated with GB and patients treated with chemotherapy. This technique uses the inverse of the estimated PS in GB patients, and the inverse of one minus the estimated PS in chemotherapy patients in order to construct weights, akin to weights found in survey sampling. The reweighting of patients within the treatment groups creates a pseudo-population that approximates sampling from a population in which there was no confounding.

Absolute standardized differences (ASD) between pre- and post-IPTW were plotted for each baseline characteristic, where ASD > 0.1 indicated an imbalance between the treatment groups. The primary analyses examined patients with no missing baseline characteristics.

Sensitivity analyses

As part of sensitivity analyses using IPTW, the submitter included patients with missing baseline characteristics.

In addition, the submitter used propensity score matching (PSM) as sensitivity analyses to compare patients treated with GB and patients treated with chemotherapy. Two PSM techniques were used: nearest neighbour and caliper matching algorithms. Nearest neighbour matches, without replacement, a patient treated with GB to a patient treated with chemotherapy based on the smallest absolute difference in PS. Caliper matching pairs a patient treated with GB to a patient treated with chemotherapy (1:1) based on a caliper width of 20% of the observed standard deviation of the logit-transformed PS.

Baseline characteristics of patients from the GB group and chemotherapy group were examined pre-PSM and post-PSM to check for balance between the groups. ASD > 0.1 indicated an imbalance. T-tests and chi-square tests were also used as checks for differences between treatment groups pre- and post-PSM.

Progression-free survival

The submitter used Cox proportional hazard models to compare PFS in the treatment groups and to account for matching. The proportionality assumption was assessed by visual inspection of the log-cumulative hazard plot, visual inspection of the Schoenfeld residuals, and statistical testing based on the scaled Schoenfeld residuals. The main results were reported as hazard ratios (HR) and corresponding 95% confidence intervals (CI).

7.1.3 Results

Systematic literature review

From the systematic literature review of comparative studies, the submitter did not identify a common comparator to connect the GADOLIN trial to the evidence network. Further, the majority of these comparative studies reported on indolent non-Hodgkin lymphoma subtypes other than FL, included patients who were not relapsed or refractory to rituximab, or included treatment comparators not relevant in Canada. Therefore, a network meta-analysis was not feasible. The submitter deemed PS analyses as the most appropriate method for synthesizing the evidence.

Primary analyses: Inverse probability of treatment weighting

Overall, a total of 160 FL patients refractory to rituximab-containing regimens had no missing baseline characteristics and were included in the IPTW analyses. Specifically, 139 patients were treated with GB and 21 patients were treated with chemotherapy relevant to Canadian patients.

Error! Not a valid bookmark self-reference. shows the baseline characteristics prior to PS weighting or matching. There were imbalances observed between the treatment groups for almost all characteristics. Figure 2 shows that imbalances remained after IPTW, as denoted by the triangle points (post-IPTW ASD) being greater than 10%.

Table 1 shows the final results of the primary analysis comparing PFS of patients treated with GB versus patients treated with relevant chemotherapies in Canada. Median PFS was not reported for either treatment group. After IPTW, the submitter noted a statistically significant improvement in PFS associated with GB (HR = 0.18; 95% CI, 0.12 to 0.27). The submitter concluded that the proportional hazard assumption was valid.

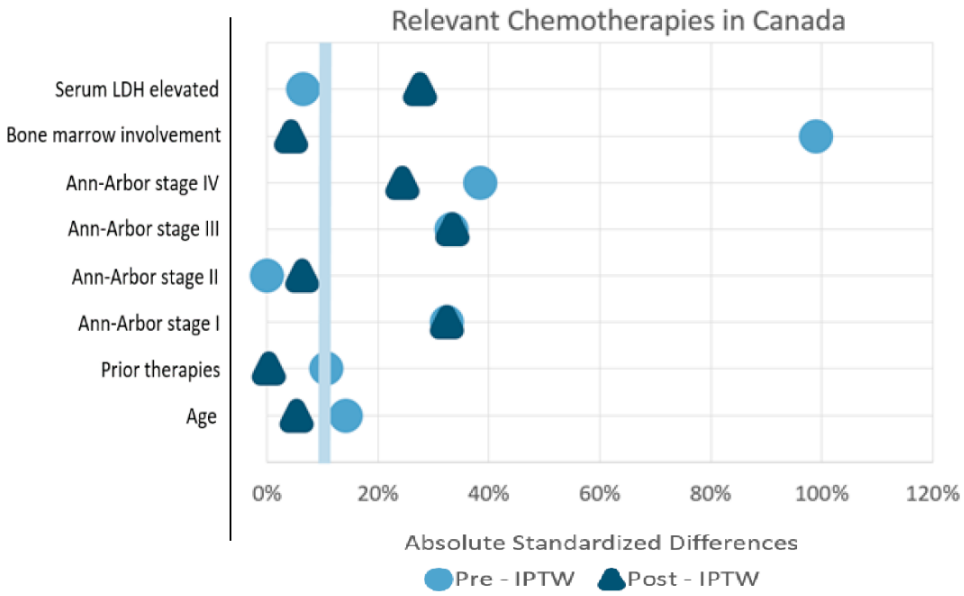
Figure 1: Baseline characteristics prior to propensity score weighting or matching among follicular lymphoma patients without missing baseline characteristics (GB, n= 139 versus Relevant Chemotherapy in Canada, n= 21)

	Prior to IPTW and PSM			
	G-Benda	Comparator	Absolute standardized Difference	P-Value for Difference between Groups
Mean Age in years	62.14	60.43	**0.14**	**0.04**
Number of prior therapies	1.81	2.24	**0.11**	**0.03**
Ann-Arbor stage	I = 5%	I = 0%	**0.32**	**<0.001**
	II = 10%	II = 10%	0	1
	III = 22%	III = 9%	**0.33**	**<0.001**
	IV = 63%	IV = 81%*	**0.38**	**<0.001**
Bone marrow involvement	31%	76%	**0.99**	**<0.001**
Serum LDH elevated	32%	29%	0.07	0.41

GB = obinutuzumab and bendamustine followed by obinutuzumab maintenance; IPTW = inverse probability treatment weighting; PSM = propensity score matching

Source: Manufacturer submission[1]

Figure 2: Absolute standardized differences of baseline characteristics, Pre- and Post-IPTW



LDH = lactate dehydrogenase

Source: Manufacturer submission[1]

Table 1: Primary analysis comparing PFS of follicular lymphoma patients treated with GB versus patients treated with relevant chemotherapies in Canada

	GB	Chemotherapy
Median PFS (95% CI), months	NR N = 139	NR N = 21
PFS HR (95% CI) Unadjusted, prior to PS methods	0.15 (0.09 to 0.27)	
PFS HR (95% CI) IPTW – Excluding patients with missing observations	0.18 (0.12 to 0.27)	

CI = confidence interval; GB = obinutuzumab and bendamustine followed by obinutuzumab maintenance; HR = hazard ratio; IPTW = inverse probability treatment weighting; PFS = progression-free survival; NR = not reported

Source: Manufacturer submission[1]

Sensitivity analyses

In the first set of sensitivity analyses using IPTW which included patients with missing baseline characteristics, a total of 164 patients were treated with GB and 36 patients were

treated with chemotherapy. The submitter's report did not specify how missing data were handled. In the PSM sensitivity analyses, a total cohort of 40 FL patients refractory to rituximab-containing regimens were caliper matched (1:1) and a total cohort of 42 patients were nearest neighbour matched (1:1).

Figure 3 and Figure 4 show that imbalances between treatment groups remained (ASD > 0.1) after caliper PSM and nearest neighbour PSM, respectively.

Table 2 shows the results of the sensitivity analyses comparing PFS of patients treated with GB versus patients treated with relevant chemotherapies in Canada. After PS adjustments, the submitter noted statistically significant improvement in PFS associated with GB in all analyses. HR's ranged between 0.18 and 0.22, and the 95% CI's did not cross the null value of 1. The results from the sensitivity analyses were similar to the primary results. The submitter concluded that the proportional hazard assumption was valid in all sensitivity analyses.

Figure 3: Baseline characteristics before and after caliper PSM

	Prior to Caliper PSM				After Caliper PSM			
Characteristic	G-Benda	Comparator	Absolute standardized Difference Pre-Match	P-Value for Difference between Groups	G-Benda	Comparator	Absolute standardized Difference Post-Match	P-Value for Difference Between Groups
Patients, N	*139*	*21*			*20*	*20*		
Mean Age in years	62.14	60.43	**0.14**	**0.04**	60.45	60.65	0.02	0.92
Number of prior therapies	1.81	2.24	**0.11**	**0.03**	2	2.10	0.03	0.88
Ann-Arbor stage	I = 5% II = 10% III = 22% IV = 63%	I = 0% II = 10% III = 10% IV = 81%*	**0.32** 0 **0.33** **0.38**	**<0.001** 1 **<0.001** **<0.001**	I = 0% II = 10% III = 20% IV = 70%	I = 0% II = 10% III = 10% IV = 80%	0 0 **0.28** **0.23**	1 1 **0.03** **0.04**
Bone marrow involvement	31%	76%	**0.99**	**<0.001**	75%	75%	0	1
Serum LDH elevated	32%	29%	0.07	0.41	25%	30%	**0.15**	**0.04**

LDH = lactate dehydrogenase; PSM = propensity score matching

Source: Manufacturer submission[1]

Figure 4: Baseline characteristics before and after nearest neighbour PSM

	Prior to Nearest Neighbour PSM				After Nearest Neighbour PSM			
Characteristic	G-Benda	Comparator	Absolute standardized Difference Pre-Match	P-Value for Difference between Groups	G-Benda	Comparator	Absolute standardized Difference Post-Match	P-Value for Difference Between Groups
Patients, N	*139*	*21*			*21*	*21*		
Mean Age in years	62.14	60.43	**0.14**	**0.04**	64.05	60.42	0.30	<0.001
Number of prior therapies	1.81	2.24	**0.11**	**0.03**	1.52	2.24	**0.18**	**0.02**
Ann-Arbor stage*	I = 5% II = 10% III = 22% IV = 63%	I = 0% II = 10% III = 10% IV = 81%*	**0.32** 0 **0.33** **0.38**	**<0.001** 1 **<0.001** **<0.001**	I = 5% II = 9% III = 19% IV = 67%	I = 0% II = 10% III = 10% IV = 81%*	0.32 0.03 0.26 0.30	**<0.001** **0.67** **<0.001** **<0.001**
Bone marrow involvement*	31%	76%	**0.99**	**<0.001**	29%	76%	**0.99**	**<0.001**
Serum LDH elevated*	32%	29%	0.07	0.41	24%	29%	**0.11**	**0.15**

LDH = lactate dehydrogenase; PSM = propensity score matching

Source: Manufacturer submission[1]

Table 2: Sensitivity analysis comparing PFS of patients treated with GB versus patients treated with relevant chemotherapies in Canada

	GB	Chemotherapy
IPTW – Including patients with missing observations		
Median PFS (95% CI), months	29.2 (20.5-NR) N = 164	NR N = 36
PFS HR (95% CI)	0.22 (0.16 to 0.31)	
Caliper matching without replacement		
Median PFS (95% CI), months	NR N = 164	NR N = 20
PFS HR (95% CI)	0.18 (0.07 to 0.47)	
Nearest neighbour matching		
Median PFS (95% CI), months	NR N = 164	NR N = 21
PFS HR (95% CI)	0.20 (0.08 to 0.50)	

CI = confidence interval; GB = obinutuzumab and bendamustine followed by obinutuzumab maintenance; HR = hazard ratio; IPTW = inverse probability treatment weighting; NR = not reported; PFS = progression-free survival

Source: Manufacturer submission[1]

7.1.4 Critical appraisal

- **Limitations**
  - In the PS analyses, both the GB and comparator group comprised of FL patients who were refractory to rituximab monotherapy or rituximab-containing regimens. This population differed slightly from the submitter's objective, which asked about patients who relapsed as well as patients who were refractory.
  - Progression was not defined in the PS analyses. This can result in bias if the definition of progression varied between the GADOLIN trial and those in the registry.
  - The comparator group may not be generalizable to the Canadian setting. The group comprised of patients from a US-based registry. There may be differences in treatment access and demographics, which may affect treatment outcomes. If patients from the registry are also not representative of all FL patients, this may introduce selection bias and limit external validity.
  - The submitter did not report the composition of comparator group (i.e., proportion of registry patients treated with bendamustine, CHOP, CVP, GDP, F versus G). The HR estimated would assume all chemotherapies have the same efficacy. However, there are likely reasons for patients to be prescribed different treatments (confounding by indication)
  - For the GB group, the submitter used the GADOLIN trial data at the May 2015 data cut-off. However, the data cut-off was not part of the protocol planned analysis. Further, the registry enrolled patients from 2004 to 2007, whereas the GADOLIN trial enrolled patients from 2010 to 2015. There may be differences in clinical practice between the time frames.
  - Not all prognostic factors deemed important by expert opinion (n = 3) were captured in the registry, and subsequently were not captured in the PS analyses. The CGP noted that major organ dysfunction (renal, hepatic, and cardiac) and performance status were important prognostic factors missing. PS analyses only account for measured confounders and not unmeasured ones. The submitter did not report other patient characteristics (i.e., time to FL diagnosis, duration of FL).

- PS adjustments did not appear to have balanced the measured baseline characteristics of the treatment groups. Given the likelihood of substantial residual confounding, the internal validity of the results may be limited.
- Sample size of the comparator group was small (n ≤ 21). There was no rationale for why the registry data were used exclusively, as opposed to other data which may increase the sample size of the chemotherapy group. Small sample sizes may lead to insufficient power, although the primary and sensitivity analyses produced statistically significant HR estimates. It was unexpected that there was sufficient power to detect a difference. Details of the statistical approaches that led to the HR and 95% CI estimates were not reported. Therefore, it was not possible to assess the internal validity.
- IPTW procedures may produce extreme weights, especially with a small sample size. It is clear from Figure 2 and from the differences in baseline characteristics after matching on PS (figures 3 and 4) that important differences in prognosis still existed between the GB and chemotherapy groups, biasing the comparison in favour of the GB group because the comparator group had a worse prognosis based on bone marrow involvement, Ann Arbor stage, elevated serum LDH, and number of prior therapies.
- As noted by the submitter, safety and adverse event outcomes were not captured in the registry, and could not be analyzed

Strengths

- The systematic literature reviews of comparative studies and of single-arm studies were comprehensive. They covered the peer-reviewed literature and grey literature, and included studies in English, French, and German.
- PS analyses provided an opportunity to examine relevant treatment comparators that were not examined in the GADOLIN trial.

7.1.5 Conclusions

Given the limitations with internal validity and external validity, no conclusions can be drawn with regards to the relative efficacy of GB and chemotherapies.

8 COMPARISON WITH OTHER LITERATURE

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Lymphoma/ Myeloma Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on obinutuzumab for follicular lymphoma. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Lymphoma/ Myeloma Clinical Guidance Panel is comprised of three oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** October 2016, **Embase** 1974 to 2016 November 16, **Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

Line #	Searches	Results
1	(Obinutuzumab* or gazyva* or afutuzumab* or haziva* or R7159 or R 7159 or GA101 or GA 101 or RO5072759 or RO 5072759 or huMABCD20 or O43472U9X8 or 949142-50-1 or "949142501").ti,ab,ot,kf,hw,rn,nm.	1383
2	Lymphoma, Follicular/ or Lymphoma, Non-Hodgkin/	77497
3	(lymphom* or lymphogranuloma* or granuloma* or lymphosarcoma* or blastoma* or lymphoid hyperplasia* or lymphoblastoma*).ti,ab,kf.	529275
4	(brill adj2 symmers).ti,ab,kf.	410
5	or/2-4	546636
6	1 and 5	544
7	6 use ppez,cctr	109
8	*obinutuzumab/	310
9	(Obinutuzumab* or gazyva* or afutuzumab* or haziva* or R7159 or R 7159 or GA101 or GA 101 or RO5072759 or RO 5072759 or huMABCD20).ti,ab,kw.	809
10	or/8-9	826
11	follicular lymphoma/ or nonhodgkin lymphoma/	74042

12	(lymphom* or lymphogranuloma* or granuloma* or lymphosarcoma* or blastoma* or lymphoid hyperplasia* or lymphoblastoma*).ti,ab,kw.	533636
13	(brill adj2 symmers).ti,ab,kw.	410
14	or/11-13	550672
15	10 and 14	335
16	15 use oemezd	239
17	7 or 16	348
18	limit 17 to english language	337
19	remove duplicates from 18	250

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#8	Search #6 AND #7	16
#7	Search publisher[sb] OR 2016/13/12:2016/11/17[edat]	1293927
#6	Search #4 AND #5	76
#5	Search Lymphoma, Follicular[mh] OR Lymphoma, Non-Hodgkin[mh:noexp] OR lymphom*[tiab] OR lymphogranuloma*[tiab] OR granuloma*[tiab] OR lymphosarcoma*[tiab] OR blastoma*[tiab] OR lymphoid hyperplasia*[tiab] OR lymphoblastoma*[tiab] OR brill symmers[tiab]	229426
#4	Search #2 OR #3	240
#3	Search Obinutuzumab*[tiab] OR gazyva*[tiab] OR afutuzumab*[tiab] OR haziva*[tiab] OR R7159[tiab] OR R 7159[tiab] OR GA101[tiab] OR GA 101[tiab] OR RO5072759[tiab] OR RO 5072759[tiab] OR huMABCD20[tiab]	223
#2	Search obinutuzumab [Supplementary Concept] OR O43472U9X8[rn] OR 949142-50-1[rn] OR 949142501[rn]	94

3. Cochrane Central Register of Controlled Trials (Central)

Searched via Ovid

4. Grey Literature search via:

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: obinutuzumab (Gazyva), follicular lymphoma

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search: obinutuzumab (Gazyva), follicular lymphoma

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

European Society for Medical Oncology (ESMO)
http://www.esmo.org/

American Society of Hematology (ASH)
http://www.hematology.org/

Search: obinutuzumab (Gazyva), follicular lymphoma - last 5 years

Literature Search Methods

Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (November 2016) via OVID; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were obinutuzumab (Gazyva) and follicular lymphoma.

No filters were applied to limit the retrieval by study type. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of March 2, 2017.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines

Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database. Abstracts from the American Society of Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO) and the American Society of Hematology (ASH) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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