CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Obinutuzumab (Gazyva) for Follicular Lymphoma

November 1, 2018

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List of Abbreviations

AE(s)	Adverse event(s)
CCI	Charlson Comorbidity Index
CGP	Clinical Guidance panel
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	Confidence interval
CR	Complete response
CT	Computed tomography
CVP	Cyclophosphamide, vincristine, and prednisone
DBCL	Diffuse large B-cell lymphoma
DFS	Disease-free survival
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
FACT-LYM	Functional Assessment of Cancer Therapy - Lymphoma
FACT-LYM TOI	Functional Assessment of Cancer Therapy – Lymphoma Trial Outcome Index
FL	Follicular lymphoma
FLIPI	Follicular lymphoma International Prognostic Index
G-CSF	Growth-colony stimulating factor
GELF	Groupe d'Etude des Lymphomes Folliculaires
HR	Hazard ratio
IDMC	Independent Data Monitoring Committee
INV	Investigator assessment
IRC	Independent review committee
ITT	Intent-to-treat
MAB	Monoclonal antibody
MCID	Minimal clinically important difference
MRI	Magnetic resonance imaging
MZL	Marginal zone lymphoma
NHL	Non-Hodgkin's lymphoma
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PAG	Provincial Advisory Group
pCODR	pan-Canadian Oncology Drug Review
pERC	pCODR Expert Review Committee
PD	Progressive disease
POD	Progression of disease at 24 months
PFS	Progression-free survival
PR	Partial response
QOL	Quality of life
RCT	Randomized controlled trial
RRCML	Revised Response Criteria for Malignant Lymphoma
SAE(s)	Serious adverse event(s)
SAP	Statistical analysis plan
SD	Stable disease
TLS	Tumour lysis syndrome

1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pERC in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding obinutuzumab (Gazyva) for FL previously untreated. 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 (Gazyva) for FL conducted by the Lymphoma 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 (Gazyva) for FL previously untreated a summary of submitted PAG Input on obinutuzumab (Gazyva) for FL previously untreated and a summary of submitted registered clinician input on obinutuzumab (Gazyva) for FL previously untreated, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

The objective of this review is to evaluate the safety and efficacy of obinutuzumab (Gazyva), in combination with chemotherapy, followed by obinutuzumab monotherapy in patients achieving a response, for the treatment of patients with previously untreated stage II bulky (≥7cm), III or IV FL.

The reimbursement request is in line with the approved Health Canada indication. Obinutuzumab received the Notice of Compliance in July 2018. Obinutuzumab is a recombinant monoclonal humanized and glycoengineered Type II anti-CD20 antibody of the IgG1 isotype. The dose of obinutuzumab is 1000mg per vial.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

Trial

One RCT, the GALLIUM trial,[1] was identified that met the selection criteria of the pCODR systematic review. GALLIUM is an ongoing, open-label, active-controlled, international and multi-centred phase 3 trial evaluating the efficacy and safety of induction treatment with obinutuzumab compared to rituximab, each combined with chemotherapy, and followed by maintenance treatment (with the same antibody) in previously untreated patients with advanced indolent NHL. The trial took place at 177 sites in 18 countries including Canada (139 patients across seven sites).[2] Patient randomization occurred between July 6, 2011 and February 4, 2014.

Patients enrolled in the GALLIUM trial had CD20-positive, indolent B-cell NHL, which included FL or MZL (splenic, nodal, or extranodal). The trial's primary objective, however, was to evaluate the primary outcome in patients with FL. Patients enrolled in GALLIUM met the following key criteria:

- Advanced stage (Ann Arbor stage III or IV, or stage II with bulk disease, and tumour ≥7 cm in greatest dimension) FL (grade 1-3a)

- At least one lesion assessable by bidimensional measurement (>2 cm by CT or MRI)
- ECOG 0-2
- Indication for treatment according to GELF criteria

The primary outcome of the trial was PFS by INV; secondary outcomes included PFS by IRC, CR rate and ORR at the end of induction treatment, DOR, EFS, DFS, OS, time-to-new anti-lymphoma treatment, health-related QOL, and safety. Efficacy by chemotherapy backbone and disease transformation were exploratory endpoints.

Randomization was stratified according to chemotherapy regimen, FLIPI risk group (low risk: ≤1 risk factor, intermediate risk: 2 risk factors, or high risk: >2risk factors), and geographic region. Patients with FL were randomized to receive intravenous obinutuzumab (1000 mg on days 1, 8, and 15 of cycle 1, and on day 1 of subsequent cycles) or rituximab (375 mg per square metre of body surface area on day 1 of each cycle). Antibodies in each treatment group were administered for six or eight cycles depending on the chemotherapy regimen; each participating site selected one of three standard chemotherapy regimens (bendamustine, CHOP, or CVP) to be used for the duration of the study. Following randomization, patients started induction treatment; only patients achieving a response at the end of induction (CR or PR) continued on to maintenance treatment.

The median duration of treatment was the same in both treatment groups; approximately 25 weeks for induction and 92 weeks for maintenance. There were 6% and 8% of patients in the obinutuzumab and rituximab treatment groups, respectively, who did not complete induction treatment; the primary reason for discontinuation in both groups was due to AEs. A similar proportion of patients in each treatment group started on maintenance treatment (90% in the obinutuzumab group and 88% in the rituximab group). Patient withdrawals during maintenance, which occurred in 20% and 22% in the obinutuzumab and rituximab groups, respectively, were primarily due to PD in each group (6% versus 11%, respectively). At the primary data cut-off date, 60% of patients had completed obinutuzumab maintenance and 10% were still receiving maintenance, compared to 57% and 9% of patients, respectively, in the rituximab group.

Most randomized patients were treated at trial sites in the UK (21%), Germany (17%), Canada (10%), Australia (10%) and Japan (9%).[3] A total of 1202 patients with FL were randomized: 601 were allocated to obinutuzumab-based chemotherapy and 601 were allocated to rituximab-based chemotherapy. Overall, the baseline characteristics of FL patients were well-balanced between the treatment groups. The median age of patients was 59 years, with approximately 31% of patients aged 65 or older. The majority of patients had an ECOG performance status of 0-1 (97%), were Ann Arbor disease stage III (35%) or IV (57%), and were classified as FLIPI intermediate- (37%) or high-risk (42%). Bone marrow involvement, extranodal involvement, and bulk disease (tumour ≥7 cm) were present in 52%, 67%, and 44% of patients, respectively; and approximately one third of patients presented with B symptoms. The distribution of patients by chemotherapy regimen was also balanced among the two treatment groups, with approximately 57% of patients receiving bendamustine, 33% CHOP, and 10% CVP.

Efficacy

The trial met its primary outcome at the third planned interim efficacy analysis, which is considered the primary analysis of the trial (January 31, 2016 data cut-off date; median follow-up of 34.5 months), by crossing the pre-specified boundary for superiority and demonstrating a statistically significant improvement in PFS by INV in the obinutuzumab-based treatment group (HR=0.66, 95% CI, 0.51-0.85; p=0.001). The estimated 3-year PFS by INV was 80% (95% CI, 75.9-83.6) in patients treated with obinutuzumab versus 73.3% (95% CI, 68.8-72.2) in patients treated with rituximab (absolute difference of 6.7%). The results of most pre-specified patient subgroup analyses showed a consistent treatment

benefit favouring obinutuzumab, and tests for treatment interaction suggested no heterogeneity of treatment effect in any patient subgroup examined. For the non-FL subgroup of patients with MZL, the treatment effect estimates also favoured obinutuzumab (HR=0.82; 95% CI, 0.45-1.46; PFS by IRC: HR=0.83; 95% CI, 0.46-1.51).[4] Conversely, for patients in the low-risk FLIPI category and with Ann Arbor stage II disease, treatment effect estimates favoured rituximab treatment. The updated efficacy analysis (September 10, 2016 data cut-off date; median follow-up of 41.1 months), performed after an additional 6.5 months of follow-up,[5] showed a sustained treatment benefit in the obinutuzumab treatment group in the FL patient population (HR=0.68, 95% CI, 0.54-0.87; p=0.0016). At both analysis time-points, results of the IRC assessment of PFS were consistent with the primary analysis, but of slightly lower magnitude (Table 1).

At the end of induction treatment the CR rate was higher in the rituximab treatment group (23.8%) compared to the obinutuzumab group (19.5%); the difference between the groups (4.3%) was not statistically significant. Since the difference in CR did not reach statistical significance at the primary analysis, the remaining secondary outcomes specified in the hierarchical testing scheme were not formally tested. These endpoints, which included ORR and OS, showed no differences between groups at the primary and updated analyses (Table 1). The remaining secondary outcomes of interest, EFS, DFS and time-to-new anti-lymphoma treatment, were consistent with the primary outcome results of the trial; however, no adjustments were made to the overall statistical significance level to account for these analyses.

Health-related QOL[6]

Patient-reported health-related QOL was measured using the FACT-LYM instrument. Compliance in completing questionnaires was high at baseline in both treatment groups (92.5% in obinutuzumab group versus 91.5% in the rituximab group) but declined over the course of treatment and follow-up. At baseline, mean FACT-LYM scores were similar in the two treatment groups for all scales, with all patients demonstrating some degree of impairment of physical function, functional wellbeing, and emotional and social function. Over the course of treatment there were no clear differences between the treatment groups in any FACT-LYM scale scores at any time point. From the end of induction treatment onwards, patients in both groups experienced clinically meaningful improvements from baseline in all scales.

Safety

The safety population included 1192 patients; 595 patients in the obinutuzumab group and 597 in the rituximab group. Compared to rituximab-based treatment, obinutuzumab was associated with a higher incidence of all grade AEs (99.5% in the obinutuzumab group versus 98.3% in the rituximab group), grade 3-4 AEs (74.6% versus 67.8%) and SAEs (46.1% versus 39.9%), and all were more frequent during induction treatment than in maintenance treatment in both groups.

During induction the most common grade 3-5 AEs (obinutuzumab versus rituximab) were neutropenia (37.1% versus 34%), leukopenia (7.7% versus 8%), and infusion-related reactions (6.6% versus 3.5%), while the most common SAEs were infusion-related reactions (4.4% versus 1.8%), neutropenia (2.9% versus 3.2%), febrile neutropenia (3% versus 2.2%), and pyrexia (2.5% versus 2.7%). During maintenance treatment the most common grade 3-5 AEs and SAEs were neutropenia (16.4% versus 10.7%) and pneumonia (2.4% versus 3%), respectively.

The frequency of second neoplasms was higher in the obinutuzumab treatment group (7.2% versus 5% with rituximab), particularly non-melanoma skin cancers (3% versus 2%) and hematologic malignancies (1% versus 0%). Bendamustine chemotherapy was associated

with a higher frequency of grade 3-5 infection and second malignancies during the maintenance and follow-up phases of the trial; while CHOP was associated with a higher frequency of grade 3-5 neutropenia. Non-relapse-related fatal AEs were also more common among patients treated with bendamustine (5.6% in obinutuzumab group versus 4.4% in the rituximab group) compared to patients treated with CHOP (1.6% versus 2%) or CVP (1.6% versus 1.8%).

A total of 81 deaths had occurred by the primary analysis data cut-off date; of these, 24 (4%) in the obinutuzumab treatment group and 20 (3.4%) in the rituximab group were attributed to AEs.

AEs of Special Interest

Infusion reactions also occurred more frequently in obinutuzumab-treated patients; 68.2% of patients compared to 58.5% of patients in the rituximab group. Of these patients, the reaction was attributed to antibody in 59.3% of patients treated with obinutuzumab and 48.9% of patients treated with rituximab. The majority of infusion reactions were low grade (1-2) with no fatal grade 5 events.[2] Infections were also common and occurred in 77.3% of patients in the obinutuzumab group and 70% in the rituximab group; the majority of infections were low grade (1-2) and SAEs due to infection were reported in 18.2% and 14.4% of patients, respectively. The incidence of grade 3-5 neutropenia was 45.9% in patients treated with obinutuzumab and 39.5% in patients treated with rituximab; and thrombocytopenia (any grade) occurred in 11.4% of patients and 7.5% of patients, respectively. The frequency of TLS (any grade) was low in both treatment groups (≤1%).

Limitations

Overall, the GALLIUM trial was well-conducted. The randomization procedure and method of allocation concealment were carried out appropriately; the treatment groups were well balanced at baseline for important patient and prognostic characteristics, and duration of treatment was the same in both treatment groups for both induction and maintenance. Patient withdrawals were higher in the rituximab treatment group but were primarily due to PD, with the other reasons for study discontinuation balanced between the treatment groups. All efficacy analyses were performed according to the ITT principle. A number of limitations were noted, however, which should be considered when interpreting the results of the trial; specifically:

- The trial met its primary endpoint at the third planned interim analysis for efficacy (median follow-up of 34.5 months) and demonstrated a statistically significant improvement in PFS by INV in the obinutuzumab-based treatment group (HR=0.66, 95% CI, 0.51-0.85; p=0.001). The superiority of obinutuzumab demonstrated at interim analysis was based on crossing a pre-specified threshold of statistical significance (p=0.012) and 245 PFS events (information fraction of 66%). Trials stopped early for benefit, before all events have accrued, are associated with exaggerated treatment effect sizes;[7] therefore, the magnitude of the treatment effect estimate observed in the GALLIUM trial may be exaggerated. At the primary analysis cut-off date all patients had been recruited into the trial and completed or withdrawn from induction treatment, approximately two-thirds of patients had been followed for 2.5 years,[8] and 10% were still receiving maintenance therapy.
- The SAP of the GALLIUM trial specified the number of efficacy analyses to be performed (primary and key secondary outcomes), and appropriately used statistical approaches to control for the probability of type 1 error that arises from multiple comparisons. The purpose of these approaches is to preserve the overall significance level across the number of planned, specified analyses, and the overall power of the trial. In GALLIUM, however, many efficacy analyses were performed

(additional secondary outcomes, subgroup analyses, updated efficacy analysis) that did not involve adjustment for multiplicity. The chance of obtaining a statistically significant result (false positive) increases as the number of tests performed increases; therefore, the magnitude of the treatment estimates obtained for these uncontrolled efficacy analyses should be interpreted with some level of caution. Further, although the assessment of heterogeneity of treatment effect in patient subgroups was analyzed appropriately using tests for interaction (though the threshold for statistical significance was not indicated), these tests are often underpowered.[9] Considering this, and the lack of adjustment for multiplicity, the subgroup analysis results of the trial should be viewed as exploratory analyses.

- The open-label design of the trial makes it prone to different biases (patient selection and performance bias), which can affect internal validity. The investigators, trial personnel, patients, as well as data analysts were all aware of study drug assignment, which can potentially bias outcome assessment in favour of obinutuzumab if assessors (investigators, patients, and data analysts) believe the study drug is likely to provide benefit. This is particularly relevant in an open-label trial stopped early for benefit, as patients became aware of the trial results while still on study. An attempt was made in the trial to mitigate bias by using an IRC, as well as conducting multiple pre-specified sensitivity analyses to measure the robustness of the primary outcome results. Results of the IRC assessment were consistent with the INV assessment, and most patient subgroup analyses and all sensitivity analyses (but one) were supportive of the primary analysis.[3] However, for subjective outcomes like health-related QOL and AEs, there is a greater risk of detection bias because patients and investigators would be aware of the specific treatment being administered.
- It is unclear whether the PFS benefit observed with obinutuzumab can be attributed to the induction and/or maintenance phase of first-line treatment; at the end of induction treatment, there was no difference in CR or ORR between the two treatment groups.
- The interpretation of outcomes examined by chemotherapy regimen should be interpreted with caution, as the treatment effect estimates are confounded by imbalances in baseline patient characteristics between treatment groups since patients were not randomized to chemotherapy regimens in the trial.
- As indicated above, the value of subjective health-related QOL data in an open-label trial are limited due to detection bias. Further, the frequency of missing data increased over the course of the trial, which also biases the QOL analysis as there are systematic differences in the characteristics of patients who complete and don't complete questionnaires.

Table 1: Highlights of key outcomes in the GALLIUM trial (FL patient population).[1]

Outcomes	GALLIUM Trial	
	Obinutuzumab + Chemotherapy (n=601)	Rituximab + Chemotherapy (n=601)
Data cut-off date	**January 31, 2016[1]**	
Median follow-up in months, range	**34.5 (0-54.5)**	
Primary Outcome		
PFS by Investigator		
No. events	101 (16.8)	144 (24)
HR (95% CI)	0.66 (0.51 to 0.85)	
p-value (log-rank)	0.001	
Estimated 3-year PFS rate, % (95% CI)	80 (75.9 to 83.6)	73.3 (68.8 to 77.2)
Secondary Outcomes		
PFS by IRC		
No. events	93 (15.5)	125 (20.8)
HR (95% CI)	0.71 (0.54 to 0.93)	
p-value (log-rank)	0.01	
Estimated 3-year PFS rate, % (95% CI)	81.9 (77.9 to 85.2)	77.9 (73.8 to 81.4)
ORR at end of induction		
ORR (CR or PR), n (%)	532 (88.5)	522 (86.9)
Difference, % (95% CI)	1.6 (-2.1 to 5.5)	
p-value (Cochran-Mantel-Haenszel)	0.33	
CR rate at end of induction		
CR, n (%)	117 (19.5)	143 (23.8)
Difference, % (95% CI)	-4.3 (-9.1 to 0.4)	
p-value (Cochran-Mantel-Haenszel)	0.07	
Time to new anti-lymphoma treatment (TNALT)		
No. events	80 (13.3)	111 (18.5)
HR (95% CI)	0.68 (0.51 to 0.91)	
p-value (log-rank)	0.009	
Estimated 3-year TNALT-free rate, % (95% CI)	87.1 (84 to 89.6)	81.2 (77.6 to 84.2)
OS		
No. deaths	35 (5.8)	46 (7.7)
HR (95% CI)	0.75 (0.49 to 1.17)	
p-value (log-rank)	0.21	
Estimated 3-year OS rate, % (95% CI)	94.0 (91.6 to 95.7)	92.1 (89.5 to 94.1)
Data cut-off date	**September 10, 2016[5]**	
Median follow-up in months, range	**41.1 (NR)**	
Primary Outcome		
PFS by Investigator		
No. events	120 (20)	161 (27)
HR (95% CI)	0.68 (0.54 to 0.87)	
p-value (log-rank)	0.0016	
Estimated 3-year PFS rate, % (95% CI)	82 (78 to 85)	75 (71 to 78)
Secondary Outcomes		
PFS by IRC		
No. events	108 (18)	141 (23)
HR (95%CI)	0.72 (0.56 to 0.93)	
p-value	0.012	
Estimated 3-year PFS rate, % (95% CI)	83 (80 to 86)	79 (75 to 82)
OS		
No. deaths	43 (7)	52 (9)
HR (95% CI)	0.82 (0.54 to 1.22)	

Outcomes	GALLIUM Trial	
	Obinutuzumab + Chemotherapy (n=601)	Rituximab + Chemotherapy (n=601)
p-value	0.32	
Estimated 3-year OS rate, % (95% CI)	94 (92 to 96)	92 (90 to 94)
Harms Outcomes, n (%)		
AE (any grade)	592 (99.5)	587 (98.3)
Grade ≥3	444 (74.6)	405 (67.8)
SAE	274 (46.1)	238 (39.9)
TRAE	564 (94.8)	547 (91.6)
TRAE leading to withdrawal of treatment	75 (12.6)	65 (10.9)
Fatal AE	24 (4)	20 (3.4)
Abbreviations: AE - adverse events; CI - confidence interval; CR - complete response; HR - hazard ratio; OS - overall survival; PFS - progression-free survival; SAE - serious adverse event; TRAE - treatment-related adverse event.		
Notes: *HR < 1 favours treatment with obinutuzumab.		

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.

Patient Advocacy Group Input

One patient group, Lymphoma Canada (LC), provided input from patients FL. LC conducted two separate online surveys for caregivers and patients. A total of 115 respondents, 96 patients and 19 caregivers, provided input to LC.

Most respondents rated longer survival (87%) and longer remission (79%) as extremely important for a new treatment when compared to current therapies. Better QOL (69%) and fewer side effects (44%) were rated as extremely important less frequently.

Among 90 patient respondents, a number of symptoms associated with FL at diagnosis were reported as impacting QOL. The most commonly reported symptom impacting QOLs were fatigue, enlarged lymph nodes and drenching night sweats. Fatigue, diarrhea, nausea/vomiting, hair loss, mouth sores, and neutropenia were the most commonly reported side effects of currently available treatments. Fatigue, nausea/vomiting, and pain were reported as being most difficult to tolerate. Only six patient respondents reported having experience with obinutuzumab treatment, and all reported that their treatment was able to manage most of their disease symptoms. Fatigue was reported as the most difficult side effect to manage with treatment with obinutuzumab.

Provincial Advisory Group (PAG) Input

Clinical factors:

- Use in other indolent lymphomas
- Comparison of obinutuzumab plus bendamustine to rituximab plus bendamustine

Economic factors:

- Additional chemotherapy chair time in the first month of treatment and in maintenance phase with obinutuzumab

Registered Clinician Input

Overall, clinicians identified that obinutuzumab meets current clinical needs for patients with FL, and that it may provide patients with a treatment option that will prolong time between treatments, compared to rituximab, for patients who will need to be eventually retreated. However, there was agreement that obinutuzumab results in greater toxicity and infusion reactions compared to rituximab. Clinician input suggested that infusion reactions would be easily manageable.

Summary of Supplemental Questions

- What is the clinical efficacy, safety and therapeutic equivalence of obinutuzumab administered every two months in the maintenance setting, compared to obinutuzumab administered every three months, for the first-line treatment of patients with FL?

Two clinical trials were identified that evaluated different maintenance therapy schedules with obinutuzumab. The GALLIUM trial,[1] a phase 3 trial comparing obinutuzumab and rituximab with a maintenance schedule of every two months, and the GAUDI trial,[10] non-comparative phase 1b trial evaluating obinutuzumab therapy with either bendamustine or CHOP chemotherapies with a maintenance schedule of every three months. A naïve indirect comparison between the trials demonstrated that patients had adverse events resulting in similar dose delays or death. Overall grade 3-5 AEs observed during maintenance were similar across both trials. Both trials reported three year PFS rates. Overall, differences in the trials, with respect to the study design, sample size, and reporting of data made a naïve comparison difficult. Limited conclusions on the clinical efficacy, safety and therapeutic equivalence of the two maintenance schedules can be drawn. It is unclear without a direct comparison of alternate obinutuzumab maintenance schedules whether a three month maintenance schedule is more favourable, less favourable or similar to a two month maintenance schedule.

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>
<tr><th></th><th>Factor</th><th>Evidence
(GALLIUM Trial)[1]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td>Population</td><td>Stage of disease</td><td>Over 50% of patients included in the trial had Ann Arbor stage IV disease.

<table><tr><th>Stage
n (%)</th><th>Obinutizumab + Chemotherapy</th><th>Rituximab + Chemotherapy</th></tr><tr><td>I</td><td>10 (1.7)</td><td>8 (1.3)</td></tr><tr><td>II</td><td>41 (6.8)</td><td>44 (7.3)</td></tr><tr><td>III</td><td>208 (34.6)</td><td>209 (34.8)</td></tr><tr><td>IV</td><td>339 (56.4)</td><td>336 (55.9)</td></tr></table>
Subgroup analyses were conducted by disease stage, and showed a PFS by INV benefit in favour of obinutuzumab in patients with stage IV (HR=0.59; 95% CI, 0.43-0.82) but not the other stages (I, II or III); the estimates obtained in the lower stages should be considered with caution due to small sample sizes (refer to Figure 4 in section 6.3.2.2). Further, the test for interaction for this subgroup was not statistically significant (p=0.87), suggesting no difference in treatment effect between Ann Arbor stage categories.</td><td>Does stage limit the interpretation of the trial results with respect to the target population?</td><td>There is no evidence to suggest there is a difference in the effect of obinutuzumab based on Ann Arbor disease stage. Thus, obinutuzumab should be available for patients with bulky stage II (≥ 7 cm), and symptomatic stage III and IV disease as defined in the GALLIUM trial.</td></tr>
<tr><td></td><td>FLIPI Risk Score</td><td>Over 40% of patients included in the trial were classified as FLIPI high-risk.

<table><tr><th>Risk score
n (%)</th><th>Obinutizumab + Chemotherapy</th><th>Rituximab + Chemotherapy</th></tr><tr><td>Low</td><td>128 (21.3)</td><td>125(20.8)</td></tr><tr><td>Intermediate</td><td>224 (37.3)</td><td>223 (37.1)</td></tr><tr><td>High</td><td>249 (41.4)</td><td>253 (42.1)</td></tr></table>
Subgroup analyses were conducted by FLIPI risk score, and showed a PFS by INV benefit in favour of obinutuzumab in patients with intermediate- (HR=0.59, 95% CI, 0.37-0.92) and high-risk FLIPI score (HR=0.58, 95% CI, 0.41-0.84), but not for low-risk patients (HR=1.17, 95% CI, 0.63-2.19). The effect estimate in the low-risk group should be interpreted with caution due to small sample size and low event rates (refer to</td><td>Does FLIPI score limit the interpretation of the trial with respect to the target population?</td><td>Although there was no difference in PFS reported in low-risk FLIPI score patients, there is no evidence to suggest that there is a difference in the effect of obinutuzumab based on FLIPI score. Thus, obinutuzumab should be available for patients regardless of FLIPI scores.</td></tr>
</table>

<table>
<tr><th></th><th>Factor</th><th>Evidence
(GALLIUM Trial)[1]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td></td><td>Figure 4 in section 6.3.2.2). Further, the test for interaction for this subgroup was not statistically significant (p=0.14), suggesting no difference in treatment effect between FLIPI risk categories.</td><td></td><td></td></tr>
<tr><td></td><td>Performance Status</td><td>The trial enrolled patients with an ECOG performance status of 0-2; 97% of patients had an ECOG PS of 0-1.[3]

<table><tr><th>ECOG Performance Status</th><th>Obinutizumab + Chemotherapy n (%)</th><th>Rituximab + Chemotherapy n (%)</th></tr><tr><td>0-1</td><td>585 (97.5)[3]</td><td>576 (96.2)[3]</td></tr><tr><td>2</td><td>15 (2.5)[3]</td><td>23 (3.8)[3]</td></tr></table>
Subgroup analyses were conducted by performance status, and showed a PFS by INV benefit in favour of obinutuzumab in patients with an ECOG status of 0-1 (HR 0.64; 95% CI, 0.52-0.87) but not in patients with an ECOG status of 2 (HR 0.85; 95% CI, 0.29-2.49); this latter estimate should be considered with caution due to very small sample size. Further, the test for interaction for this subgroup was not statistically significant (p=0.05), suggesting no difference in treatment effect between ECOG performance status categories.</td><td>Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>There is no evidence to suggest that there is a difference in the effect of obinutuzumab based on ECOG performance status. Thus, obinutuzumab should be available for patients with ECOG status 0-2.

The results of the GALLIUM trial should be applied to patients regardless of performance status. If PS ≥ 2 due to lymphoma-related PS or treatment related fatigue or other toxicities, then patients may be considered eligible for obinutuzumab.</td></tr>
<tr><td></td><td>Age</td><td>The median age of included patients was 59 years. Approximately 31% of patients were aged ≥65 years.[3]</td><td>Does the age restriction in the trial limit the interpretation of the trial results with respect to the target population?</td><td>It is the opinion of the CGP that age is not an effect modifier. Thus, Obinutuzumab should be considered for all patients able to tolerate chemotherapy, regardless of age.</td></tr>
<tr><td></td><td>Organ dysfunction</td><td>The trial enrolled patients with adequate hematologic function (unless abnormalities were related to NHL), which was defined as follows:
• Hemoglobin ≥9.0 g/dl
• Absolute neutrophil count ≥1.5 x 10^9/l
• Platelet count ≥75 x 10^9/l</td><td>Does the exclusion of patients with organ dysfunction limit the interpretation of the trial results with respect to the target population (e.g.,</td><td>While organ dysfunction is not a reason to limit the patient population to receive obinutuzumab, dosing of obinutuzumab should follow product</td></tr>
</table>

	Factor	Evidence (GALLIUM Trial)[1]	Generalizability Question	CGP Assessment of Generalizability
		Patients with CVD, pulmonary disease or active infections were excluded.	Canadian clinical practice, patients without the factor, etc.)?	monograph and/or standard protocol guidelines for both the chemotherapy and the obinutuzumab.
	Ethnicity or Demographics	The trial was conducted at trial sites in 18 countries; the majority of patients were white (81%) and Asian (17%).[3]	If the trial was conducted outside of Canada, is there a known difference in effect based on ethnicity that might yield a different result in a Canadian setting? Also, if the demographics of the study countries differ from Canada, the average treatment effect in the trial might not be representative of a Canadian setting.	It is the opinion of the CGP that ethnicity is not an effect modifier. Thus, The results of the GALLIUM trial can be applied equally to Canadians, regardless of ethnicity.
	Other related lymphoma	The trial was designed (and powered) to evaluate study treatment in patients with FL (n=1202); however, a subgroup of patients with MZL were included (n=195). There were 99 MZL patients randomized to obinutuzumab and 96 randomized to rituximab, of whom 61 patients had extranodal MZL, 66 nodal MZL and 68 splenic MZL. The baseline demographics of this patient subgroup appeared similar to the FL patient population except for notable higher percentages of patients classified as stage IV Ann Arbor disease (82.6% versus 56.5%), high-risk FLIPI score (49% versus 41%) and treated with bendamustine chemotherapy (71% versus 57%).[4] Extranodal involvement, bone marrow involvement, bulky disease, and B symptoms were reported as more common in the obinutuzumab treatment group at baseline.[4] The treatment effect estimate for PFS by INV favoured treatment with obinutuzumab (HR=0.82; 95% CI, 0.45-1.46).[4]	Can the results from the FL subgroup be extrapolated to all subtypes of low grade lymphoma including marginal zone lymphoma (MZL) patients?	The overall magnitude of benefit in the GALLIUM trial is small. Therefore, it is the opinion of the CGP that there are insufficient data to recommend obinutuzumab across all subtypes of low grade lymphoma, including MZL patients.
Intervention	Line of therapy and Sequencing	First-line treatment.	Are the results of the trial generalizable to other lines of therapy?	Obinutuzumab should be administered in the first line setting. At this time, the CGP is unaware of evidence to guide sequencing of therapy for

	Factor	Evidence (GALLIUM Trial)[1]	Generalizability Question	CGP Assessment of Generalizability
				subsequent lines of therapy at the time of relapse.
	Administration of intervention	Obinutuzumab 1000 mg IV, days 1, 8, and 15 of cycle 1, and on day 1 of subsequent 6 or 8 cycles depending on chemotherapy regimen (CHOP, CVP, or BENDA). Followed by obinutuzumab maintenance (1000 mg IV) every 2 months for 2 years until PD.	Are the results of the trial generalizable to a different dose or administration schedule?	The current standard of care in Canada is administering rituximab every three months in the maintenance setting. There is insufficient evidence at this time to support administering obinutuzumab maintenance treatment with an alternate schedule than studied in the GALLIUM trial.
	Standard of Care	The chemotherapy regimens in the trial were CHOP, CVP or BENDA.	Are the results of the trial applicable in the Canadian setting based on the chemotherapy regimen backbone?	The benefits of obinutuzumab are seen regardless of the chemotherapy backbone it is combined with.
Setting	Countries Participating in the Trial	The trial was conducted in the following countries (n reported for highest recruiting countries): Australia (n=136), Belgium, Canada (n=138), China, Czechia, Finland, France, Germany (n=237), Hungary, Israel, Italy, Japan (n=129), Russian Federation, Spain, Sweden, Taiwan, United Kingdom (n=293), and United States.[3]	If the trial was conducted in other countries, is there any known difference in the practice pattern between those countries and Canada? Differences in the patterns of care might impact the clinical outcomes or the resources used to achieve the outcomes.	It is the opinion of the CGP that the trial results are generalizable to Canada.
	Supportive medications, procedures, or care	Premedication prior to infusion with obinutuzumab/rituximab treatment included oral acetaminophen/paracetamol (e.g., 650–1000 mg) and an antihistamine such as diphenhydramine (e.g., 50–100 mg); and TLS in patients at risk for tumour lysis. Due to a moderate risk of emesis with cyclophosphamide, doxorubicin, and bendamustine, it was recommended infusions be administered following premedication with a	Are the results of the trial generalizable to a setting where different supportive medications, procedures, or care are used?	In Canada G-CSF is not routinely used. Although some patients in Canada may receive this as secondary prophylaxis, other strategies such as dose delay or dose reduction would be used.

	Factor	Evidence (GALLIUM Trial)[1]	Generalizability Question	CGP Assessment of Generalizability
		serotonin (5-HT3) antagonist (e.g., dolasetron, ondansetron) or per institutional practice. G-CSF was used to support patients with neutropenia (48.1% in the rituximab group and 49.6% in the obinutuzumab group, respectively).[11]		G-CSF use is not a requirement for the treatment of patients with FL.

Abbreviations: **BENDA** - bendamustine; **CGP** - Clinical Guidance Panel; **CHOP** - cyclophosphamide, doxorubicin, vincristine, prednisone; **CI** - confidence interval; **CVD** - cardiovascular disease; **CVP** - cyclophosphamide, vincristine, prednisone; **FLIPI** - Follicular lymphoma International Prognostic Index; **G-CSF** - growth colony stimulating factor; **INV** - investigator assessment; **IV** - intravenous; **MZL** - marginal zone lymphoma; **NHL** - non-Hodgkin's lymphoma; **PD** - progressive disease; **PFS** - progression-free survival; **TLS** - tumour lysis syndrome.

1.2.4 Interpretation

Burden of Illness and Need

Follicular lymphoma is the most common type of low grade lymphoma. Although this disease has a very high response rate to many different chemotherapy regimens, it remains incurable. The current treatment strategy is one of managing a chronic disease, and at times of symptomatic progression, treatment is offered. From the patient experience, this can be unsettling by not knowing when treatment is necessary, and for some, it can significantly impact their life because this uncertainty makes long term future planning more difficult. It also has an impact on caregivers increasing anxiety and future planning due to the uncertainty of when treatment is going to be needed. Based on the responses from patient groups there is ongoing need to find therapies that are well tolerated, and lead to the longest survival and duration of disease control for all patients with this disease.

Effectiveness

Progression Free Survival[1]

Progression free survival was the primary endpoint of the GALLIUM trial. The estimated 3-year PFS by INV was 80.0% for the obinutuzumab group versus 73.3% for the rituximab group, reaching statistical significance at the planned interim analysis (HR=0.66, 95% CI, 0.51-0.85; p=0.001). The PFS based on independent review had a smaller 3-year PFS rate in both treatment groups than the investigator-assessed PFS; (obinutuzumab group 81.9% versus. rituximab group 77.9%; HR=0.71, p=0.01). Although this is statistically significant, the absolute magnitude of benefit of 6.7% in the PFS by INV, and 4.0% in the PFS by IRC is small. The clinical significance of this difference is difficult to determine. Longer follow up are necessary to see the impact of this change. Furthermore, at the time of the data analysis, PFS data were immature, and the median PFS was not reached, making the actual degree of long term benefit unknown.

Apart from patients with low FLIPI score, PFS favoured the obinutuzumab group consistently throughout differences in baseline characteristics and subgroup analysis of the FL patients. For patients with low FLIPI score, the trend favoured the rituximab group. The significance of this result is uncertain given the small number of events that occurred (14 patients progressed). It should be noted that tests for treatment interaction suggested no heterogeneity of treatment effect in any patient subgroup examined, including the subgroup of FLIPI score. Thus, obinutuzumab should be available for patients regardless of FLIPI score.

Although not powered to determine differences in PFS by the backbone of chemotherapy, the results were also consistent regardless of the chemotherapy backbone used. In Canada, the standard of care is bendamustine chemotherapy with rituximab as first-line therapy for FL. Fifty-seven percent of patients received this chemotherapy, and consequently, this patient group is consistent with standard of care in Canada.

Overall Survival[1]

Overall survival was a secondary endpoint of the GALLIUM trial. There were no differences between the two treatment groups. The estimated 3 year OS was 94.0% in the obinutuzumab arm, and 92.1% in the rituximab arm, with an HR=0.75 (95% CI 0.49-1.17; p=0.21). Due to the long survival in this patient population, OS analysis at this time point is not expected to be different. Long-term follow up is necessary to draw definitive conclusions. Furthermore, at the time of the data analysis, OS data were immature,

making the actual degree of long term benefit unknown. With sufficient follow-up OS could be evaluated, but any benefit will be confounded by post-trial treatments.

Other Secondary Endpoints[1]

Response rates at the end of induction treatment did not differ significantly between the two groups in the GALLIUM trial. The ORR for the obinutuzumab group was 88.5%, compared to the rituximab group at 86.9% (p=0.33). Similarly, the CR rate after induction therapy was not statistically significant, and favoured the rituximab group (19.5% versus 23.8%; p=0.07). With the hierarchical testing scheme used, other secondary endpoints were not formally tested, and can only be interpreted as exploratory outcomes.

The GALLIUM trial had many other secondary endpoints. There were no differences in the secondary endpoints except for EFS and start of new anti-lymphoma therapy. EFS is a composite endpoint from the time of randomization to progression, relapse, death or start of new lymphoma therapy. This is a similar endpoint to PFS, and the results are consistent with the primary endpoint. The time to new anti-lymphoma treatment also favored the obinutuzumab group with 13.3% of patients needing treatment, compared to 18.5% in the rituximab group (HR=0.68, 95% CI, 0.51-0.91; p=0.009). In absolute terms, this translates into 31 more patients going back on treatment in the rituximab group compared to the obinutuzumab group.

Health-related Quality of Life[6]

The FACT-LYM instrument was used in the GALLIUM trial to measure HRQOL. Three summary scales were reported, including FACT-LYM Total, FACT-LYM TOI, and FACT-LYM Lymphoma specific. From the end of induction treatment onwards, patients in both groups experienced clinically meaningful improvements from baseline in all scales. Furthermore, in the maintenance setting, approximately 50% of patients in each treatment group reported clinically meaningful improvements in mean score for each scale. However, over the course of treatment, there were no differences between the two groups in any FACT-LYM scale scores at any time point. Based on these data, there appears to be no detrimental impact on HRQOL with obinutuzumab.

Safety[1]

In the GALLIUM trial, the group receiving obinutuzumab had a higher incidence of AEs and SAEs compared to rituximab. Grade 3 -4 toxicity was 74.6% versus 67.8% in the obinutuzumab arm, compared to rituximab. Infusion-related reactions were common in both arms. The rate of grade 3-5 infusion-related reactions was 6.6% with obinutuzumab compared with 3.5% with rituximab. These reactions accounted for the highest number of SAEs (4.4% versus 1.8%). Neutropenia was also common, yet the more clinically relevant rate of febrile neutropenia was low in both arms (3% versus 2.2%). The main grade 3 - 4 toxicities reported are common and expected with lymphoma therapy and would be considered manageable to support a patient through such events. The death rate secondary to AEs was 4% in the obinutuzumab group compared to 3.4% in the rituximab group, with the same relative proportion of deaths equal throughout the induction, maintenance and follow up phases of the study.

Second malignancies were higher in the obinutuzumab group compared to the rituximab group. The difference was most striking in the follow up phase of the trial where 5.2% of

patients receiving bendamustine-obinutuzumab developed a second malignancy compared to 0.8% who received bendamustine-rituximab. The reason for this is unclear. Further analysis with respect to the types of secondary malignancies and the clinical relevance of this will be necessary, and should be the topic of further research.

The Submitter provided feedback on pERC's Initial Recommendation, and noted that progression of disease at 24 months (POD24) may be a relevant endpoint to consider in FL trials that may help to further characterize clinical benefit[13]; and cited a retrospective study that demonstrated POD24 is an accurate predictor of poor OS.[14] The Submitter noted that in the GALLIUM trial obinutuzumab combined with chemotherapy was associated with a reduction in the risk of a PFS event; and a reduction in the risk of a POD event relative to rituximab-chemotherapy at 24 months, based on an exploratory analysis.[15].

In response to the Submitter's feedback, the CGP noted that there is currently insufficient evidence to support the use of POD24 as a surrogate endpoint for OS. The analysis of POD24 in the GALLIUM trial was considered exploratory and requires prospective evaluation and validation as a surrogate endpoint for OS. Longer-term follow up data are necessary to draw definitive conclusions on the clinical benefit of obinutuzumab in previously untreated patients with FL.

1.3 Conclusions

The CGP concluded that there ***may be*** a net clinical benefit to the use of obinutuzumab combined with chemotherapy, followed by obinutuzumab monotherapy in patients who have a response for the treatment of previously untreated FL with bulky stage II disease (≥7 cm), or symptomatic stage III or IV disease, based on one high-quality RCT that demonstrated a statistically significant benefit in PFS for obinutuzumab compared with rituximab. Adverse event profiles were similar between the two treatment regimens.

Progression free survival is a clinically relevant endpoint in FL. Given the indolent nature of the disease and long survival, OS analysis is very difficult. The difference in PFS by INV was 6.7% by and 4% by IRC. This is a small benefit and whether this is clinically meaningful is difficult to determine. Over time, the clinical significance of the difference in PFS will likely be clarified. Other factors to consider include the response rate and safety concerns. There is no significant difference in response rates at the end of induction treatment to support the use of obinutuzumab over rituximab. Also, from a safety perspective, there appears to be a higher rate of secondary malignancies in patients treated with obinutuzumab. Although further analysis is necessary, this is an area of concern that requires further analysis to determine the impact on patients.

In making this conclusion, the CGP also considered the following:

1) PFS is an appropriate measure of effectiveness for FL, as mentioned above.
2) Maintenance obinutuzumab was given every two months in the GALLIUM trial. The current standard of care is giving rituximab every three months. There is insufficient evidence at this time to support administering obinutuzumab maintenance treatment every three months.
3) Obinutuzumab increases chair time for administration because of the more frequent administration during maintenance therapy as well the need for IV administration compared to rituximab, which can be given less frequently, and subcutaneously in some provinces.

4) The side effect profile is predictable and manageable.
5) The benefits of obinutuzumab are seen regardless of the chemotherapy backbone..
6) Further data are necessary with respect to the risk of secondary malignancies with the combination of bendamustine and obinutuzumab.
7) There is currently no evidence to guide sequencing of therapy for subsequent lines of therapy at the time of relapse.
8) At the present time, given that the overall magnitude of benefit is small, there is insufficient data to recommend obinutuzumab across all subtypes of low grade lymphoma.
9) In the GALLIUM trial, G-CSF was used to support patients with neutropenia (48.1% in the rituximab group and 49.6% in the obinutuzumab group, respectively).[12] In Canada this is not routinely used. Although some patients in Canada may receive this as secondary prophylaxis, other strategies such as dose delay or dose reduction would be used. G-CSF use is not a requirement for the treatment of patients with FL.

2 BACKGROUND CLINICAL INFORMATION

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

2.1 Description of the Condition

Follicular lymphoma is the most common type of indolent NHL, and is the second most common NHL accounting for 35% of cases. NHL is the 6th most common cancer diagnosed in Canada with an incidence of 25 cases per 100,000 people.[16] The median age at the time of diagnosis of 59 years old. Prognosis is based on several patient-specific and disease specific variables at the time of diagnosis and is calculated by the FLIPI.[17] Based on this model the 10 year survival for patients with high risk disease is 42%, compared to 84% in the low-risk group.

The diagnosis of FL is typically made on an excisional lymph node biopsy. The classification of lymphoma is standardized by the World Health Organization based on the histologic features of the lymph node. The grade of lymphoma is also determined based on the number of blasé cells seen by microscopy. In FL, grade 1, 2, and 3a are all considered indolent lymphoma, and are managed similarly. Grade 3b FL is classified as an aggressive lymphoma because it has a higher percentage of blast cells, and therefore, its behaviour, management and prognosis differs from the indolent subtypes.

Staging of lymphoma is based on the Ann Arbour staging system. Initial investigations to determine the stage requires a CT scan of the chest, abdomen and pelvis, as well as a bone marrow biopsy. stage I and II disease are defined as disease confined to the same side of the abdomen. Stage III disease has widespread adenopathy above and below the diaphragm, and stage IV disease is defined as bone marrow involvement or diffuse extralymphatic organ involvement. For patients with stage I or II disease, they may be considered for radiation alone as a potentially curable option. Early stage bulky disease or advanced stage disease is considered incurable. In symptomatic patients with extensive disease, chemoimmunotherapy is used to treat the widespread disease.

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.[18] However, early intervention in asymptomatic patients using single agent rituximab immunotherapy resulted in improved PFS.[19] Long-term outcomes of such therapy remain 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, DOR and OS.[20] In Canada, standard first line therapy for FL is with bendamustine and rituximab. This regimen had an improvement in PFS, and improved time-to-next-treatment compared to R-CHOP chemotherapy in the first line setting.[21] The side effects of bendamustine and rituximab are less than with R-CHOP chemotherapy, further solidifying this regimen as standard therapy. Prior to the widespread availability of bendamustine, R-CHOP or CVP-R chemotherapy was considered standard of

care. Although there may be occasional patients where these regimens would be preferred, the vast majority of Canadian patients with FL would receive bendamustine and rituximab.

Upon completion of chemoimmunotherapy, maintenance rituximab for two years is given based on evidence confirming maintenance therapy improves PFS and OS. Various dosing regimens for maintenance therapy have been studied, but never compared to determine the optimal treatment regimen.[20] For the majority of Canada, the dosing frequency for maintenance therapy is every three months for two years.

Eventually patients with advanced FL will develop progressive disease after first line and maintenance therapy. A "watch and wait" strategy can be used until patients develop symptomatic disease arises as outlined above. Many chemoimmunotherapy regimens have demonstrated activity in the second line setting, but they have never been compared against each other. Consequently, there is no standard of care for treating relapsed disease. For patients with remissions longer than six months after their last dose of rituximab, retreatment with a rituximab-containing regimen is common. Also, retreating with the same regimen as in first line, can also be considered if the remission was prolonged after first line therapy (7).[22] Consequently, the choice of regimen is partly dependent on what was used in the past if the duration of remission is greater than 12-24 months, or whether the introduction of a drug with a different mechanism of action is necessary. Aside from chemoimmunotherapy, for a small select group of patients with high risk disease under the age of 70, autologous stem cell transplant can be considered in the relapsed setting, although the benefits of such therapy are controversial.[23] An even smaller group of patients under the age of 40 could also be considered for allogeneic stem cell transplant. However, the magnitude of benefit is also uncertain compared to the advances made in chemoimmunotherapy.

Despite the advances in treatment, FL remains an incurable disease that can be fatal. There is an ongoing need for novel therapeutic approaches and agents to improve survival and maintain QOL. Obinutuzumab is one such agent to potentially improve outcomes in these patients with FL. Obinutuzumab is a glycoengineered antiCD20 monoclonal antibody with enhanced functional activities leading to greater direct cell death and antibody-dependent cell-mediated cytotoxicity.[24] In patients refractory to rituximab, obinutuzumab has proven to be an effective agent to prolong PFS and OS compared to bendamustine alone.[25] Whether such benefits are seen in the rituximab-naïve population for both induction and maintenance therapy is still under investigation and will be discussed in this review.

2.3 Evidence-Based Considerations for a Funding Population

The population under consideration is symptomatic patients with FL who are treatment naïve. This includes patients with bulky stage II disease (greater than 7 cm), or stage III or IV disease. The proposal is to replace the standard first-line therapy of bendamustine and rituximab with bendamustine and obinutuzumab in Canada. No additional testing diagnostic or pathologic testing would be necessary beyond standard of care.

2.4 Other Patient Populations in Whom the Drug May Be Used

Currently, there is insufficient evidence to extrapolate this data to other subtypes of low grade lymphoma. These data do not extrapolate to high grade/aggressive lymphoma.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient group, Lymphoma Canada (LC), provided input from patients with FL. LC conducted two separate online surveys for caregivers and patients; the surveys were sent to patients between February 26th, 2018 and March 25th2018, and to caregivers between June 5th, 2017 and June 30th, 2017. Links to the surveys were made available through email, LC Twitter and Facebook accounts, and through international lymphoma organizations' own accounts. The surveys contained multiple choice, rating, and open-ended questions on disease symptoms and treatment side effects, their impact on QOL, as well as expectations for new treatment. The surveys used built-in skipping logic so respondents could only answer questions relevant to them.

A total of 115 respondents, 96 patients and 19 caregivers, provided input to LC. Demographic information on the 115 respondents is summarized in Tables 1 and 2. A total of 79 patients provided information regarding their country of residence, 67% of whom reported they resided in Canada. Additional demographic data were obtained from 78 patients, of whom 50% were between 40-59 years old, and 44% were 60 years or older. At the time of completing the survey, seven (36.8%) of the 19 caregivers were retired and 12 (63.2%) were still working. Six of the 96 patients have experience with obinutuzumab; these patients (three female, two male) are between the ages of 20 and 59 and all reside in the US.

Table 1: Country of survey respondents (n=79)

Respondents	CAN	USA	UK	Other	Skipped	Total
Patients WITH obinutuzumab experience	0	6	0	0	0	6
Patients WITHOUT obinutuzumab experience	53	5	14	1	17	90
Caregivers	12	3	2	0	2	19

Table 2: Gender and age of survey respondents (n=78)

Respondents	Age Range					Gender		
	< 20	20-39	40-59	≥ 60	Did not answer	Female	Male	Did not answer
Patients WITH obinutuzumab exp.	0	1	4	0	1	3	2	1
Patients WITHOUT obinutuzumab exp.	0	4	35	34	17	54	19	17
Caregivers	0	4	4	10	1	14	4	1

Most respondents rated longer survival (87%) and longer remission (79%) as extremely important for a new treatment when compared to current therapies. Better quality of life (69%) and fewer side effects (44%) were rated as extremely important less frequently.

Among 90 patient respondents, a number of symptoms associated with FL at diagnosis were reported as impacting QOL. The most commonly reported symptoms were fatigue, enlarged lymph nodes and drenching night sweats. Anxiety and worry were symptoms associated with FL that were specifically noted as having a negative impact on the QOL of patient respondents.

Seventy-eight respondents reported having experience with treatments for FL. Fatigue, diarrhea, nausea/vomiting, hair loss, mouth sores, and neutropenia were the most commonly reported side effects of currently available treatments. Fatigue, nausea/vomiting, and pain were reported as being most difficult to tolerate.

Only six patient respondents reported having experience with obinutuzumab treatment, and all reported that their treatment was able to manage most of their disease symptoms. LC reported that obinutuzumab was well-tolerated among the six patients. Fatigue was reported as the most

difficult side effect to manage, as five of the six respondents reported their fatigue symptoms as ongoing, and worsening throughout treatment. Fatigue was reported to have also been a symptom that negatively impacted the respondents' QOL.

Below is a summary of the specific input received from LC. Quotes are reproduced as they appeared in interviews with no modifications made for spelling, punctuation or grammar. The statistical data that are 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 FL

The symptoms of FL that most commonly affected patient respondent's QOL at diagnosis (n=90) included fatigue or a lack of energy (45%), enlarged lymph nodes (46%), drenching night sweats (24%), pain (23%), and shortness of breath (17%). Other symptoms affecting QOL in ≥10% of respondents included unexplained weight loss, frequent infections, anemia and an enlarged spleen. LC also noted that 26% of respondents reported experiencing no symptoms at diagnosis.

LC noted that the majority of respondents (76%) also reported that FL negatively affected their QOL by mental and emotional problems associated with their disease, with the main symptom or problem being anxiety or worry (54%). Other reported mental and emotional symptoms affecting QOL included problems concentrating (28%), stress of diagnosis (27%), difficulty sleeping (25%), memory loss (20%), depression (20%), and loss of sexual desire (14%). There was also a proportion of respondents (24%) who reported none of the aforementioned symptoms.

Eight-nine patient respondents reported on the aspects of their lives that have been negatively impacted by FL. The most commonly reported aspect of life negatively impacted by FL was the ability to work (45%). Other aspects included family obligations (39%), personal image (39%), intimate relations (20%), and friendships (18%). Twenty-six percent of these patients reported that no aspects of their lives were affected by FL.

3.1.2 Patients' Experiences with Current Therapy for FL

Information regarding experience with FL treatments was obtained from 78 respondents. At the time of the survey the majority of the 78 patient respondents (46%) were in remission following one or more lines of therapy, 18% had not yet received any treatment and were under a "watch and wait" period following their diagnosis, 13% were undergoing first-line treatment, 14% had relapsed after one or more lines of therapy, and 9% of respondents selected "other" with no additional information provided. Sixty-one respondents provided information about their first-line therapy; 75% of these patients received combination chemotherapy and rituximab (R) treatment (R-bendamustine: 34%; R-CVP: 26%; R-CHOP: 15%). CHOP, CVP, rituximab monotherapy, radiation therapy and chlorambucil were other reported first-line therapies. Approximately 30% of the respondents reported having received two or more lines of therapy for FL.

The side effects of current FL therapies, reported by 61 respondents, are summarized in Table 4; the side effects listed were experienced any time during a patient's treatment, which included induction, maintenance, salvage and consolidation therapies. According to LC, fatigue, diarrhea, nausea/vomiting, hair loss, mouth sores, and neutropenia were the most commonly reported side effects by the 61 respondents. Fatigue (18/49; 37%),

nausea/vomiting (5/49; 10%), and pain (5/49; 10%) were cited as being most difficult side effects to tolerate among the 49 patient respondents providing this information.

At the time of being surveyed, of the 61 respondents who reported their side effects, 43 (70%) had received or were currently receiving maintenance rituximab therapy, 60% had completed the full course of maintenance treatments, 30% were still receiving maintenance treatments, 7% stopped maintenance early due to disease relapse, and 5% stopped early due to treatment side effects.

The patients surveyed reported a number of side effects while taking rituximab maintenance therapy; the most common included fatigue (40%), infection (10%), headache (10%), skin rash (10%), and neutropenia (10%). No side effects were reported by 40% of respondents. When asked about whether they would take rituximab again if the treatment was recommended by their doctor, a majority of 39 respondents (79%) selected "yes", 15% selected "did not know", and 5% selected "no".

Table 4: Side effects of current FL therapies (61 respondents)

Side effect	% of respondents	Side effect	% of respondents
Fatigue	85%	Infusion reaction	18%
Nausea/vomiting	51%	Low platelets	16%
Hair loss	39%	Cough	13%
Mouth sores	30%	Breathing difficulties	12%
Neutropenia	28%	Viral reactivation (e.g.	10%
Skin rashes/severe itching	21%	I did not experience any SEs	7%
Diarrhea	53%	Back pain	7%
Infections	18%	Bowel obstruction	7%

LC asked respondents to rate, on a scale of 1 to 5 (with 1 being not important, and 5 being extremely important), the importance of a number of outcomes related to a new treatment for the first-line treatment of FL. The number of respondents providing ratings was 77 or 78 depending on the outcome. Most respondents rated longer survival (87%) and longer remission (79%) as extremely important for a new treatment when compared to current therapies. Better QOL (69%) and fewer side effects (44%) were rated as extremely important less frequently among respondents.

Respondents also expressed a willingness to endure potentially serious side effects if a new treatment was deemed the best choice for them by their doctor. According to LC, 36% of respondents reported that they would take a drug with known, potentially serious side effects if their doctor recommended it as their best treatment choice, while 15% reported that they would not.

3.1.3 Impact of FL and Current Therapy on Caregivers

LC asked caregivers to rate, on a scale from 1 to 10, how their own QOL and day-to-day activities were impacted due to caring for someone with FL. Factors with an average rating of ≥5 were found to have a greater than neutral impact on day-to-day life.

For caregivers who are currently in the work force, aspects of day-to-day living with an average rating of ≥5 included the ability to travel (rating=5.8), work (rating=5.4), concentrate (rating=5.3), and volunteer (rating=5.0). For caregivers who were retired, aspects of day-to-day

living with an average rating of ≥5 were the ability to volunteer (rating=7.4) and travel (rating=6.8). LC noted that the ability to travel was also the most skipped survey question among caregivers. Other aspects of life that were negatively impacted for caregivers are listed in Table 3.

Table 3: Impact of FL on Caregivers

Impact on Day-to-Day Life of Retired Caregivers (n= 7)	Rating of ≥7 n (%)	Rating Average	Impact on Day-to-Day Life of Not 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

LC provided the following two quotes from caregivers to describe further challenges that emphasize the emotional and psychological toll that FL can have on both patients and the caregivers, as well as the amount of time and effort involved with being a caretaker.

- *"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)
- *"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)

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with Obinutuzumab

Among all 115 respondents, only six reported having experience with obinutuzumab. All six respondents resided in the USA, and the majority were between 40 and 49 years of age (Table 6). The six respondents accessed the drug through a clinical trial or private insurance.

Table 5: FL patient respondents with obinutuzumab experience

Patient	Gender	Age	Location	Date of diagnosis	Access to drug	Date started treatment
1	Male	40-49	USA	2018	Private insurance	2018
2	Female	40-49	USA	2014	Clinical trial	2015
3	Male	50-59	USA	2013	Clinical trial	2013
4	-	-	USA	2017	Private insurance	2018
5	Female	40-49	USA	2014	Clinical trial	2014
6	Female	20-39	USA	2012	Clinical trial	2013

All six patient respondents with obinutuzumab experience reported that their treatment of chemotherapy and obinutuzumab was able to manage most of their disease symptoms, which included enlarged lymph nodes, fever, shortness of breath, anemia and night sweats. LC reported that obinutuzumab was well-tolerated as a treatment by all six patients, and that side effects were tolerable in most cases. Fatigue was reported as the most difficult side effect to manage, with five of the patients reporting that their symptoms of fatigue were ongoing, and worsened throughout their treatment. Four of the six patients reported that, among all side effects, fatigue was the hardest to tolerate. One of the six patients reported that constipation was the worst experienced side effect. An infusion reaction was reported by one patient, however LC noted that this patient only experienced this reaction once.

Table 6: Side effects experienced with obinutuzumab (n=6)

Side effect	Number of responses
Fatigue	5 (83%)
Neutropenia	4 (67%)
Infections	3 (50%)
Hair loss	2 (33%)
Viral reactivation (e.g. shingles)	2 (33%)
Mouth sores	1 (17%)
Diarrhea	1 (17%)
Skin rashes/severe itching	1 (17%)
Infusion reaction	1 (17%)
Back pain	1 (17%)
Breathing difficulties	1 (17%)

Table 6: Side effects experienced with obinutuzumab (n=6)	
Side effect	**Number of responses**
Constipation	1 (17%)

On a scale from 1 to 5, the six respondents were asked to rate how obinutuzumab impacted their QOL (1=little negative impact; 5=significant negative impact). Treatment-related fatigue and activity level were rated by most patients (n=4) as having a significant negative impact on their QOL, while one patient rated toleration of the treatment as having a significant negative impact. None of the respondents indicated that infusion time, number of clinic visits, infusion reactions, or number or frequency of infections as having a significant negative impact on their QOL.

LC reported that four of the patients received, or were still receiving maintenance obinutuzumab therapy following first-line treatment. All four respondents completed their full course of obinutuzumab maintenance therapy. Neutropenia (75%), fatigue (50%), infection (25%), headache (25%), and skin rash (25%) were commonly reported side effects of obinutuzumab among the four respondents. One respondent was reported by LC as not having experienced any side effects related to obinutuzumab maintenance treatment.

The following are quotes provided by LC from five patient respondents after being asked how treatment on chemotherapy and obinutuzumab affected their well-being and health:

- *"The treatments weren't as bad as I thought they'd be. I was able to look after my kids even though I was really tired a lot of the time."*
- *"really draining, but I'm happy it worked and the lymphoma seems to be gone....at least for now."*
- *"I haven't had any problems yet, but I have only had 2 treatments"*
- *"Aside from having to sleep a lot, the treatment wasn't that hard to go through."*
- *"Remission in two months but have to travel long distance for clinical trial."*

Among the five patients who provided quotes, they all reported that they would consider taking obinutuzumab therapy again if it was recommended by their physician as their best choice of treatment.

3.3 Additional Information

LC provided respondents with a written summary containing results of a clinical trial comparing standard of care first-line treatment for FL (chemotherapy and rituximab) against an experimental treatment (chemotherapy and obinutuzumab). The information contained in the summary was reported by LC to have been confirmed by a clinical expert as accurate. Briefly, the results of the trial indicated the following:

- 5% more people in the experimental treatment group were in remission following three years of treatment compared to standard of care
- The types of side effects occurring in the two treatment groups were the same but some side effects occurred more frequently in the experimental group, including neutropenia and infusion reactions that can cause itching, rash, wheezing and swelling
- Rates of infections and treatment-related deaths were the same in both treatment groups
- It's too early to determine if overall survival is improved with the experimental treatment compared to the standard of care

Upon reading the summary, 78 respondents were asked whether they would want the combination of rituximab and chemotherapy, or obinutuzumab and chemotherapy as their first-line treatment for FL if they had the choice. There were 38% of respondents who reported that they would choose the experimental treatment (obinutuzumab and chemotherapy), 10% who would choose the standard of care (rituximab and chemotherapy), 31% who would choose the treatment option recommended to them by their oncologist, and 22% who did not know which treatment option they would choose.

LC reported respondents' preference of therapy (based on the summary) according to their current treatment stage (Table 7). Overall, a greater proportion of respondents who were currently on treatment or on "watch and wait" after a relapse, and who were on treatment or in remission for less than six months, reported choosing the combination of obinutuzumab and chemotherapy as their first-line treatment option after reading the summary. The treatment recommended by an oncologist was reported most often among patients in remission for at least six months, and second most often for patients in treatment or in remission for less than six months and for patients who were in treatment or on "watch and wait" after a relapse.

Table 7: Treatment choice of respondents at various stages of treatment

Respondent's treatment choice	Respondent's treatment stage			
	Watch & wait after diagnosis (n=14)	In treatment or in remission < 6 months (n=17)	In remission ≥ 6 months (n=36)	In treatment or watch & wait after relapse (n=11)
Standard of care	0%	12%	11%	18%
Experimental Treatment	29%	47%	31%	55%
Treatment recommended by oncologist	14%	35%	36%	28%
I don't know	57%	6%	22%	0%

Among respondents who chose experimental treatment as their chosen treatment option after reading the summary, LC obtained responses as to why respondents chose the treatment option. Many of the patient responses, as reported by LC, expressed a hope that with the experimental treatment, patients could stay in remission for as long as possible without undergoing further harsh treatments. The following are quotes provided by LC as responses from individuals who chose the treatment of obinutuzumab and chemotherapy after reading the summary:

- *"want to stay in remission as long as possible"*
- *"Short term side effects versus chance of longer remission. I'm relatively young with a teenage son, this is very important to me."*
- *"longer remission is more appealing despite more initial side effects"*
- *"I would want the chance of staying longer in remission, despite potentially more side effects."*
- *"Chemo sucked - the longer the remission, the better."*
- *"The longer my remission the better. The less treatment the better for me!"*
- *"would want to take the drug treatment that kept me in remission the longest regardless of short term side effects"*

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 nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of obinutuzumab for FL.

Clinical factors:

- Use in other indolent lymphomas
- Comparison of obinutuzumab plus bendamustine to rituximab plus bendamustine

Economic factors:

- Additional chemotherapy chair time in the first month of treatment and in maintenance phase with obinutuzumab

Please see below for more details.

4.1 Currently Funded Treatments

The standard of care in Canada is bendamustine plus rituximab. The comparator arm in the GALLIUM trial was rituximab plus CHOP, rituximab plus CVP or rituximab plus bendamustine. If available, PAG is seeking data of the group of patients who were treated with rituximab plus bendamustine compared to the group of patients treated with obinutuzumab plus bendamustine, as this would be the most relevant comparison in Canadian practice.

4.2 Eligible Patient Population

The GALLIUM trial and funding request is for patients with FL. The pERC recommendation and the funding of rituximab plus bendamustine are for indolent non-Hodgkin lymphoma and mantle cell lymphoma. PAG is seeking information on the use of obinutuzumab plus bendamustine (or chemotherapy) in patients with other types of indolent lymphomas such as marginal zone lymphoma, lymphoplasmacytic lymphoma, MALT lymphoma and mantle cell lymphoma.

4.3 Implementation Factors

Additional resources and chemotherapy chair time are required for the administration of obinutuzumab. In cycle 1, obinutuzumab is administered on days 1, 8 and 15, which requires an incremental two chemotherapy visits compared to cycle 1 rituximab. In addition, obinutuzumab is infused over approximately four hours after cycle 1, whereas rituximab after cycle 1 can be infused over 90 minutes, and if rituximab subcutaneous injection is available after cycle 1, administration time is 5 minutes.

Obinutuzumab maintenance is administered every two months while rituximab maintenance is usually administered every three months. PAG is seeking data on whether there is an alternate dosing schedule for obinutuzumab in the maintenance setting.

Additional resources may be required to monitor and treat adverse events, which appear

to be more frequent with obinutuzumab than with rituximab.

The dose of obinutuzumab is 1000mg and the vials are available as 1000mg. There is no drug wastage.

4.4 Sequencing and Priority of Treatments

PAG is seeking data on the use of rituximab plus chemotherapy after obinutuzumab plus chemotherapy.

4.5 Companion Diagnostic Testing

None.

4.6 Additional Information

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two clinician inputs were provided on obinutuzumab for first line therapy of FL. One clinician input was provided by an individual oncologist from Cancer Care Ontario, while the other was a joint submission from oncologists at CancerCare Manitoba. Overall four clinicians provided input, and two of them had experience with obinutuzumab.

Overall, clinicians identified that obinutuzumab meets current clinical needs for patients with FL, and that it may provide patients with a treatment option that will prolong time between treatments, compared to rituximab, for patients who will need to be eventually retreated. However, there was agreement that obinutuzumab results in greater toxicity and infusion reactions compared to rituximab. Clinician input suggested that such infusion reactions would be easily manageable. Further clarification was sought after regarding downstream maintenance therapies for patients.

Please see below for details from the clinician inputs. Please see below for a summary of specific input received from the registered clinician(s).

5.1 Current Treatment(s) for FL

The clinicians providing input indicated that first line therapy for patients with FL in Canada was chemotherapy and rituximab, specifically bendamustine and rituximab. It was noted that in most provinces, bendamustine is given at a dose of 90mg/m^2 on days 1 and 2, and that rituximab is given on day 1 of a 28-day cycles for six cycles. Rituximab maintenance therapy was administered every three months for two years or for eight cycles. The clinicians providing input noted that RCHOP can be used as an alternative option for patients.

5.2 Eligible Patient Population

The clinicians providing input expressed that the patient population in the funding request of the submitter was relevant, and met the needs present in clinical practice. It was noted that FL is the most common non-Hodgkin lymphoma, and that newly diagnosed patients, as well as those previously followed with a watch and wait strategy who develop a need for treatment, would be eligible for obinutuzumab. The clinicians providing input would like to extend the use of obinutuzumab to other CD20+ indolent lymphomas.

5.3 Relevance to Clinical Practice

Referring to the GALLIUM trial (comparing first line obinutuzumab and chemotherapy versus first line rituximab and chemotherapy), clinicians providing input reported that the obinutuzumab and chemotherapy arm resulted in lower risk of progression, relapse and death at three years compared to the rituximab and chemotherapy arm. They noted that patients in the GALLIUM trial taking obinutuzumab and chemotherapy were also less likely to require retreatment during the follow-up period, compared to patients taking rituximab and chemotherapy. The GALLIUM trial was unable to detect differences in survival between the groups; however, the clinician input suggested that this was expected, as patients with FL have relatively long survival making it unlikely to detect any significant differences with such a short follow-up period. The obinutuzumab and chemotherapy arm also faced greater toxicity, greater infusion-related events, and grade 3-5 adverse events. Both treatment arms faced equal deaths. The clinicians providing input suggested that infusion-related events do not occur frequently after the first cycle of treatment, therefore management of these side effects should be controllable. Clinicians providing input indicated that there was no difference in QOL between obinutuzumab and chemotherapy and rituximab and chemotherapy. They also noted that the GALLIUM trial enrolled patients with marginal zone lymphoma subtypes; the published literature includes results for patients with FL, grades 1-3a only. Therefore, the clinicians providing

input suggested that obinutuzumab and chemotherapy should be used as first line treatment for patients with FL, grades 1-3a only.

In one of the clinician input it was stated that the increased infusion reactions with obinutuzumab and other adverse events related to obinutuzumab were as expected. The clinician providing input noted a strong PFS benefit, greater chair time and an insignificant difference in OS with obinutuzumab compared to rituximab. It was mentioned that the PFS difference was good for an indolent lymphoma, and that the nonsignificant OS may be due to the early follow-up time in the study.

In one of the clinician input, it was noted that the observed advantage in PFS among patients taking obinutuzumab and chemotherapy versus rituximab and chemotherapy was clinically meaningful. The clinician input suggested that overall, this improvement translates into greater time between anti-lymphoma therapies for patients who will eventually need retreatment.

5.4 Sequencing and Priority of Treatments with New Drug Under Review

The clinicians providing input stated that obinutuzumab would be used as first line therapy and prior treatments are irrelevant: only patients who were not previously treated with chemo-immunotherapy would be eligible.

After follow-up with one of the clinicians providing input, clarification regarding sequencing with obinutuzumab was provided. Specifically, clarification regarding what would be provided to patients who had no response to obinutuzumab or to patients who have a relapse at any time after receiving obinutuzumab. It was stated by the clinician that they did not expect very many patients who were previously untreated not to have at least a partial response to obinutuzumab and chemotherapy; if a patient did not exhibit a response, it was suggested that they should be investigated for transformed lymphoma.

The clinician suggested that for patients who show early relapse (less than two to five years), patients would be treated with a different chemotherapy backbone plus a monoclonal antibody. For example, patients who received CHOP initially would then receive bendamustine, and vice versa; the clinician noted that currently there is no evidence to dictate which treatment to use. Similar to current practices with rituximab refractoriness, the clinician suggested that if patients were to relapse within six months of receiving obinutuzumab, it would be very unlikely that they would continue to use obinutuzumab.

For patients who showed later relapse, the clinician suggested the use of a different chemotherapy backbone regimen, or the repeat of the same regimen previously given in addition to a monoclonal antibody. Once again, they stated that there is no evidence currently to suggest which treatment path to choose for patients.

5.5 Companion Diagnostic Testing

Not applicable.

5.6 Additional Information

No further additional information was provided.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of obinutuzumab in combination with chemotherapy, followed by obinutuzumab monotherapy, in previously untreated patients with FL.

A Supplemental Question relevant to the pCODR review and to the Provincial Advisory Group was not identified:

- What is the clinical efficacy, safety and therapeutic equivalence of obinutuzumab administered every two months in the maintenance setting, compared to obinutuzumab administered every three months, for the first-line treatment of patients with FL?

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. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 3. Selection Criteria

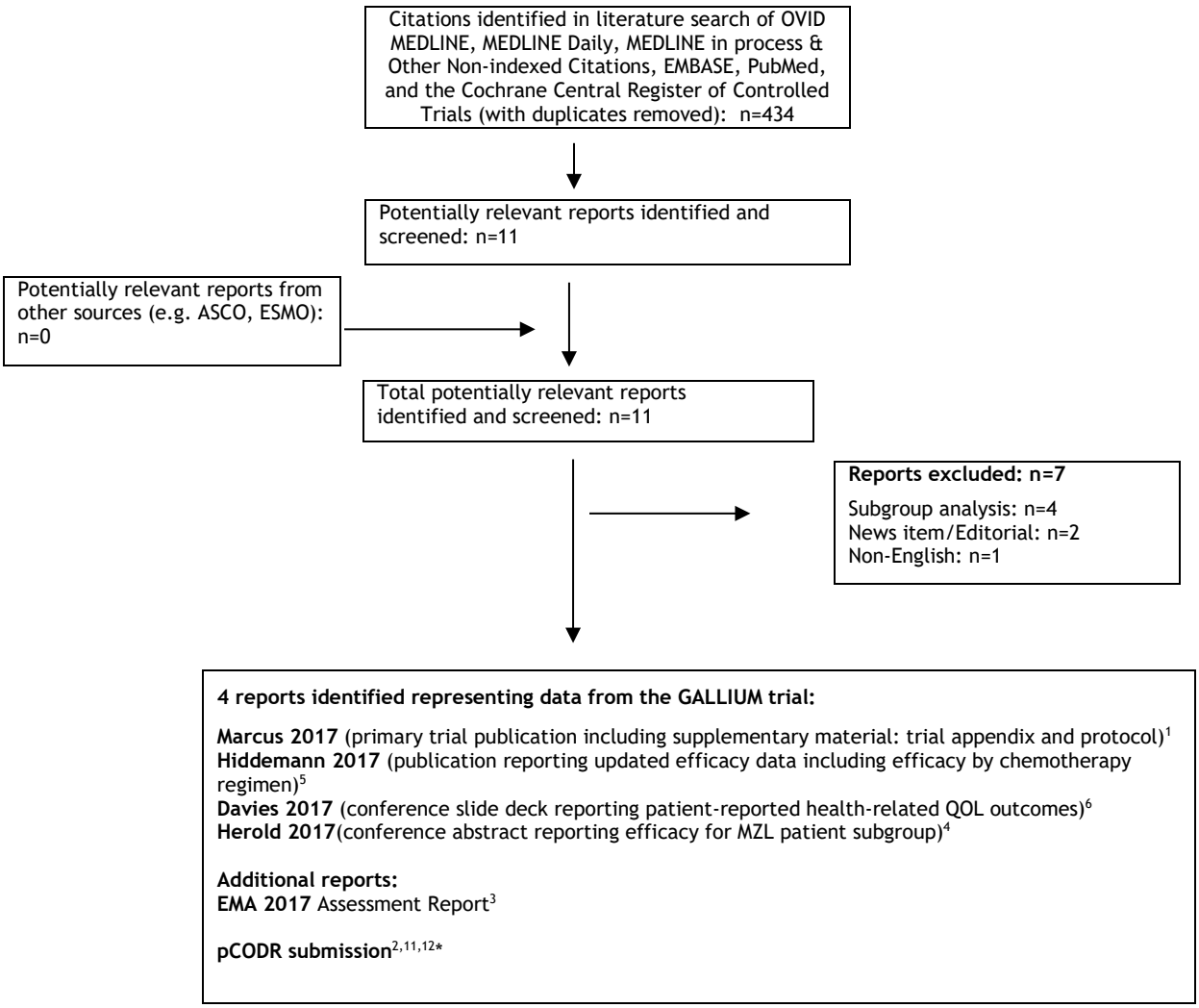
Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators[†]	Outcomes
• Published and unpublished RCTs • In the absence of RCTs, fully published clinical trials investigating the efficacy and safety of obinutuzumab and chemotherapy should be included. • Trials with a dose escalation design should be excluded[‡]	• Previously untreated adult patients with advanced stage (stage III, IV, or stage II with bulky disease), CD-positive, indolent B-cell follicular lymphoma (grade 1, 2, or 3a). Patient subgroups of interest: • FLIPI risk groups	Induction: obinutuzumab IV plus chemotherapy Maintenance: obinutuzumab IV	Rituximab plus chemotherapy Chemotherapy may include: • Bendamustine • CHOP • CVP	• PFS • ORR and CR • OS • Time-to-next treatment • HRQOL • Safety o Infusion reactions o TLS o Neutropenia o Thrombocytopenia o Infections
Abbreviations: CHOP - cyclophosphamide + doxorubicin + vincristine + prednisone; **CR** - complete response; **CVP** - cyclophosphamide + vincristine + prednisone; **FLIPI** - Follicular Lymphoma Prognostic Index; **HRQOL** - health-related quality of life; **IV** - intravenous; **ORR** - overall response rate; **OS** - overall survival; **PFS** - progression-free survival; **RCT** - randomized controlled trials; **TLS** - tumour lysis syndrome.				
Notes: [†] Standard and/or relevant therapies available in Canada. [‡] Mixed trial designs could be included if efficacy results for dose of interest were reported separately.				

6.3 Results

6.3.1 Literature Search Results

Of the 434 potentially relevant reports identified, four reports[1,4-6] were included in the pCODR systematic review and seven reports[15,26-31] were excluded. Studies were excluded because they were exploratory subgroup analyses of the GALLIUM trial data not of interest to this review,[15,26,27,31] news items or editorials,[28,29] or a non-English publication.[30]

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



**Note: Additional data related to the GALLIUM trial was obtained through requests to the Submitter by pCODR.*

6.3.2 Summary of Included Studies

One RCT was identified that met the selection criteria of the pCODR systematic review. Details of the included GALLIUM trial[1] are summarized in Table 4.

6.3.2.1 Detailed Trial Characteristics

Table 4: Characteristics of the Included GALLIUM Trial.[1]

Trial Design	Eligibility Criteria	Intervention and Comparator	Trial Outcomes
GALLIUM (NCT01332968) Two group, parallel, open-label phase 3 trial, 1:1 randomization Patient enrolment dates: July 6, 2011 to February 4, 2014 No. randomized FL patients: 1202 No. of randomized FL patients treated: 1192 Primary analysis: January 31, 2016 Final analysis: 2020 177 sites[3] in 18 countries (Australia, Belgium, Canada, China, Czechia, Finland, France, Germany, Hungary, Israel, Italy, Japan, Russian Federation, Spain, Sweden, Taiwan, United Kingdom, United States)[32] Funded by Hoffman-La Roche Ltd.	<u>Key Inclusion Criteria</u>: • Age ≥18 years • Histologically documented, CD20-positive indolent B-cell FL (grades 1-3a) or MZL • Biopsy material from an excisional, performed 12 months prior to randomization • Ann Arbor stage III or IV disease, or stage II bulky (nodal or extranodal mass ≥7cm in diameter) • At least one bidimensionally measurable lesion (>2cm by CT or MRI) • FL requiring treatment according to GELF criteria[a] • ECOG 0,1 or 2 • Adequate hematologic function[b] <u>Key Exclusion Criteria:</u> • Prior treatment for NHL by chemotherapy, immunotherapy or radiotherapy[c] • CNS lymphoma, leptomeningeal lymphoma or histologic evidence of transformation to a high-grade or diffuse large B-cell lymphoma • Grade 3b FL, SLL, or Waldenström's macroglobulinemia • Ann Arbour stage 1 disease • History of severe allergic or anaphylactic reactions to MAB therapy, or hypersensitivity to any of the study drugs • Regular treatment with corticosteroids during four weeks prior to the start of	<u>Intervention:</u> *Induction* Obinutuzumab 1000 mg IV, days 1, 8, and 15 of cycle 1, and on day 1 of subsequent 6 or 8 cycles depending on chemotherapy regimen (CHOP, CVP, or BENDA)[d] *Maintenance*[e] Obinutuzumab 1000 mg IV every 2 months for 2 years until PD <u>Comparator:</u> *Induction* Rituximab 375 mg/m^2 IV on day 1 of 6 or 8 cycles depending on chemotherapy regimen (CHOP, CVP, or BENDA) [d] *Maintenance*[e] Rituximab 375 mg/m^2 IV every 2 months for 2 years until PD No patient crossover permitted	<u>Primary:</u> PFS assessed by INV in patients with FL <u>Secondary:</u> • PFS assessed by IRC • ORR (CR + PR) at end of induction therapy[f] • OS • CR rate • EFS • DFS • DOR • Time-to-new anti-lymphoma treatment • HRQOL (FACT-Lym) • Safety

Trial Design	Eligibility Criteria	Intervention and Comparator	Trial Outcomes
	cycle 1, unless administered for indications other than NHL at a dose equivalent to ≤30mg/day of prednisone • Evidence of significant CVD or pulmonary disease • Known active infection requiring IV antibiotics or hospitalization within four weeks prior to cycle 1 • Life expectancy <12 months		

Abbreviations: **BENDA** - bendamustine; **CHOP** - cyclophosphamide, doxorubicin, vincristine, and prednisone; **CNS** -central nervous system; **CR** - complete response; **CVD** - cardiovascular disease; **CVP** - cyclophosphamide, vincristine, and prednisone; **DFS** - disease-free survival; **DOR** - duration of response; **ECOG** - Eastern Cooperative Oncology Group; **EFS** - event-free survival; **FACT-Lym** - Functional Assessment of Cancer Therapy-Lymphoma; **FL** - follicular lymphoma; **GELF** - Groupe d'Etude des Lymphomes Folliculaires; **IRC** - independent review committee; **IV** - intravenous; **MZL** - marginal zone lymphoma; **NHL**= indolent non-Hodgkin's lymphoma; **ORR** - overall response rate; **OS** - overall survival; **PD** - progressive disease; **PFS** - progression-free survival; **PR** - partial response; **SLL** - small lymphocytic lymphoma.

Notes:

[a] - GELF Criteria:
- High tumour bulk (tumour ≥7 cm diameter), three nodes in three distinct areas each measuring >3cm in diameter, symptomatic spleen enlargement, organ compression, or ascites or pleural effusion.
- Presence of systemic symptoms
- ECOG performance status >1
- Serum lactate dehydrogenase or beta2-microglobulin level above normal values.

[b] - Adequate hematologic function (unless abnormalities are related to NHL) was defined as:
- Hemoglobin ≥9.0 g/dl
- Absolute neutrophil count ≥1.5 x 10^9/l
- Platelet count ≥75 x 10^9/l

[c] - Low dose methotrexate for rheumatoid arthritis was not considered chemotherapy for lymphoma.

[d] - Chemotherapy dose and schedule were chosen by trial site for FL patients (and by patient for MZL):
- CHOP for 6 cycles (21-day cycles): cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2 and vincristine 1.4 mg/m^2 (maximum dose 2 mg) by IV on day 1, plus prednisone 100 mg orally per day on days 1 to 5 of six 21-day cycles
- CVP for 8 cycles (21-day cycles): cyclophosphamide 750 mg/m^2 and vincristine 1.4 mg/m^2 (maximum dose 2 mg) by IV on day 1, plus prednisone 100 mg orally per day on days 1 to 5 of eight 21-day cycles
- BENDA for 6 cycles (28-day cycles): bendamustine 90 mg/m^2 by IV on days 1 and 2 of six 28-day cycles

[e] - Patients who had a CR or PR at the end of induction therapy received maintenance therapy with the same MAB received in induction. Patients with SD at the end of induction therapy were followed on the same schedule but received no maintenance therapy.

[f] - Assessed with and without the use of FDG-PET.

a) Trial

Trial Design

GALLIUM[1] is an ongoing, open-label, active-controlled, international and multi-centred phase 3 trial evaluating the efficacy and safety of induction treatment with obinutuzumab compared to rituximab, each combined with chemotherapy, and

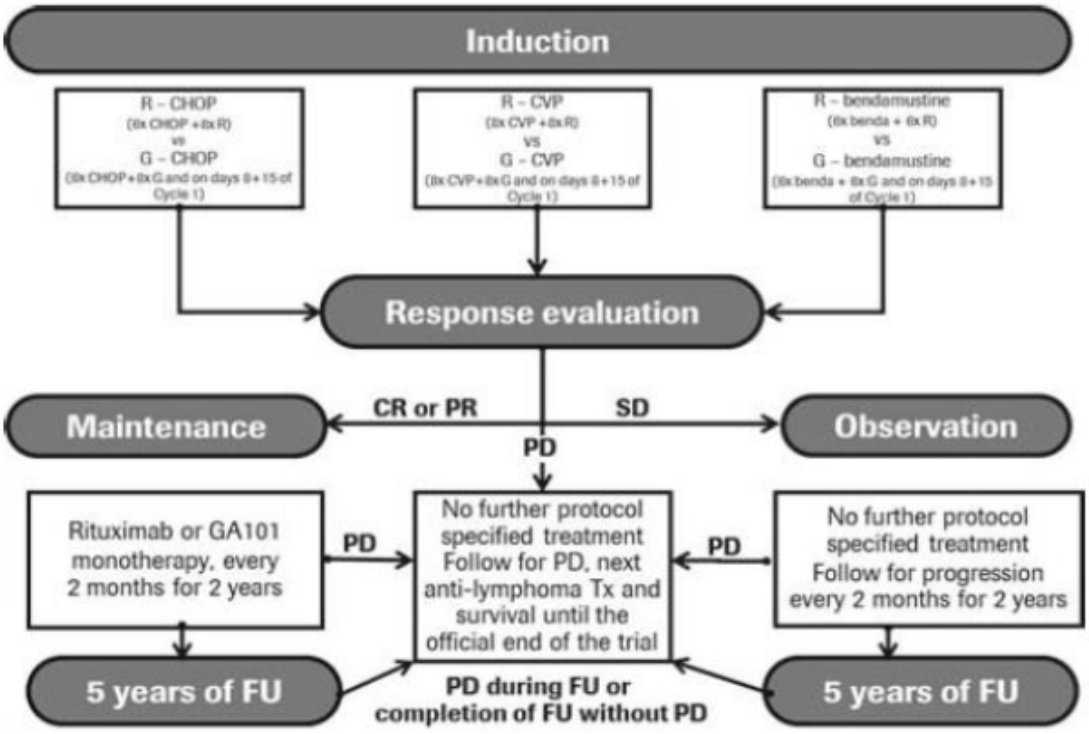
followed by maintenance treatment with the same antibody in previously untreated patients with advanced indolent NHL. Patient enrolment took place at 177 sites in 18 countries, including Canada (139 patients across seven sites).[11]

The design of the GALLIUM trial is depicted in Figure 2. Prior to the initiation of the trial, each participating trial site selected one of three chemotherapy regimens (bendamustine, CHOP, or CVP), considered to be standard of care for FL, to be used for the duration of the trial. For non-FL patients, the chemotherapy regimen used was chosen by trial investigators for individual patients. Following randomization, patients entered the induction treatment phase of the trial. Only patients achieving a response at the end of induction (CR or PR) continued to the maintenance treatment phase of the trial; patients with SD entered observation and were followed on the same assessment and follow-up schedule as responding patients but did not receive maintenance therapy. Patients who discontinued induction treatment for any reason (e.g., toxicity) were discontinued from the trial and directly entered into trial follow-up. No treatment crossover was permitted.

The GALLIUM trial used an open-label design (versus a blinded placebo-controlled design) primarily due to differences in the dosing (flat vs. weight-based) and administration schedules of the study drugs. There was also a perceived risk that differences in the frequency or severity of infusion-related reactions between the treatment groups could unblind investigators and/or patients to treatment assignment in a blinded trial. To minimize the risk of bias imposed by an open-label design, the trial used an IRC to independently assess disease response and progression.

The trial was funded by Hoffman La Roche Ltd. The trial sponsor had an active role in the design and conduct of the trial including data analysis, interpretation and publication.

Figure 2: Study design of the GALLIUM trial.[3]



Eligibility criteria

Patients enrolled in the GALLIUM trial had CD20-positive, indolent B-cell NHL, which included FL or MZL (splenic, nodal, or extranodal). However, the trial's primary objective was to evaluate the primary outcome (PFS) in patients with FL; recruitment of MZL patients was capped at 200 patients and considered a subgroup analysis of the trial.

FL patients enrolled in the GALLIUM trial met the following key criteria:

- Advanced stage (Ann Arbor stage III or IV, or stage II with bulk disease, and tumour ≥7 cm in greatest dimension) FL (grade 1-3a)
- At least one lesion assessable by bidimensional measurement (>2 cm by CT or MRI)
- ECOG 0-2
- Indication for treatment according to GELF criteria (refer to the notes section of Table 4 specific criteria)

For a more comprehensive list of the key eligibility criteria used in the trial, including exclusion criteria, refer to Table 4.

Outcomes

The primary outcome of the trial was PFS by INV in patients with FL. The secondary outcome of interest was PFS in the overall patient population (FL and MZL patients). Other secondary outcomes included PFS by IRC, ORR at the end of induction treatment, CR rate, DOR, EFS, DFS, OS, time-to-new anti-lymphoma

treatment, health-related QOL, and safety. Efficacy by chemotherapy backbone and disease transformation were included as exploratory endpoints of the trial.

Tumour response, which was assessed according to the revised response criteria for non-Hodgkin's lymphoma, included CT (or MRI if CT was contraindicated) and bone marrow biopsy. An assessment of CR based solely on CT imaging with no confirmation by biopsy was considered a PR. Depending on the chemotherapy regimen, response was assessed after three (bendamustine) or four treatment cycles (CVP, CHOP), again after induction treatment, every two months for two years during maintenance treatment, and then every three to six months until progression or withdrawal from the trial.

Randomization, Sample Size and Statistical Analyses

Information on randomization, required sample size, statistical assumptions, and other indicators of trial quality are detailed in Table 5.

Patients with FL were randomized in a 1:1 ratio to receive obinutuzumab or rituximab treatment using a centralized voice or online response system. Randomization was stratified according to chemotherapy regimen, FLIPI risk group (low risk: ≤1 risk factor, intermediate risk: 2 risk factors, or high risk: >2 risk factors; refer to the Notes section in Table 5 for the list of risk factors used in the calculation of risk groups), and geographic region (Western Europe, Eastern Europe, South and Central America, North America, Asia and Other). Region was a stratification factor to ensure treatment balance within geographic regions but was not used in stratified primary or secondary data analyses. Non-FL patients were randomized separately from FL patients, with randomization continuing until the 200 enrollment cap was reached for this patient subgroup.

Five amendments were made to the protocol of the GALLIUM trial, which included the following notable changes:[3]

- Amendment 1 (July 26, 2011): an early futility analysis of the first 170 FL patients was added, and was based on the response rates at the end of induction treatment.
- Amendment 5 (March 22, 2014): guidelines were added regarding the management of patients with thrombocytopenia, with special attention during the first treatment cycle and considering patients who were receiving concomitant anti-coagulants or platelet inhibitors.

The SAP of the trial pre-specified three interim analyses, which included two for futility and one for efficacy (for details, see Table 5), and a final analysis. The interim analyses were tested at significance levels determined by an O'Brien-Fleming α-spending function in order to maintain the overall type I error rate of 0.05. The third interim analysis was planned for when 67% (248) of the required number of PFS events (370) had occurred and the α-spending was set at p=0.012. This pre-specified boundary for statistical significance was crossed at the third interim analysis and the IDMC considered the results to be clinically meaningful. The trial Sponsor proceeded to analyze the trial results, in full, based on the recommendation of the IDMC. The third interim analysis, conducted when 245 PFS events (66%) had occurred, is therefore considered the primary analysis of the trial with a data cut-off date of January 31, 2016. An updated and unplanned analysis of the trial data was also performed, and provides an additional 6.5 months of follow-up time with a data cut-off date of September 10, 2016.[5]

The GALLIUM trial was designed and powered to evaluate the primary outcome (PFS) in the FL patient population (refer to Table 5), and therefore, the primary efficacy analysis of PFS was carried out in FL patients. The analyses of secondary outcomes were carried out in FL patients as well as the overall patient population that included non-FL patients. Results of analyses performed in the overall patient population were not reported in the trial publication and therefore are not reviewed in this report.

A fixed sequence testing approach was used to account for multiple testing of key secondary efficacy endpoints in the trial and control the type I error rate at p=0.05, such that secondary outcomes were tested in a pre-specified order and only if the preceding outcome was statistically significant. The order was as follows:

- PFS in overall patient population
- CR rate at the end of induction therapy in FL patients
- CR rate at the end of induction in the overall population
- OS in the FL population
- OS in the overall population
- ORR at the end of induction therapy in the FL population
- ORR at the end of induction therapy in the overall population

The remaining secondary outcomes of the trial, which included EFS, DFS, DOR, and time-to-next anti-lymphoma treatment, were not specified in the sequence of testing, and therefore analyses of these endpoints were not adjusted to account for multiple comparisons.

All efficacy analyses were performed in the ITT population according to treatment and stratification assignment at randomization. For all time-to-event outcomes, HRs and 95% CIs were estimated using a stratified Cox proportional hazard regression model. As median PFS was not expected to be reached in the trial, three-year PFS rates were also examined. Response rates in the treatment groups were compared using stratified Cochran-Mantel-Haenszel tests. Multiple subgroup analyses were planned a priori to explore the internal consistency of the treatment effect based on baseline characteristics, however, they were considered exploratory in nature and therefore uncontrolled for type 1 error. Statistical tests for interaction were performed for these analyses, however, the p-value used for determining the statistical significance of these tests was not reported. For patients with MZL, outcome analyses were interpreted as subgroup analyses, however, this patient subgroup was not powered to detect statistically significant differences between the treatment groups.[4]

Quality of life data from the GALLIUM trial have been published in conference form.[6] Patient-reported QOL was measured using the FACT-LYM instrument, which is comprised of 42 items within five subscales covering different aspects of well-being (lymphoma specific, and physical, functional, emotional, social/family well-being) and three summary scales, including the FACT-LYM Total, FACT-LYM TOI, and FACT-LYM Lymphoma Specific. The summary scales are formulated by summing specific subscales to derive a summary score. The summary scales and their associated MCID, which were used to calculate the proportion of patients reporting improvement on each scale, are as follows:

- FACT-LYM Total scale is the sum of all five subscale scores (MCID ≥7 points)
- FACT-LYM TOI scale is the sum of the lymphoma specific, physical well-being, and functional well-being subscales (MCID ≥6 points)

- FACT-LYM Lymphoma Specific is the sum of the lymphoma specific subscale (MCID ≥3 points)

For the QOL analysis, mean scores (95% CI) were calculated at all assessment time-points for each FACT-LYM scale, as well as mean changes from baseline for each FACT-LYM scale. Questionnaires were administered on day 1 of cycles 1 and 3 during induction treatment, at the end of induction, and at month two and 12 during maintenance/follow-up treatment. The analysis of QOL did not include imputations for missing data.

The safety analysis included an assessment of AEs, SAEs and AEs of special interest. Adverse events and SAEs were recorded for the following periods after the last dose of study drug: up to 28 days (any AE), up to 6 months (grade ≥3), up to 12 months (unrelated SAEs) and up to 24 months (grade 3-4 infections). Drug-related SAEs were collected for the duration of the trial. Infusion-related events were considered AEs of special interest and defined as any AE occurring either during infusion or within 24 hours after the infusion of any trial treatment that was judged by investigators to be related to drug administration (either antibody or chemotherapy). Other AEs of special interest included TLS and serious neutropenia and infections.

Table 5: Select quality characteristics of the included GALLIUM Trial.

Trial Quality Characteristics	GALLIUM Trial[1]
Treatment vs. Comparator	• Obinutuzumab + chemotherapy induction, followed by obinutuzumab maintenance *vs.* • Rituximab + chemotherapy induction, followed by rituximab maintenance
Primary outcome	• PFS by INV in FL patients
Required sample size	• 1200 FL patients (370 events) required to provide the trial with 80% power to detect an HR=0.74, which corresponds to a 26% lower risk of progression, relapse or death, and a 3-year improvement in PFS, from 70.7% to 77.4% (or median PFS from 6 years to 8.1 years), with obinutuzumab-based chemotherapy compared to rituximab-based chemotherapy (two-sided log rank test, alpha=0.05)
Randomization method	• Central randomization by interactive voice-response or online-response system using a hierarchical dynamic randomization scheme stratified by chemotherapy regimen, FLIPI risk group (low, intermediate or high)[a] and geographic region
Allocation concealment (yes/no)	• Yes
Blinding	• Open label • Blinded IRC outcome assessment
ITT analysis (yes/no)	• Yes
Interim analyses	• Three pre-specified interim analyses, with O'Brien-Fleming α-spending function: o One for futility based on CR (performed on first 170 patients at the end of induction therapy) o One for futility based on PFS (111 PFS events, 30%; p=0.000085) o One for efficacy based on PFS (248 PFS events, 67%; p=0.012) • After the interim analysis for efficacy was performed, the IDMC recommended the trial be fully analyzed based on the pre-specified boundary for statistical significance of the primary outcome being met, and the results considered clinically meaningful (data cut-off date: January 31, 2016) • Trial treatment assignment was unblinded to the Sponsor on May 25, 2016. The interim analysis, conducted when 245 PFS events (66%) had occurred, is considered the primary analysis of the trial
Final analysis (yes/no)	• No • Final analysis expected in 2020, based on 370 (100%) PFS by INV events (p=0.05)
Early termination (yes/no)	• Yes
Ethics approval (yes/no)	• Yes

Abbreviations: CR - complete response; **FL -** follicular lymphoma; **FLIPI** - Follicular Lymphoma International Prognostic Index; **HR** - hazard ratio; **IDMC** - Independent Data Monitoring Committee; **INV** - investigator assessment; **IRC** - independent review committee; **ITT** - intent-to-treat; **PFS** - progression-free survival; **vs.** versus.

Notes:
[a] -FLIPI risk groups: low risk defined as ≤1 risk factor, intermediate risk=2 risk factors, and high-risk >2 risk factors. Each risk factor counts as one point. A patient's FLIPI score is the total number of points. The following risk factors are used to calculate the FLIPI score:

- Age of >60 years
- Stage III or IV disease
- At least five nodules or tumours detected, or involvement of at least five lymph node groups
- Serum hemoglobin < 12 g/dL
- Elevated serum lactate dehydrogenase.

b) Populations

Patient randomization occurred between July 6, 2011 and February 4, 2014. Most randomized patients (overall population) were treated at trial sites in the UK

(21%), Germany (17%), Canada (10%), Australia (10%) and Japan (9%).[3] A total of 1202 patients with FL were randomized in the GALLIUM trial: 601 were allocated to obinutuzumab-based chemotherapy and 601 were allocated to rituximab-based chemotherapy. Overall, the baseline characteristics of FL patients were well-balanced between the treatment groups (Table 6). The median age of patients was 59 years, with approximately 31% of patients aged 65 or older.[3] The majority of patients had an ECOG performance status of 0-1 (97%),[3] were Ann Arbor disease stage III (35%) or IV (57%), and were classified as FLIPI intermediate- (37%) or high-risk (42%). Bone marrow involvement, extranodal involvement, and bulk disease (tumour ≥7 cm) were present in 52%, 67%, and 44% of patients, respectively; and approximately one third of patients presented with B symptoms. The distribution of patients by chemotherapy regimen was also balanced among the two treatment groups, with approximately 57% of patients receiving bendamustine, 33% CHOP, and 10% CVP.

There were 195 patients who comprised the subgroup of patients with non-FL; 99 were randomized to obinutuzumab and 96 to rituximab, of whom 61 patients had extranodal MZL, 66 nodal MZL and 68 splenic MZL.[4] The baseline demographics of this patient subgroup appeared similar to the FL patient population except for notable higher percentages of patients classified as stage IV Ann Arbor disease (82.6% versus 56.5%), high-risk FLIPI score (49% versus 41%) and treated with bendamustine chemotherapy (71% versus 57%).[4] Extranodal involvement, bone marrow involvement, bulky disease, and B symptoms were reported as more common in the obinutuzumab treatment group at baseline.[4]

Table 6: Baseline characteristics of FL patients in the GALLIUM Trial.[1]

Characteristic	Obinutuzumab Group (N=601)	Rituximab Group (N=601)
Age — yr		
Median	60	58
Range	26–88	23–85
Weight — kg		
Median	75.0	74.0
Range	35.3–155.0	32.4–158.0
Body-surface area — m^2		
Median	1.8	1.8
Range	1.2–2.6	1.1–2.8
Male sex — no. (%)	283 (47.1)	280 (46.6)
Ann Arbor stage at diagnosis — no. (%)		
I†	10 (1.7)	8 (1.3)
II	41 (6.8)	44 (7.3)
III	208 (34.6)	209 (34.8)
IV	339 (56.4)	336 (55.9)
Missing data	3 (0.5)	4 (0.7)
FLIPI risk status — no. (%)‡		
Low risk	128 (21.3)	125 (20.8)
Intermediate risk	224 (37.3)	223 (37.1)
High risk	249 (41.4)	253 (42.1)
B symptoms — no./total no. (%)§	201/601 (33.4)	206/600 (34.3)
Bone marrow involvement — no./total no. (%)	318/592 (53.7)	295/598 (49.3)
Extranodal involvement — no. (%)¶	392 (65.2)	396 (65.9)
Bulk disease — no./total no. (%)‖	255/600 (42.5)	271/600 (45.2)
Time from initial diagnosis to randomization — mo		
Median	1.5	1.4
Range	0.1–121.6	0.0–168.1
Chemotherapy regimen — no. (%)		
Bendamustine	345 (57.4)	341 (56.7)
CHOP	195 (32.4)	203 (33.8)
CVP	61 (10.1)	57 (9.5)

* The demographic and disease characteristics, including prognostic factors, of the patients at baseline were well balanced between the two treatment groups. Percentages may not total 100 because of rounding. CHOP denotes cyclophosphamide, doxorubicin, vincristine, and prednisone; and CVP cyclophosphamide, vincristine, and prednisone.
† A total of 18 patients who underwent randomization after being assessed by the investigators as having follicular lymphoma of Ann Arbor stage II, III, or IV, thus meeting trial eligibility criteria, had their classification revised to stage I disease after medical review; these patients were classified as having protocol violations.
‡ The risk groups according to the Follicular Lymphoma International Prognostic Index (FLIPI) are based on the number of risk factors: zero or one risk factor indicates low risk, two risk factors intermediate risk, and more than two risk factors high risk.
§ B symptoms are systemic symptoms such as weight loss, night sweats, and fever.
¶ Patients with bone marrow involvement were classified as having extranodal disease.
‖ Bulk disease was defined as a tumor that was 7 cm or larger in the greatest dimension.

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c) Interventions

After randomization, patients in the experimental group were treated with intravenous infusions of obinutuzumab at a dose of 1000 mg (on days 1, 8, and 15 of cycle 1, and day 1 of subsequent cycles) and patients in the control group received rituximab at a dose of 375 mg per square metre of body surface area (on day 1 of each cycle). Antibodies in each treatment group were administered for six or eight cycles depending on the chemotherapy regimen; six 28-day cycles when the antibody was combined with bendamustine, six 21-day cycles when combined with CHOP (followed by two additional cycles of antibody alone), or eight-21 day cycles when combined with CVP. Standard chemotherapy doses were used, which are presented in Table 4. At the end of induction treatment, patients with a CR or PR continued to receive their assigned antibody as maintenance treatment, administered at the same dose (as induction), given every two months for two years or until disease progression or withdrawal from the trial.

All patients received pre-medication prior to receiving obinutuzumab and rituximab; acetaminophen and an antihistamine were administered 30 to 60 minutes prior to antibody infusions. Additional pre-medications were recommended in the trial protocol and included corticosteroids (administered at least one hour before the first antibody dose in cycle 1) and anti-emetics.

Concomitant medications were taken by almost all patients in the trial (98% and 99% in the obinutuzumab and rituximab groups, respectively), and the types and frequency of medications taken were generally comparable between the treatment groups.[11] The most common (≥50% of patients) concomitant medications in both groups were analgesics, antihistamines, steroids, and 5-HT3 antagonists.[11]

Antibody treatment dose delays were permitted in the trial in the event of grade 3-4 hematologic AEs or grade 2-4 non-hematologic AEs for up to three weeks during induction treatment or up to six weeks during maintenance. Patients were withdrawn from the trial if AEs did not resolve within these timeframes. Dose reductions were permitted for chemotherapy but not for antibody treatment.

Drug exposure to antibody by treatment group is presented in Table 7. During the induction phase of the trial, almost all patients in both treatment groups were exposed to >90% of the planned dose intensity of antibody. The median duration of treatment was the same in both groups at approximately 25 weeks. Treatment interruptions and delays of >7 days occurred in slightly more patients receiving obinutuzumab (43.7% and 15.4%) than rituximab (37.9% and 13.7%).

Among patients receiving maintenance antibody treatment, the median duration of treatment exposure was approximately 92 weeks in both treatment groups; and almost all patients received >90% of the planned dose intensity of antibody. Compared to the induction phase, treatment interruption was less frequent in both groups during maintenance (approximately 6%) but dose delays >7 days were more frequent in both treatment groups, with slightly higher rates with obinutuzumab (62.7% versus 55.1%).

Table 7: Exposure to study MAB (obinutuzumab and rituximab) in the safety population (FL patient population) of the GALLIUM trial.[1]

	Obinutuzumab + Chemotherapy	Rituximab + Chemotherapy
	n=595	n=597
Induction Phase*		
Number of obinutuzumab or rituximab doses received - median (range)	8.0 (1-10)	6.0 (1-8)
Patients with interruptions to obinutuzumab or rituximab dose	260/595 (43.7)	226/597 (37.9)
Patients with delays to obinutuzumab or rituximab of >7 days	92/595 (15.4)	82/597 (13.7)
Patients with ≥90% planned dose intensity of obinutuzumab or rituximab	593 (99.7)	594 (99.5)
Duration of exposure to obinutuzumab or rituximab - weeks, median (range)	25.1 (3.3-35.3)	25.1 (2.6-32.3)
Cumulative dose of obinutuzumab or rituximab in mg, median (range)	8000 (20-10093)	4526.5 (525-7230)
Maintenance Phase*		
Number of obinutuzumab or rituximab doses received - median (range)	12 (1-12)	12 (1-12)
Patients with interruptions to obinutuzumab or rituximab doses	33/540 (6.1)	35/526 (6.7)
Patients with delays to obinutuzumab or rituximab doses of >7 days	373/595 (62.7)	329/597 (55.1)
Patients with ≥90% planned dose intensity of obinutuzumab or rituximab	539/540 (99.8)	522/526 (99.2)
Duration of exposure to obinutuzumab or rituximab - weeks, median (range)	92.3 (0-117.3)	92.1 (2.1-117.7)
Cumulative dose of obinutuzumab or rituximab in mg - median (range)	12000 (1000-12088)	7679 (555-12000)

* Data are n and % unless otherwise specified.

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d) Patient Disposition

The disposition of FL patients through the GALLIUM trial is summarized in Table 8. Of the 1202 patients (601 in each group) with FL that were randomized, seven patients (1%) in the obinutuzumab group and three patients (<1%) in the rituximab group did not receive any study medication; the reasons for withdrawal from study included patient or physician decision, protocol violations, and AEs.[2] There were 37 (6%) and 47 (8%) patients in the obinutuzumab and rituximab treatment groups, respectively, who did not complete induction treatment; the primary reason for discontinuation in both groups was due to AEs.

A similar proportion of randomized patients in each treatment group started on maintenance treatment; 539 patients (90%) in the obinutuzumab group and 527 patients (88%) in the rituximab group. There was a small proportion of patients in each group who were allocated to maintenance but did not receive it for various reasons (3% in the obinutuzumab group and 4% in the rituximab group; Table 8). Patient withdrawals during maintenance, which occurred in 118 patients (20%) and 132 patients (22%) in the obinutuzumab and rituximab groups, respectively, were

primarily due to PD in each group (6% versus 11%, respectively). At the primary data cut-off date, the number of patients who completed obinutuzumab maintenance was 361 (60%), while 60 patients (10%) were still receiving maintenance; compared to 341 (57%) and 54 (9%) patients in the rituximab group, respectively.

At the updated data cut-off date (September 10, 2016), the number of patients who had discontinued obinutuzumab maintenance was 120 (20%), compared to the 134 (22%) patients who discontinued rituximab maintenance.[5]

Information on the protocol deviations that took place during the trial was not reported in the trial publication, and therefore a request for this information was made to the Submitter and data were supplied for deviations that had occurred up to the primary analysis data-cut-off date. At least one protocol deviation occurred in 57% of patients in both treatment groups; the majority of deviations related to tumour or response assessment (approximately 28% in both treatment groups).[12] Deviations considered by the Submitter to potentially have an impact on the trial data, in terms of efficacy or patient safety, were also examined; this included deviations specific to not meeting inclusion criteria (i.e., wrong stage or type of lymphoma, no evidence of disease in need of treatment via GELF criteria), inclusion of patients with previous malignancies, and patient receiving wrong investigational study drug.[11] There were 30 (2.5%) of these deviations, which were more frequent in the obinutuzumab treatment group (3.3% versus 1.7%).[11] Overall, the frequency of these important deviations was higher in the obinutuzumab treatment group; however, considering their low frequency and generally even distribution between the treatment groups for most categories, it's unlikely they influenced the efficacy findings of the trial.

The disposition of patients[2] and distribution of protocol deviations in the overall patient population (FL and non-FL patients)[3] was comparable to the FL patient population.

Table 8: Patient disposition in the GALLIUM trial (FL patient population).[1]

Patient Disposition, n (%)	GALLIUM Trial Treatment Groups	
	Obinutuzumab + Chemotherapy	Rituximab + Chemotherapy
Analysis Data Cut-off Date	January 31, 2016	
Screened	1606[a]	
Randomized total (FL patients)	1202	
Randomized per group (FL patients)	601	601
Received allocated induction treatment	594 (98.8)	598 (99.5)
Did not receive allocated induction treatment	7 (1)	3 (<1)
Reasons:[2]		
Chose not to participate	3 (<1)	2 (<1)
Protocol violation	2 (<1)	1 (<1)
Physician decision	1 (<1)	-
AEs	1 (<1)	-
Discontinued induction treatment	37 (6)	47 (8)
Reasons:		
AEs	19 (3)	19 (3)
PD	5 (<1)	14 (2)
Physician decision	5 (<1)	5 (<1)
Chose not to participate	3 (<1)	3 (<1)
Protocol violation	2 (<1)	2 (<1)
Other	2 (<1)	2 (<1)
Death	1 (<1)	1 (<1)
Non-compliance	-	1 (<1)
Allocated to maintenance treatment	557 (93)[b]	551 (92)
Received maintenance treatment	539 (90)	527 (88)
Did not receive maintenance treatment	18 (3)	24 (4)
Reasons:		
PD between induction and maintenance	10 (2)	10 (2)
Started observation (SD)	8 (1)	9 (1)
Chose not to participate	1 (<1)	3 (<1)
Physician decision	-	1 (<1)
Other	-	1 (<1)
Discontinued maintenance treatment	118 (20)	132 (22)
Reasons:		
PD	37 (6)	64 (11)
AEs	51 (8)	38 (6)
Physician decision	15 (2)	11 (2)
Chose not to participate	5 (<1)	10 (2)
Death	4 (<1)	4 (<1)
Other	3 (<1)	3 (<1)
Lost to follow-up	2 (<1)	1 (<1)
Protocol violation	1 (<1)	1 (<1)
Completed maintenance treatment	361 (60)	341 (57)
Still receiving maintenance treatment at data cut-off	60 (10)	54 (9)
Included in primary analysis	601 (100)	601 (100)
Included in safety analysis	595 (99.0)	597 (99.3)
Total number protocol deviations	746[12]	821[12]
No. of patients with at least one protocol deviation	344 (57)[12]	345 (57)[12]

Abbreviations: AEs - adverse events; FL - follicular lymphoma; PD - progressive disease; SD - stable disease.

Notes:
[a] - Reflects overall patient population including 199 patients with MZL and other non-FL lymphomas; 205 patients did not meet the trial eligibility criteria.
[b] - One patient entered maintenance treatment but did not complete induction treatment.[2]

e) Limitations/Sources of Bias

Critical appraisal of the GALLIUM trial was based on the primary trial publication, updated data published in posters presented at international symposia, and unpublished data provided to pCODR by the Submitter. Overall, the trial was well-conducted. The randomization procedure and method of allocation concealment were carried out appropriately, the treatment groups were well balanced at baseline for important patient and prognostic characteristics, and length of time on treatment was the same in both treatment groups for both induction and maintenance, with almost all patients receiving >90% of the planned dose intensity of antibody in both treatment groups. There was also transparent reporting of the disposition of patients through the trial; patient withdrawals were higher in the rituximab-based treatment group but were primarily due to PD, with the other reasons for study discontinuation balanced between the treatment groups, and all efficacy analyses were performed according to the ITT principle. However, a number of limitations were noted, which should be considered when interpreting the results of the trial; specifically:

- The trial met its primary endpoint at the third planned interim analysis for efficacy (median follow-up of 34.5 months) and demonstrated a statistically significant improvement in PFS by INV in the obinutuzumab-based treatment group (HR=0.66, 95% CI, 0.51-0.85; p=0.001). The superiority of obinutuzumab demonstrated at interim analysis was based on crossing a pre-specified threshold of statistical significance (p=0.012) and 245 PFS events (information fraction of 66%). Trials stopped early for benefit, before all events have accrued, are associated with exaggerated treatment effect sizes;[7] therefore, the magnitude of the treatment effect estimate observed in the GALLIUM trial may be exaggerated. At the primary analysis cut-off date all patients had been recruited into the trial and completed or withdrawn from induction treatment, approximately two-thirds of patients had been followed for 2.5 years,[8] and 10% were still receiving maintenance therapy.
- The SAP of the GALLIUM trial specified the number of efficacy analyses to be performed of the primary and key secondary outcomes, and appropriately used statistical approaches to control for the probability of type 1 error that arises from multiple comparisons. The purpose of these approaches is to preserve the overall significance level across the number of planned, specified analyses, and the overall power of the trial. In the GALLIUM trial, however, there were many efficacy analyses performed (secondary outcomes, subgroup analyses, updated efficacy analysis) that did not involve adjustment for multiplicity. The chance of obtaining a statistically significant result (false positive) increases as the number of tests performed increases; therefore, the magnitude of the treatment estimates obtained for these uncontrolled efficacy analyses should be interpreted with some level of caution. Further, although the assessment of heterogeneity of treatment effect in patient subgroups was analyzed appropriately using tests for interaction (though the threshold for statistical significance was not indicated), these tests are often underpowered.[9] Considering this, and the lack of adjustment for multiplicity, the subgroup analysis results of the trial should be viewed as exploratory analyses.
- The open-label design of the trial makes it prone to different biases (patient selection and performance bias), which can affect internal validity.

The investigators, trial personnel, patients, as well as data analysts were all aware of study drug assignment, which can potentially bias outcome assessment in favour of obinutuzumab if assessors (investigators, patients, and data analysts) believe the study drug is likely to provide benefit. This is particularly relevant in an open-label trial stopped early for benefit, as patients became aware of the trial results while still on study. An attempt was made to mitigate bias by using an IRC to assess the primary outcome using standardized criteria (mRRCML), as well as conducting multiple pre-specified sensitivity analyses to measure the robustness of the primary outcome results. Results of the IRC assessment were consistent with the INV assessment, all sensitivity analyses (but one) were supportive of the primary analysis results,[3] and most patient subgroup analyses supported the primary outcome results. However, for subjective outcomes like health-related QOL and AEs, there is a greater risk of detection bias because patients and investigators would be aware of the specific treatment being administered.

- It is unclear whether the PFS benefit observed with obinutuzumab can be attributed to the induction and/or maintenance phase of first-line treatment; at the end of induction treatment, there was no difference in CR or ORR between the two treatment groups.
- The interpretation of outcomes examined by chemotherapy regimen should be interpreted with caution, as the treatment effect estimates are confounded by imbalances in baseline patient characteristics between treatment groups since patients were not randomized to chemotherapy regimens in the trial. For example, more patients who received CHOP chemotherapy were in the high-risk FLIPI group (47%, versus 40% with bendamustine and 35% with CVP) and had bulky disease (52%, versus 40% and 40%, respectively); while patients with comorbidities were more common in patients who received bendamustine (24% with CCI score ≥1, versus 17% with CHOP and 19% with CVP).[5]
- As indicated above, the value of subjective QOL data in an open-label trial are limited due to detection bias. Further, the frequency of missing data increased over the course of the trial, which biases the QOL analysis as there are systematic differences in the characteristics of patients who complete and do not complete questionnaires.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

The efficacy outcomes in the GALLIUM trial are summarized in Tables 9 and 10. The median duration of patient follow-up was 34.5 months at the primary analysis,[1] and 41 months at the updated analysis.[5]

Primary Outcome - Progression-free survival by Investigator Assessment (FL patient population)

Progression-free survival was defined as the time from randomization to the earliest event of progression, relapse, or death from any cause.

As previously mentioned, the trial met its primary outcome at the third planned interim analysis (primary analysis) for efficacy, and crossed the pre-specified boundary for superiority, demonstrating a statistically significant improvement in PFS by INV in the obinutuzumab-based treatment group (HR=0.66, 95% CI, 0.51-0.85; p=0.001). At this time, 101 (16.8%) and 144 (24%) progression events had occurred in the obinutuzumab and rituximab treatment groups, respectively. The estimated 3-year PFS by INV was 80% (95% CI, 75.9-83.6) in patients treated with obinutuzumab versus 73.3% (95% CI, 68.8-72.2) in patients treated with rituximab. The Kaplan Meier survival curves for PFS by INV are presented in Figure 2 (A).

The results of all pre-specified subgroup analyses are available in Figure 3, for baseline stratification variables (A) and patient characteristics (B).

Overall, results of the patient subgroup analyses showed a consistent treatment benefit favouring obinutuzumab, and tests for treatment interaction suggested no heterogeneity of treatment effect in any patient subgroup examined. For the non-FL subgroup of patients with MZL, treatment effect estimates also favoured obinutuzumab (PFS by INV: HR=0.82; 95% CI, 0.45-1.46; PFS by IRC: HR=0.83; 95% CI, 0.46-1.51).[4] Conversely, for patients in the low-risk FLIPI category and with Ann Arbor stage II disease, treatment effect estimates favoured rituximab treatment.

The updated efficacy analysis,[5] performed after an additional 6.5 months of follow-up, showed a sustained treatment benefit in the obinutuzumab treatment group in the FL patient population (HR=0.68, 95% CI, 0.54-0.87; p=0.0016). At both analysis time-points, results of the IRC assessment of PFS were consistent with the primary analysis, but of slightly lower magnitude (Table 10). At the primary analysis, concordance between INV and IRC assessment methods was 92.1%, and balanced between the obinutuzumab (91%) and rituximab (93.2%) treatment groups.[3]

Following the posting of the Initial Recommendation, the Submitter provided feedback requesting that pERC consider funding obinutuzumab- chemotherapy for FL patients with intermediate or high risk FLIP score (high-risk group). The Submitter commented on pERC's Initial Recommendation noting that subgroup analyses for PFS by INV by patient FLIPI score were conducted. The Submitter inferred that the FLIPI score subgroup data suggest obinutuzumab-chemotherapy may work better than rituximab-chemotherapy in high-risk previously untreated FL patients.

In response to the Submitter's feedback, the pCODR Methods team noted that the subgroup analyses were conducted by FLIPI risk score at the primary analysis (January 31, 2016 data cut-off date), and showed a PFS by INV benefit in favour of

obinutuzumab in patients with intermediate- (HR=0.59, 95% CI, 0.37-0.92) and high-risk FLIPI score (HR=0.58, 95% CI, 0.41-0.84), but not for low-risk patients (HR=1.17, 95% CI, 0.63-2.19). As mentioned previously, the effect estimate in the low-risk group should be interpreted with caution due to small sample size and low event rates. Further, the test for interaction for the FLIPI score subgroup analysis was not statistically significant (p=0.14), suggesting no difference in treatment effect between FLIPI risk categories. As previously mentioned (Section 6.3.2.1 (e) Limitations/Sources of Bias), the lack of adjustment for multiplicity and the risk of type 1 error associated with these analyses makes it difficult to interpret whether there is a difference in treatment effect based on FLIPI score.

The GALLIUM trial was not designed or powered to compare efficacy by type of chemotherapy backbone, as the choice of chemotherapy was not randomized but chosen by trial sites at the start of the trial. The pre-specified subgroup analyses by chemotherapy regimen (bendamustine, CHOP or CVP) are presented in Table 10 (as well as Figure 4), and demonstrate a consistent treatment benefit in favour of obinutuzumab at both analysis time points, with the greatest magnitude of treatment benefit observed with obinutuzumab combined with bendamustine (HR=0.63, 95% CI, 0.46-0.88 at updated analysis).[5]

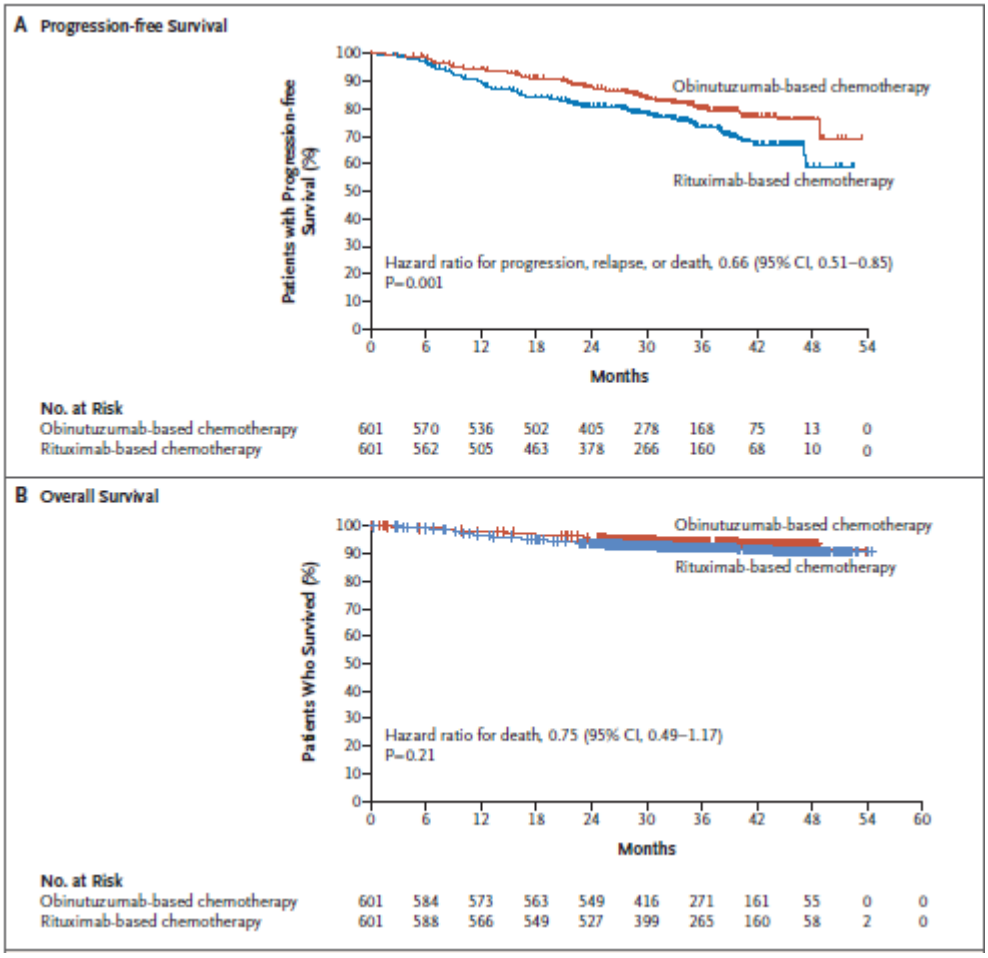

Figure 3: Kaplan Meier survival curves for (A) PFS by INV and (B) OS in the GALLIUM trial at primary analysis (January 31, 2016 data cut-off; FL patient population, ITT).[1]

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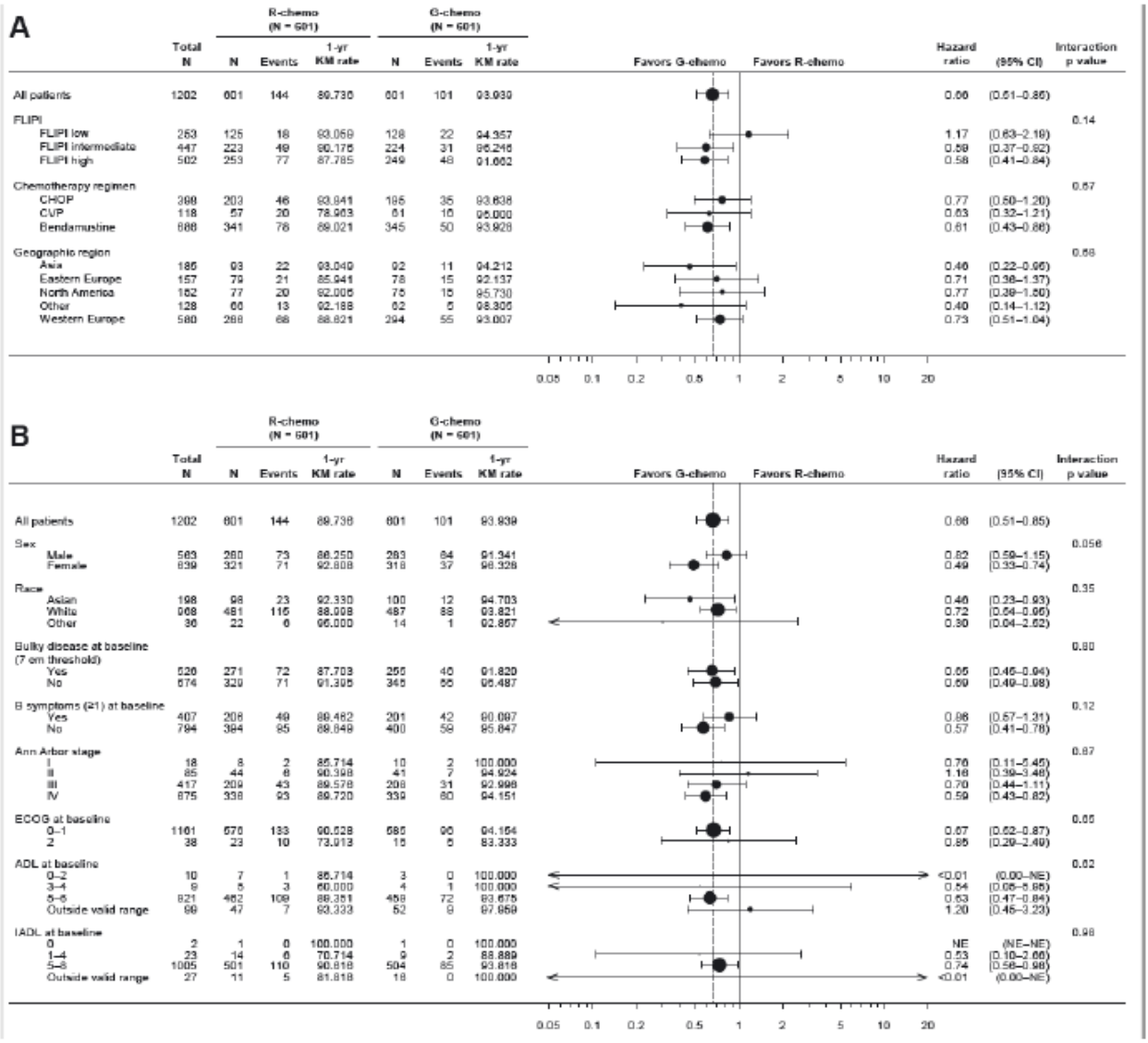

Abbreviations: ADL- activities of daily living; **CHOP**- cyclophosphamide, doxorubicin, vincristine and prednisone; **CI** - confidence interval, **CVP** - cyclophosphamide, vincristine and prednisone; **ECOG**- Eastern Cooperative Oncology Group; **FL**- follicular lymphoma; **G-chemo** - obinutuzumab plus chemotherapy; **HR** - hazard ratio; **IADL**- instrumental activities of daily living; **IPI** - International Prognostic Index; ITT - intent-to-treat; **KM** - Kaplan-Meier; **PFS** - progression-free survival; **R-chemo** - rituximab plus chemotherapy.

Figure 4: Subgroup analyses in the GALLIUM Trial for PFS by INV in FL patient population (ITT): (A) stratification factors, and (B) baseline characteristics.[1]

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Secondary Outcomes

Treatment Response at the End of Induction Treatment
At the end of induction treatment the CR rate was higher in the rituximab treatment group (n=143, 23.8%) compared to the obinutuzumab group (n=117, 19.5%); the difference between the groups (4.3%) was not statistically significant.

Since the difference in CR did not reach statistical significance at the primary analysis, the remaining secondary outcomes specified in the hierarchical testing scheme were not formally tested. These endpoints, which included ORR and OS, were still examined (Table 9) but should be interpreted as exploratory outcomes. Both ORR and OS showed no differences between groups at the primary (ORR, OS) and updated analyses (OS).[1,5]

Event-free Survival, Disease-free Survival, and Time-to-new Anti-lymphoma Treatment

As previously mentioned, no adjustments were made to the overall statistical significance level of the trial to account for the additional secondary analyses listed below; therefore, any reported p-values (in Table 9) should be viewed as descriptive. Overall, EFS, DFS and time-to-new anti-lymphoma treatment endpoints were consistent with the primary outcome results of the trial; and treatment effect estimates for these endpoints at the updated analysis (data not shown) were similar to the primary analysis results.[5]

Event-free Survival
Event-free survival (by INV) was defined in the trial as the time from randomization to progression, relapse, death from any cause, or start of new anti-lymphoma treatment. The risk of progression, relapse, death, or start of new anti-lymphoma treatment was significantly lower among patients in the obinutuzumab treatment group compared to patients in the rituximab group (HR=0.65, 95% CI, 0.51-0.83).

Disease-free Survival
Disease-free survival by INV was defined as the time from the date of first occurrence of a documented CR to the date of disease progression, relapse, or death from any cause among patients who had a CR at any time before the start of new anti-lymphoma treatment. Among patients with a CR (298 patients in the obinutuzumab group, and 281 in the rituximab group), the risk of progression, relapse or death was reduced in the obinutuzumab treatment group but not significantly different compared to rituximab (HR=0.81, 95% CI, 0.48-1.35).

Time-to new Anti-lymphoma Treatment
Time-to new anti-lymphoma treatment was defined as the time from the date of randomization to the start date of the next anti-lymphoma treatment or death from any cause. At the time of the primary analysis, there were 80 (13.3%) patients in the obinutuzumab group and 111 (18.5) in the rituximab group who had started a new anti-lymphoma treatment; the risk of starting new treatment or death from any cause was significantly reduced in patients treated with obinutuzumab-based therapy (HR=0.68, 95% CI, 0.51-0.91). No data were reported on the specific subsequent treatments taken by patients in the trial.

Transformation Rate
Disease (histological) transformation, from an indolent to a more aggressive NHL at first progression, was defined as the appearance of diffuse areas of large lymphoma cells within a tumour site in patients with a repeated biopsy at the time of disease

progression or relapse. Disease transformation to a high grade lymphoma or DBCL was reported for 18 and 29 patients in the obinutuzumab and rituximab groups, respectively.[3] When considered as a percentage of patients with disease progression, 22.5% of patients treated with obinutuzumab and 22.3% of patients treated with rituximab progressed with disease transformation.[3]

The Submitter commented on pERC's Initial Recommendation noting that POD24 may be a relevant endpoint to consider in FL trials and may help further characterize clinical benefit. It should be noted that POD24 was not considered an outcome of interest of the systematic review performed by the pCODR Methods Team and the CGP.

Table 9: Efficacy outcomes in the GALLIUM trial at primary analysis (January 31, 2016 data cut-off; FL patient population, ITT).[1]

Variable	Obinutuzumab Group (N=601)	Rituximab Group (N=601)
Median observation time (range) — mo	34.8 (0 to 53.8)	34.4 (0 to 54.5)
Primary end point: investigator-assessed progression-free survival		
Patients with progression, relapse, or death — no. (%)	101 (16.8)	144 (24.0)
Rate of estimated 3-yr progression-free survival (95% CI) — %	80.0 (75.9 to 83.6)	73.3 (68.8 to 77.2)
Hazard ratio for progression, relapse, or death (95% CI)	0.66 (0.51 to 0.85)	
P value by log-rank test	0.001	
Independent review committee–assessed progression-free survival		
Patients with progression, relapse, or death — no. (%)	93 (15.5)	125 (20.8)
Rate of estimated 3-yr progression-free survival (95% CI) — %	81.9 (77.9 to 85.2)	77.9 (73.8 to 81.4)
Hazard ratio for progression, relapse, or death (95% CI)	0.71 (0.54 to 0.93)	
P value by log-rank test	0.01	
Treatment response at end of induction phase†		
Complete response or partial response	532 (88.5)	522 (86.9)
Difference (95% CI) — percentage points	1.6 (–2.1 to 5.5)	
P value by Cochran–Mantel–Haenszel test	0.33	
Complete response	117 (19.5)	143 (23.8)
Difference (95% CI) — percentage points	–4.3 (–9.1 to 0.4)	
P value by Cochran–Mantel–Haenszel test	0.07	
Duration of response in patients with complete or partial response†		
Patients with progression, relapse, or death — no./total no. (%)	88/571 (15.4)	124/567 (21.9)
Hazard ratio for progression, relapse, or death (95% CI)‡	0.66 (0.50 to 0.87)	
Disease-free survival among patients with complete response†		
Patients with progression, relapse, or death — no./total no. (%)	27/298 (9.1)	33/281 (11.7)
Hazard ratio for progression, relapse, or death (95% CI)‡	0.81 (0.48 to 1.35)	
Event-free survival as assessed by investigator		
Patients with progression, relapse, death, or start of new antilymphoma treatment — no. (%)	112 (18.6)	159 (26.5)
Hazard ratio for progression, relapse, death, or start of new antilymphoma treatment (95% CI)	0.65 (0.51 to 0.83)	
P value by log-rank test	<0.001	
Start of new antilymphoma treatment		
Patients who started new antilymphoma treatment — no. (%)	80 (13.3)	111 (18.5)
Estimated 3-yr rate of new antilymphoma treatment — % (95% CI)	87.1 (84.0 to 89.6)	81.2 (77.6 to 84.2)
Hazard ratio for new antilymphoma treatment (95% CI)	0.68 (0.51 to 0.91)	
P value by log-rank test	0.009	
Overall survival		
Patients who died — no. (%)	35 (5.8)	46 (7.7)
Estimated percentage of patients alive at 3 yr — % (95% CI)	94.0 (91.6 to 95.7)	92.1 (89.5 to 94.1)
Hazard ratio for death (95% CI)	0.75 (0.49 to 1.17)	
P value by log-rank test	0.21	

* All analyses were stratified according to FLIPI risk status and chemotherapy regimen. Percentage differences may not sum as expected because of rounding. Disease-free survival was defined as the time from the date of first occurrence of a documented complete response to the date of disease progression, relapse, or death from any cause among patients who had had a complete response at any time before the start of new antilymphoma treatment. Event-free survival was defined as the time from randomization to progression, relapse, death from any cause, or start of new antilymphoma treatment.
† The treatment response and duration of response were assessed by the investigator.
‡ No P value was be calculated for this analysis, as specified in the protocol.

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Table 10: Progression-free survival and overall survival efficacy data from the GALLIUM trial at primary and updated analyses (FL patient population).

Outcome	Primary Analysis[1]		Updated Analysis[5]	
	Obinutuzumab + Chemotherapy (n=601)	Rituximab + Chemotherapy (n=601)	Obinutuzumab + Chemotherapy (n=601)	Rituximab + Chemotherapy (n=601)
Data cut-off date	January 31, 2016		September 10, 2016	
Median follow-up in months (range)	34.5 (0-54.5)		41.1 (NR)	
PFS by INV				
No. (%) PFS events	101 (16.8)	144 (24.0)	120 (20)	161 (27)
HR (95% CI)	0.66 (0.51 to 0.85)		0.68 (0.54 to 0.87)	
p-value (log-rank)	0.001		0.0016	
Estimated 3-year PFS rate, % (95% CI)	80.0 (75.9 to 83.6)	73.3 (68.8 to 77.2)	82 (78 to 85)	75 (71 to 78)
PFS by IRC				
No. (%) PFS events	93 (15.5)	125 (20.8)	108 (18)	141 (23)
HR (95% CI)	0.71 (0.54 to 0.93)		0.72 (0.56 to 0.93)	
p-value (log-rank)	0.01		0.012	
Estimated 3-year PFS rate, % (95% CI)	81.9 (77.9 to 85.2)	77.9 (73.8 to 81.4)	83 (80 to 86)	79 (75 to 82)
OS				
No. (%) deaths	35 (5.8)	46 (7.7)	43 (7)	52 (9)
HR (95% CI)	0.75 (0.49 to 1.17)		0.82 (0.54 to 1.22)	
p-value (log-rank)	0.21		0.32	
Estimated 3-year OS rate, % (95% CI)	94.0 (91.6 to 95.7)	92.1 (89.5 to 94.1)	94 (92 to 96)	92 (90 to 94)
PFS by Chemotherapy Regimen				
BENDA, PFS by INV	n=345	n=341	n=345	n=341
No. (%) PFS events	50 (14.4)	78 (22.9)	60 (17)	88 (26)
HR (95% CI)	0.61 (0.43 to 0.86)		0.63 (0.46 to 0.88)	
Estimated 3-year PFS rate, % (95% CI)	NR	NR	84 (79 to 88)	76 (71 to 81)
CHOP, PFS by INV	n=196	n=203	n=196	n=203
No. (%) PFS events	35 (17.9)	46 (22.6)	39 (20)	53 (26)
HR (95% CI)	0.77 (0.50 to 1.20)		0.72 (0.48 to 1.10)	
Estimated 3-year PFS rate, % (95% CI)	NR	NR	81 (74 to 86)	76 (68 to 81)
CVP, PFS by INV	n=60	n=57	n=60	n=57
No. (%) PFS events	16 (26.7)	20 (35.1)	21 (35)	20 (35)
HR (95% CI)	0.63 (0.32 to 1.21)		0.79 (0.42 to 1.47)	
Estimated 3-year PFS rate, % (95% CI)	NR	NR	71 (57 to 81)	64 (49 to 76)

Abbreviations: BENDA - bendamustine; **CHOP** - cyclophosphamide + doxorubicin + vincristine + prednisone; **CI** - confidence interval; **CVP** - cyclophosphamide + vincristine + prednisone; **FL** - follicular lymphoma; **HR** - hazard ratio; **INV** - investigator assessment; **NR** - not reported; **PFS** - progression-free survival.

Health-Related QOL[6]

Compliance in completing FACT-LYM questionnaires was high at baseline in both treatment groups (92.5% in obinutuzumab group versus 91.5% in the rituximab group), but declined over the course of treatment and follow-up. At each assessment time point, compliance rates in the treatment groups were similar and did not fall below 65% in either treatment group. At baseline, mean FACT-LYM scores were similar in the two treatment groups for all scales, with all patients demonstrating some degree of impairment of physical function, functional wellbeing, and emotional and social function.

Over the course of treatment, there were no clear differences between the treatment groups in any FACT-LYM scale scores at any time point. From the end of induction treatment onwards, patients in both groups experienced clinically meaningful improvements from baseline in all scales including FACT-G (Figure 5), FACT-LYM Lymphoma Specific (Figure 6), and both summary scales that included this subscale, FACT-LYM TOI (Figure 7) and FACT-LYM Total (Figure 8). By the first maintenance assessment and onwards, approximately 50% of patients in each treatment group reported improvements in mean scores that met the MCID for each respective scale (Figure 9).

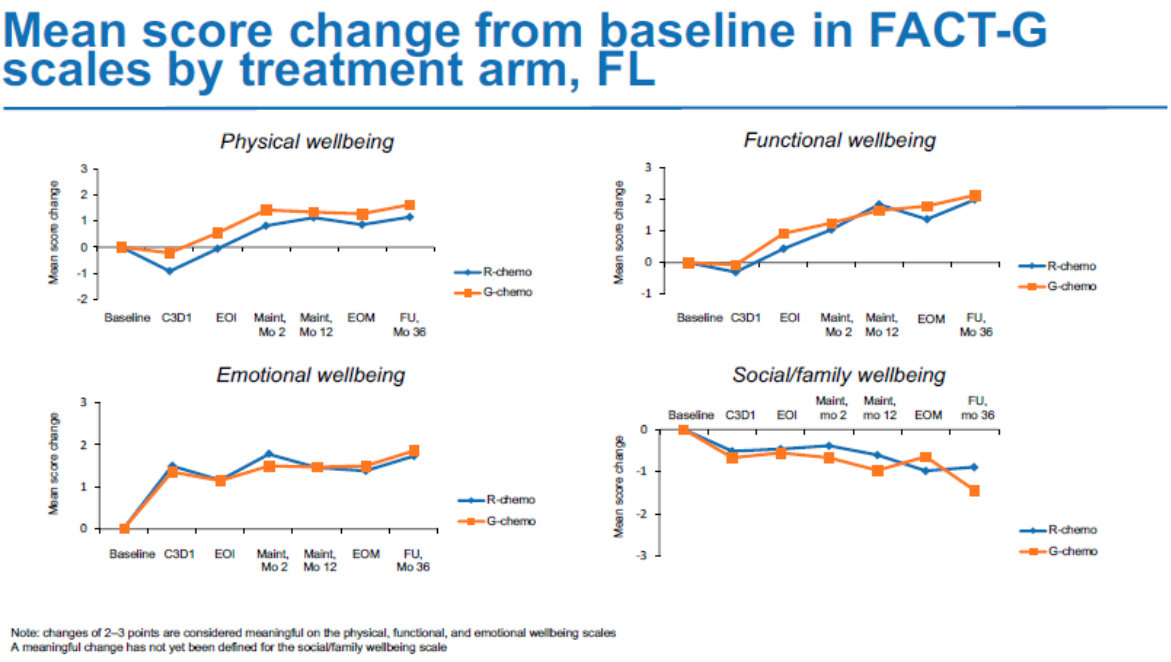

Figure 5: Change from baseline in patient-reported FACT-G scales during treatment and follow-up (FL patient population).[6]

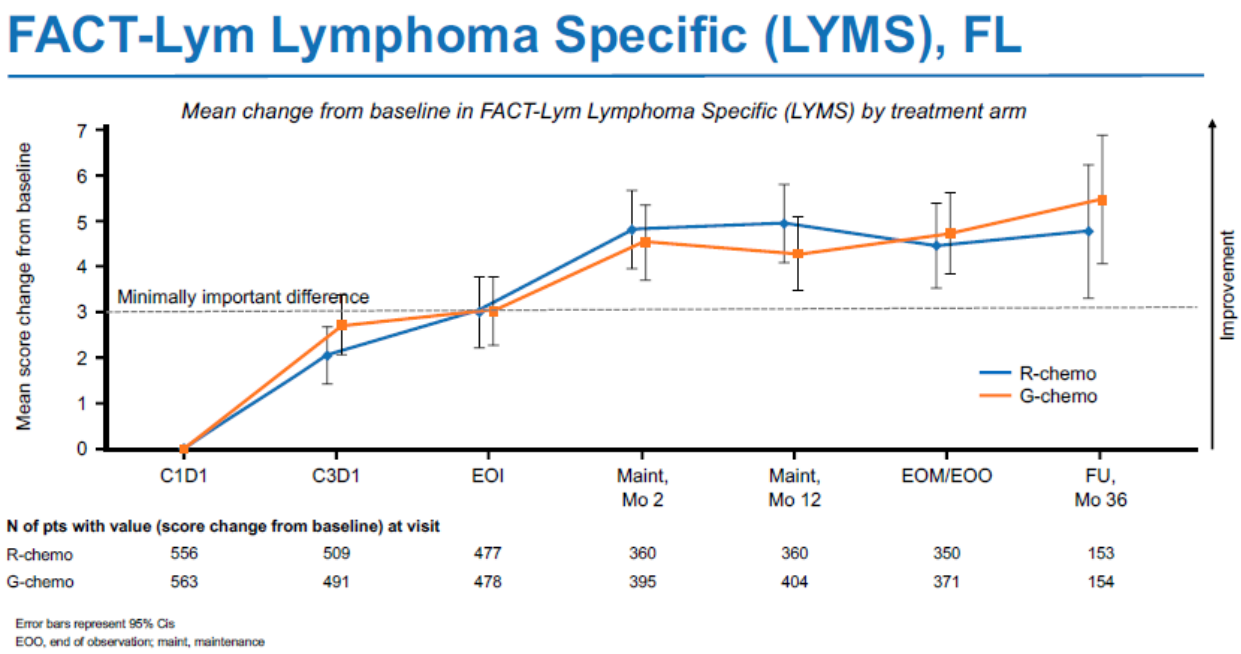

Figure 6: Change from baseline in patient-reported FACT-Lym Lymphoma Specific Scale during treatment and follow-up (FL patient population).[6]

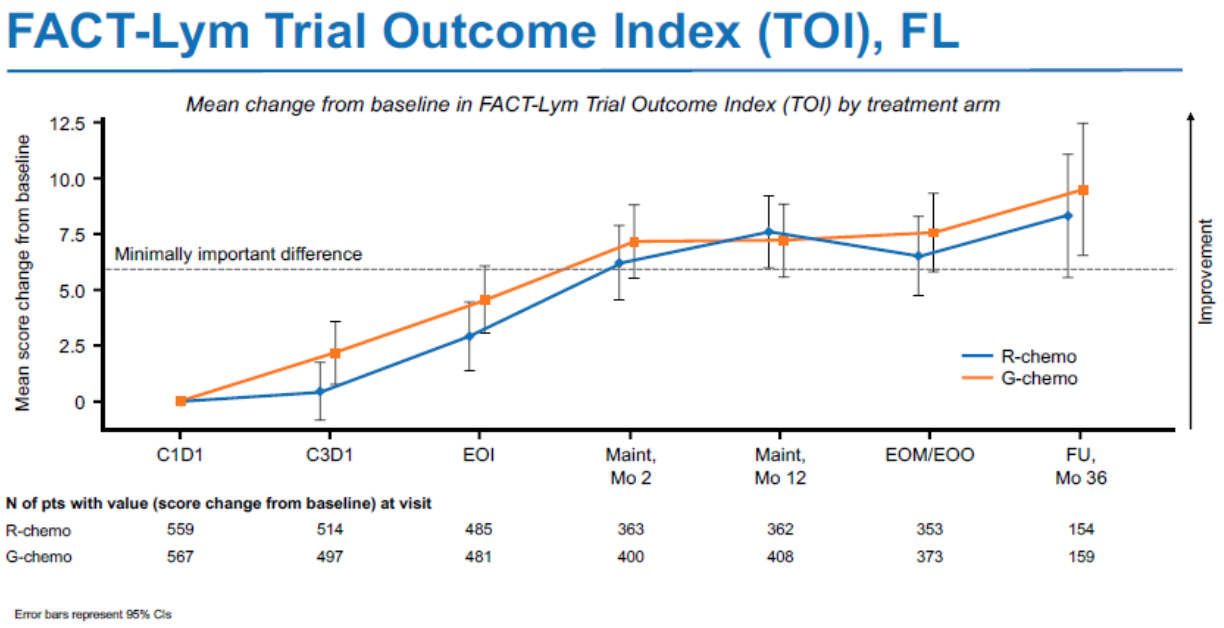

Figure 7: Change from baseline in patient-reported FACT-Lym Trial Outcome Index (TOI) Scale during treatment and follow-up (FL patient population).[6]

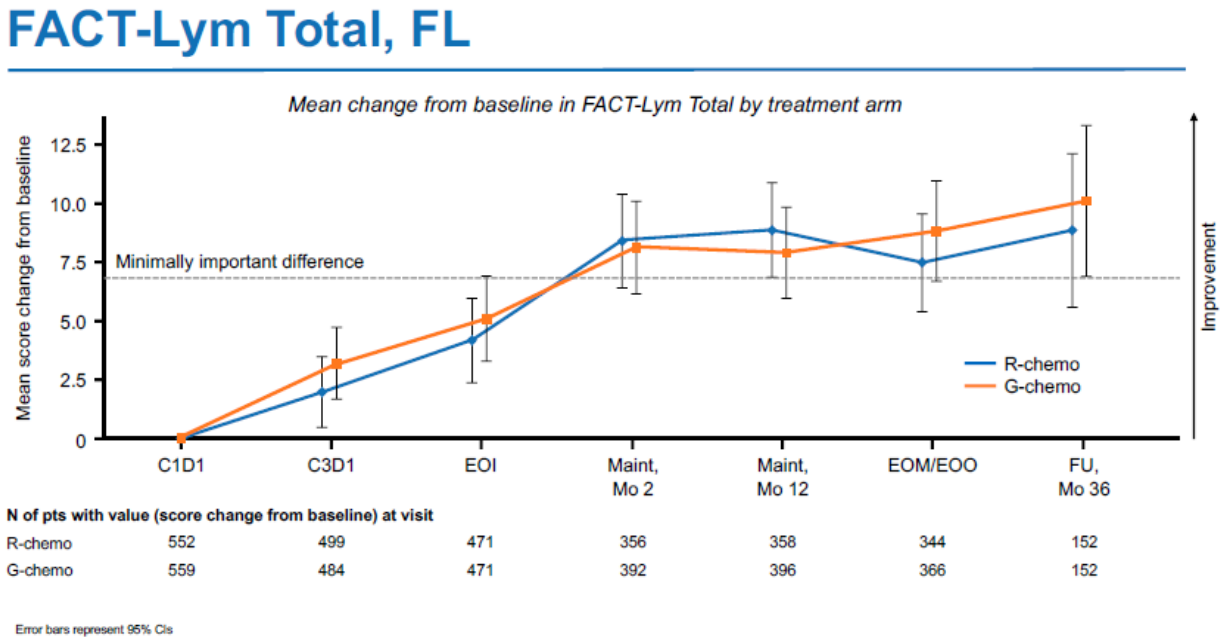

Figure 8. Change from baseline in patient-reported FACT-Lym Total Scale during treatment and follow-up (FL patient population).[6]

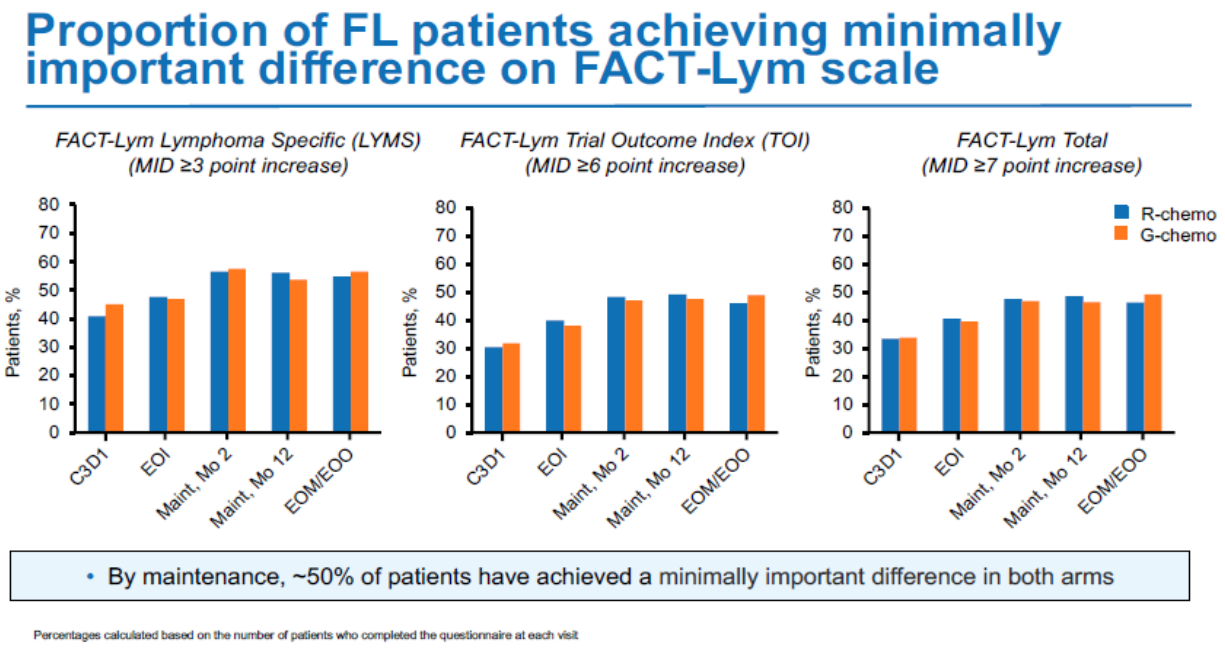

Figure 9: Summary of the proportion of patients achieving a MCID on FACT-Lym Summary Scales during treatment and follow-up (FL patient population).[6]

Harms Outcomes

The safety population of the GALLIUM trial included 1192 patients, 595 patients in the obinutuzumab group and 597 in the rituximab group, which is fewer than the FL ITT population, since 10 patients did not receive a dose of study drug. The adverse events occurring in the trial are summarized by treatment phase in Table 11 and by AEs of special interest in Table 12. The presentation of safety data is focused on the primary analysis,[1] as event rates were only marginally changed at the updated analysis.[5]

Safety

Overall, when compared to rituximab-based treatment, obinutuzumab was associated with a higher incidence of all grade AEs (99.5% in the obinutuzumab group versus 98.3% in the rituximab group), grade 3-4 AEs (74.6% versus 67.8%) and SAEs (46.1% versus 39.9%), and all were more frequent during induction treatment than in maintenance in both treatment groups.

The most common AEs observed in the trial, of any grade occurring in at least 10% of patients in either treatment group (obinutuzumab versus rituximab) during the course of the trial, were infusion-related reactions (59% versus 48.9%), nausea (46.9% versus 46.6%), and neutropenia (48.6% versus 43.6%). Slightly more patients treated with obinutuzumab experienced treatment-related AEs that led to dose reductions (17.3% versus 14.9%) and withdrawal from treatment (12.6% versus 10.9%).

During the induction phase of treatment the most common grade 3-5 AEs (obinutuzumab versus rituximab) were neutropenia (37.1% versus 34%), leukopenia (7.7% versus 8%), and infusion-related reactions (6.6% versus 3.5%), while the most common SAEs were infusion-related reactions (4.4% versus 1.8%), neutropenia (2.9% versus 3.2%), febrile neutropenia (3% versus 2.2%), and pyrexia (2.5% versus 2.7%). The most common grade 3-5 AEs and SAEs during maintenance treatment were neutropenia (16.4% versus 10.7%) and pneumonia (2.4% versus 3%), respectively. Over the course of the trial the frequency of second neoplasms (occurring at least six months after the start of treatment) was higher in the obinutuzumab treatment group (n=43, 7.2% with obinutuzumab versus n=30, 5% with rituximab), particularly non-melanoma skin cancers (n=18, 3% versus 14, 2%) and hematologic malignancies (n=6, 1% versus 0).

Considering AEs associated with the three different chemotherapy backbones, bendamustine was associated with a higher frequency of grade 3-5 infection and second malignancies during the maintenance and follow-up phases of the trial; while CHOP was associated with a higher frequency of grade 3-5 neutropenia (Table 11). Non-relapse-related fatal AEs were also more common among patients treated with bendamustine (5.6% in obinutuzumab group versus 4.4% in the rituximab group) compared to patients treated with CHOP (1.6% versus 2%) or CVP (1.6% versus 1.8%).

AEs of special interest to this review included infusion reactions, infections, neutropenia, thrombocytopenia and TLS. These AEs were also considered of special interest in the GALLIUM trial and are summarized in Table 12, and include events occurring during induction and maintenance treatment (or observation). All the AEs of special interest occurred more frequently in obinutuzumab-treated patients. Infusion reactions were reported as typically occurring during the first infusion of antibody, with a marked decline in frequency from cycle 2 onward. A total of 406 patients in the obinutuzumab group and 349 patients in the rituximab group

experienced an infusion reaction; of these patients, investigators' attributed to the reaction to antibody in 59.3% of patients treated with obinutuzumab and 48.9% of patients treated with rituximab. The majority of infusion reactions were low grade (1-2) with no fatal grade 5 events.[2] Infections were very common and occurred in 77.3% of patients in the obinutuzumab group and 70% in the rituximab group; the majority of infections were low grade (1-2) and SAEs due to infection were reported in 18.2% and 14.4% of patients, respectively. Grade 3-5 neutropenia occurred in a substantial proportion of patients in both treatment groups (45.9% with obinutuzumab versus 39.5% with rituximab). Thrombocytopenia (any grade) occurred in 11.4% of patients treated with obinutuzumab and 7.5% of patients with rituximab-based treatment. The frequency of TLS (any grade) was low in both treatment groups (≤1%).

Deaths

A total of 81 deaths had occurred by the primary data cut-off date; of these, 24 (4%) in the obinutuzumab treatment group and 20 (3.4%) in the rituximab group were judged by investigators to be due to AEs. The fatal AEs that occurred by trial phase are summarized below:

- Induction
  - Obinutuzumab (n=4): cardiogenic shock, pneumonia (two patients), dehydration
  - Rituximab (n=3): multi-organ failure, septic shock, and polyneuropathy
- Maintenance
  - Obinutuzumab (n=10): cardiogenic shock, gastric hemorrhage, death, pneumonia, staphylococcal bacteremia, acute lymphocytic leukemia, acute myeloid leukemia, hepatic neoplasm, acute lung injury, and respiratory failure
  - Rituximab (n=10): cardiac arrest, myocardial infarction, death, multi-organ failure, colon cancer, gastric cancer, lung adenocarcinoma, malignant melanoma, neuroendocrine carcinoma of the skin, and encephalopathy
- Follow-up
  - Obinutuzumab (n=10): gastrointestinal hemorrhage, ill-defined disorder, pneumonia, lower respiratory tract infection, lung infection, respiratory tract infection, sepsis, NSCLC, and NSCLC stage IV, and clostridium difficile, colitis myelodysplastic syndrome, and prostate cancer (all in one patient)
  - Rituximab (n=7): general physical health deterioration, pneumonia, hypercalcemia, cerebral hematoma, cerebrovascular accident, ischemic stroke, and chronic obstructive pulmonary disease

Table 11: Safety outcomes according to treatment phase and chemotherapy regimen in the GALLIUM trial (FL safety population).[1]

Event	Overall Trial†		Induction Phase		Maintenance and Observation Phases		Follow-up	
	Obinutuzumab Group (N=595)	Rituximab Group (N=597)	Obinutuzumab Group (N=595)	Rituximab Group (N=597)	Obinutuzumab Group (N=548)	Rituximab Group (N=535)	Obinutuzumab Group (N=427)	Rituximab Group (N=428)
No. of events	10,311	9343	7012	6533	3002	2578	295	230
Patients with ≥1 adverse event — no. (%)								
Any event	592 (99.5)	587 (98.3)	580 (97.5)	577 (96.6)	501 (91.4)	458 (85.6)	130 (30.4)	106 (24.8)
Event of grade 3 to 5	444 (74.6)	405 (67.8)	357 (60.0)	336 (56.3)	205 (37.4)	169 (31.6)	56 (13.1)	33 (7.7)
Event of grade 5‡	24 (4.0)	20 (3.4)§	4 (0.7)	3 (0.5)	10 (1.8)	10 (1.9)	10 (2.3)	7 (1.6)
Patients with ≥1 serious adverse event — no. (%)	274 (46.1)	238 (39.9)	166 (27.9)	144 (24.1)	134 (24.5)	110 (20.6)	47 (11.0)	34 (7.9)
Treatment-related adverse event — no. (%)								
Any event	564 (94.8)	547 (91.6)	—	—	—	—	—	—
Event leading to withdrawal of treatment	75 (12.6)	65 (10.9)	—	—	—	—	—	—
Event leading to any dose reduction	103 (17.3)	89 (14.9)	—	—	—	—	—	—
Serious adverse event leading to withdrawal of treatment — no. (%)	44 (7.4)	36 (6.0)	—	—	—	—	—	—
Serious adverse event leading to dose reduction — no. (%)	12 (2.0)	10 (1.7)	—	—	—	—	—	—
Grade 3 to 5 event, according to chemotherapy regimen — no./total no. (%)								
Neutropenia	—	—						
Bendamustine	—	—	73/338 (21.6)	87/338 (25.7)	49/312 (15.7)	29/305 (9.5)	6/270 (2.2)	1/263 (0.4)
CHOP	—	—	124/193 (64.2)	103/203 (50.7)	36/179 (20.1)	26/187 (13.9)	2/128 (1.6)	0
CVP	—	—	24/61 (39.3)	13/56 (23.2)	5/57 (8.8)	2/43 (4.7)	0	0
Infection¶	—	—						
Bendamustine	—	—	27/338 (8.0)	26/338 (7.7)	52/312 (16.7)	39/305 (12.8)	25/270 (9.3)	6/263 (2.3)
CHOP	—	—	14/193 (7.3)	13/203 (6.4)	7/179 (3.9)	11/187 (5.9)	2/128 (1.6)	2/143 (1.4)
CVP	—	—	3/61 (4.9)	4/56 (7.1)	5/57 (8.8)	1/43 (2.3)	1/44 (2.3)	2/45 (4.4)
Second neoplasm‖	—	—						
Bendamustine	—	—	0	0	21/312 (6.7)	18/305 (5.9)	14/270 (5.2)	2/263 (0.8)
CHOP	—	—	0	0	8/179 (4.5)	8/187 (4.3)	1/128 (0.8)	1/143 (0.7)
CVP	—	—	0	0	0	1/43 (2.3)	0	0

* Events included preferred terms defined with the use of the *Medical Dictionary for Regulatory Activities* (MedDRA), version 18.1. All the adverse events were assessed and graded throughout the trial (see the Supplementary Appendix). Adverse events of grade 3, 4, and 5 indicate severe, life-threatening, and fatal adverse events, respectively. Serious adverse events include fatal or life-threatening events or events that cause (or prolong) in-patient hospitalization or substantial disability or incapacity. Regardless of grading (severity), some adverse events may also meet the criteria for a serious adverse event.

† Data include adverse events occurring during the pretreatment, induction, maintenance and observation, and post-treatment follow-up phases; patients who had a given adverse event in more than one study phase are counted only once in the overall trial column. Data also include deaths in patients who had no other adverse events.

‡ Fatal adverse events (grade 5) during induction (which occurred in one patient each unless otherwise specified) were cardiogenic shock, pneumonia (in two), and dehydration in the obinutuzumab group and multiorgan failure, septic shock, and polyneuropathy in the rituximab group. Fatal adverse events that occurred after induction (in one patient each) were cardiogenic shock, gastric hemorrhage, death, pneumonia, staphylococcal bacteremia, acute lymphocytic leukemia, acute myeloid leukemia, hepatic neoplasm, acute lung injury, and respiratory failure in the obinutuzumab group and cardiac arrest, myocardial infarction, death, multiorgan failure, colon cancer, gastric cancer, lung adenocarcinoma, malignant melanoma, neuroendocrine carcinoma of the skin, and encephalopathy in the rituximab group. Fatal adverse events occurring in the follow-up phase were upper gastrointestinal hemorrhage, ill-defined disorder, pneumonia, lower respiratory tract infection, lung infection, respiratory tract infection, sepsis, non–small-cell lung cancer, and non–small-cell lung cancer of stage IV (in one patient each) and *Clostridium difficile* colitis, the myelodysplastic syndrome, and prostate cancer (all in one patient) in the obinutuzumab group; and general physical health deterioration, pneumonia, hypercalcemia, cerebral hematoma, cerebrovascular accident, ischemic stroke and chronic obstructive pulmonary disease (in one patient each) in the rituximab group.

§ Four additional deaths in the rituximab group are not included in this total. In line with the reporting rules in the protocol, they were considered to be temporally unrelated to the use of an investigational medicinal product and so were not reported as adverse events.

¶ Events were in the MedDRA system organ class "Infections and Infestations."

‖ Second neoplasm is the standardized MedDRA query for malignant or unspecified tumors that are diagnosed 6 months after the start of the study treatment.

Table 12: Adverse events of special interest during treatment in the GALLIUM trial (FL safety population).[1]

Table 4. Adverse Events of Special Interest during Treatment, According to Prespecified Category, in the Safety Population.

Category	All Adverse Events		Adverse Events of Grade 3 to 5		Serious Adverse Events	
	Obinutuzumab Group (N=595)	Rituximab Group (N=597)	Obinutuzumab Group (N=595)	Rituximab Group (N=597)	Obinutuzumab Group (N=595)	Rituximab Group (N=597)
	number of patients (percent)					
Infection*	460 (77.3)	418 (70.0)	119 (20.0)	93 (15.6)	108 (18.2)	86 (14.4)
Neutropenia	301 (50.6)	269 (45.1)	273 (45.9)	236 (39.5)	50 (8.4)	44 (7.4)
Infusion-related event†						
Any event	406 (68.2)	349 (58.5)	74 (12.4)	40 (6.7)	33 (5.5)	14 (2.3)
Antibody-related event	353 (59.3)	292 (48.9)	63 (10.6)	30 (5.0)	28 (4.7)	12 (2.0)
Tumor lysis syndrome	6 (1.0)	3 (0.5)	6 (1.0)	3 (0.5)	3 (0.5)	1 (0.2)
Cardiac event‡	78 (13.1)	58 (9.7)	22 (3.7)	17 (2.8)	26 (4.4)	12 (2.0)
Thrombocytopenia	68 (11.4)	45 (7.5)	36 (6.1)	16 (2.7)	4 (0.7)	1 (0.2)
Second neoplasm§	43 (7.2)	30 (5.0)	28 (4.7)	16 (2.7)	31 (5.2)	17 (2.8)
Nonmelanoma skin cancer	18 (3.0)	14 (2.3)	7 (1.2)	3 (0.5)	9 (1.5)	3 (0.5)
Hematologic event¶	6 (1.0)	0	6 (1.0)	0	6 (1.0)	0
Other	22 (3.7)	18 (3.0)	17 (2.9)	15 (2.5)	18 (3.0)	16 (2.7)
Myelodysplastic syndrome	2 (0.3)	0	2 (0.3)	0	2 (0.3)	0
Gastrointestinal perforation	4 (0.7)	3 (0.5)	3 (0.5)	0	3 (0.5)	0
Hemorrhagic event	57 (9.6)	62 (10.4)	5 (0.8)	7 (1.2)	6 (1.0)	5 (0.8)

* Events were in the MedDRA system organ class "Infections and Infestations."
† Data included any adverse event that occurred during or within 24 hours after the infusion of obinutuzumab or rituximab and was considered by the investigator to be drug-related. Because this category included adverse events in any system organ class, some patients in this category are also counted in other categories (e.g., infection, neutropenia, tumor lysis syndrome, cardiac events, and thrombocytopenia).
‡ Events were in the MedDRA system organ class "Cardiac Disorders."
§ Details regarding second neoplasms are provided in Table S5 in the Supplementary Appendix.
¶ Hodgkin's disease developed in three patients as a second neoplasm, only one of whom had a baseline sample centrally analyzed (confirmed to be follicular lymphoma); samples for the other patients could not be evaluated or were not obtained. Other hematologic neoplasms were acute myeloid leukemia (in two patients) and acute lymphocytic leukemia (in one).

6.4 Ongoing Trials

No ongoing trials meeting the selection criteria of this review were identified.

7 SUPPLEMENTAL QUESTIONS

A supplemental question was identified during the development of the review protocol for the pCODR review on obinutuzumab as first-line treatment of FL. In the GALLIUM trial, obinutuzumab and rituximab were compared as maintenance therapy administered every two months for two years or until disease progression or withdrawal from the trial. PAG noted that the more frequent dosing schedule of obinutuzumab every two months would require greater resources to monitor and treat adverse events, which appear to occur more frequently in patients treated with obinutuzumab compared to rituximab. Further, maintenance therapy administered every two months would also require more frequent hospital visits by patients. Consequently, PAG inquired whether there is evidence to support an alternate dosing schedule for obinutuzumab in the maintenance setting.

The pCODR review team determined the following question would be adequate to address the concern of PAG:

- What is the clinical efficacy, safety and therapeutic equivalence of obinutuzumab administered every two months in the maintenance setting, compared to obinutuzumab administered every three months, for the first-line treatment of patients with FL?

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7 Clinical efficacy, safety and therapeutic equivalence of obinutuzumab administered every two months in the maintenance setting, compared to obinutuzumab administered every three months, for the first-line treatment of patients with FL

7.1.1 Background

Currently, rituximab maintenance therapy administered every three months for a maximum of two years, is the standard of care for patients with previously untreated FL. In Canada, current guidelines recommend rituximab maintenance therapy be administered every three months for a duration of two years for the treatment of FL.[1,33,34] The CCO clinical practice guidelines for rituximab for lymphoma and chronic lymphocytic lymphoma indicate that rituximab maintenance therapy is effective, and should be administered at the schedule administered in phase three trials; however, the guidelines acknowledge that there are different schedules.[34] Health Canada approved rituximab as maintenance therapy for previously untreated patients with FL (who demonstrate a CR or PR after rituximab and chemotherapy induction treatment) based on evidence from a phase 3 trial that evaluated a rituximab maintenance schedule of every two months for a maximum of two years.[35] Conversely, rituximab was approved in patients with relapsed or refractory FL based on phase 3 evidence that evaluated maintenance rituximab therapy every three months until disease progression for up to two years.[35] The Lymphoma Canada treatment guide recognizes within their treatment recommendations that alternative maintenance therapy schedules for rituximab exist in the first-line setting, however, at the time of the publication it was indicated that there was no evidence to support that one maintenance schedule (every two versus every three months for two years) was more efficacious than the other.[36]

7.1.2 Methods

A search was conducted using multiple databases (including Medline, Embase – including conference abstracts from 2013 – present, Cochrane Central via Ovid, and PubMed), to identify relevant data on maintenance dosing schedules for obinutuzumab in patients with previously untreated FL. Search terms for obinutuzumab (Gazyva) and FL were used and no study design filters were applied to the search. All articles were limited to the English language. Conference abstracts were limited to having been published within the last five years. A more complete description of the literature search methods and the full search strategy is available in Appendix A.

7.1.3 Results

The literature search identified two published trials that evaluated the efficacy of obinutuzumab maintenance therapy; the GALLIUM trial[1] evaluated a schedule of two months for two years, and the GAUDI trial evaluated a schedule of every three months for two years.[10] Data from the trials, including patient disposition, dosing, and efficacy and safety outcomes, are summarized in Table 13.

Trial Design[1,10]

The GALLIUM trial evaluated a maintenance schedule with obinutuzumab of every two months. GALLIUM is the pivotal trial submitted for this pCODR review and therefore has been previously described in Section 6. Briefly, GALLIUM is an ongoing, two-group, open-label randomized phase 3 trial that assigned 601 patients to receive obinutuzumab-based induction chemotherapy followed by obinutuzumab maintenance, and 601 patients to receive rituximab-based induction chemotherapy followed by rituximab maintenance. Only patients who had a CR or PR at the end of induction therapy received maintenance treatment. The maintenance schedule was the same in both arms (i.e., for obinutuzumab and for rituximab) every two months for two years or until disease progression or withdrawal from the trial. Refer to Section 6 for details on the GALLIUM trial.

The GAUDI trial evaluated a maintenance schedule of every three months. GAUDI was an open-label, multi-centre, non-comparative phase 1b trial that evaluated the safety and efficacy of obinutuzumab (1000 mg intravenously on days 1 and 8 of cycle 1, and day 1 of subsequent cycles) combined with induction chemotherapy consisting of either CHOP plus obinutuzumab (6-8 cycles at 3 week intervals: cyclophosphamide, 750mg/m^2 intravenously on day 1; doxorubicin, 50mg/m^2 intravenously on day 1; vincristine, 1.4mg/m^2 capped at 2mg intravenously on day 1; prednisone 100mg orally on days 1 to 5), or bendamustine plus obinutuzumab (4-6 cycles at 4 week intervals: 90mg/m^2 intravenously on days 2 and 3 of cycle 1 and days 1 and 2 of subsequent cycles). Patients who achieved a CR or PR at the end of induction were eligible for maintenance with obinutuzumab (1000 mg intravenously) starting at 12 weeks after their last dose of chemotherapy and administered every three months for two years or until disease progression.

The patient baseline characteristics in the GALLIUM and GAUDI trials were generally similar. The median age of patients in the GALLIUM trial was between 58 and 60 years with an age range of 23 years to 88 years, while the median age in the GAUDI trial was 55 years (range, 27 years to 84 years). There were slightly more females in the GALLIUM trial compared to men (53% versus 47%, respectively).Similarly, there were also slightly more females than males (56% versus 44%) in the GAUDI trial. In the GALLIUM trial, most patients were receiving bendamustine as their chemotherapy regimen (n=686, 57%) compared to CHOP (n=398, 33%) or CVP (n=119, 9%). In the GAUDI trial, a relatively equal number of patients received bendamustine (n=41, 100%) and CHOP (n=40, 100%) as their chemotherapy regimen; none of the patients had CVP as the chemotherapy backbone. A greater proportion of patients in both trials (GALLIUM versus GAUDI) were of high risk

FLIPI status (42% versus 46%) and had Ann Arbor stage IV at diagnosis (56% versus 60%).The proportions of patients with other important baseline characteristics, including presence of bulky disease, bone marrow involvement, and extra-nodal involvement were also similar between both trials.

In the GALLIUM and GAUDI trials, similar proportions of patients in each treatment group started maintenance therapy (88% and 90%, respectively), and withdrew from maintenance therapy (23% and 24%, respectively). A higher proportion of patients in the GAUDI trial completed maintenance compared to the GALLIUM trial (76% versus 66%, respectively). However, patients in the GAUDI trial also experienced a higher proportion of dose interruptions/delays compared to patients in the GALLIUM trial (11% versus 6%, respectively). Of note, the cumulative dose of obinutuzumab during maintenance was higher in the GALLIUM trial as compared to the GAUDI trial (12,000 mg versus 7,222) as the frequency of dosing was higher due to a more frequent schedule. The mean number of doses received during maintenance in the GALLIUM trial was 12 (range 1-12) doses in both the obinutuzumab and rituximab arms; the mean number of doses was not reported for the GAUDI trial. A total of 81 patients were included in the GAUDI trial; 41 received CHOP plus obinutuzumab and 40 received bendamustine plus obinutuzumab. Nine patients (11.1%) discontinued treatment during induction or completed induction but did not continue with maintenance therapy. Seventy-two patients (88. 9%) continued to the maintenance phase of the trial; of these patients, 81% of patients who received bendamustine plus obinutuzumab (n=36) and 72% of patients who received CHOP plus obinutuzumab (n=36) completed the maximum eight cycles of obinutuzumab maintenance.

Efficacy[1,10]

In the GALLIUM trial, at the primary analysis, after a median follow-up of 34.5 months (range, 0-54.5), the estimated 3 year PFS by INV was 80.0% (95% CI, 75.9-83.6) in the obinutuzumab group and 73.3% (95% CI, 68.8-77.2) in the rituximab group. In the GAUDI trial after a median follow-up of 51.0 months (range 0.3-60) the PFS by INV was estimated at three years to be 90.0% (95% CI, 0.80-0.99) for the bendamustine plus obinutuzumab group and 84.0% (95% CI, 0.72-0.96) in the CHOP plus obinutuzumab group.

Safety[1,10]

Overall, in the GALLIUM trial, a greater number of AEs occurred in the obinutuzumab group (n=3002) compared to the rituximab group (n=2578) during maintenance. There were more patients in the obinutuzumab group (n=501, 91.4%) who experienced one or more AEs (any grade) compared to the rituximab group (n=458, 85.6%); of these, a greater proportion of grade 3-5 AEs occurred in the obinutuzumab group (n=205, 37.4%) versus the rituximab group (189, 31.6%). A similar proportion of grade 5 AEs occurred in both the obinutuzumab and rituximab groups (n=10,~2%) during the maintenance phase. Similar to the GALLIUM trial, 37.5% of patients (n=27/72) experienced grade 3-5 AEs in the maintenance phase of the GAUDI trial. In the bendamustine plus obinutuzumab group, five patients withdrew from maintenance due to an adverse event (giardiasis with anemia, neutropenic infection, flare-up of Crohn's disease, nasopharyngitis, and neutropenia in one patient each). In the CHOP plus obinutuzumab group, four patients withdrew from maintenance due to an AE (three due to infection, and one due to peripheral sensory neuropathy).

In the GALLIUM trial, serious AEs also occurred more frequently in the obinutuzumab group (n=134, 24.5%) compared to the rituximab group (n=110, 20.6%) during maintenance. No serious AEs were observed in the eight patients who entered follow-up directly after induction. Neutropenia was the most common grade 3 to 5 SAE occurring in 16.4% of patients in the

obinutuzumab group and 10.7% of the rituximab group. Infections were the most frequent cause of grade 3-4 non-hematologic AEs in the GAUDI trial, with six patients in the bendamustine plus obinutuzumab group and five patients in the CHOP plus obinutuzumab group experiencing them; all infections were grade 3 except for one patient in the bendamustine plus obinutuzumab group who had a grade 4 neutropenic infection. All hematologic adverse events experienced during maintenance were in the bendamustine plus obinutuzumab group (n=8). Grade 3 to 4 neutropenia was experienced by six patients, and grade 3 to 4 febrile neutropenia was experienced by one patient, all of which were noted 81-91 days after each patient's last dose of obinutuzumab; two patients experienced febrile/infective complications.

During the maintenance phase of the GALLIUM trial, 33/540 (6.1%) and 35/526 (6.7%) patients experienced dose interruptions in the obinutuzumab and rituximab arms, respectively; 373/595 (62.7%) and 329/597 (55.1%) of patients experienced treatment delays of greater than seven days in the obinutuzumab and rituximab arms, respectively. In the GAUDI trial, dose delays or interruptions occurred in six patients in the bendamustine plus obinutuzumab group, and two patients in the CHOP plus obinutuzumab group. One treatment-related death occurred in a patient in the CHOP plus obinutuzumab group, occurring 59 days after the only dose of maintenance therapy.

Ten fatalities occurred during maintenance in the GALLIUM trial in the obinutuzumab group, and one patient died in the GAUDI trial during maintenance in the CHOP plus obinutuzumab group and there were no deaths due to treatment reported in the bendamustine plus obinutuzumab group during maintenance.

7.1.1 Conclusions

There were no trials identified that directly compared different obinutuzumab maintenance schedules in patients with previously untreated FL; however, two trials were identified that reported on the efficacy and safety of obinutuzumab maintenance, each evaluating a different maintenance schedule. Obinutuzumab was administered every two months in the GALLIUM trial, while obinutuzumab was administered every three months in the GAUDI trial. The GALLIUM trial compared induction chemotherapy plus obinutuzumab followed by obinutuzumab maintenance with induction chemotherapy plus rituximab, followed by rituximab maintenance, and therefore was not designed to compare the efficacy of different maintenance schedules of obinutuzumab. The purpose of the GAUDI trial was to evaluate the efficacy and safety of obinutuzumab in combination with either CHOP or bendamustine, followed by maintenance obinutuzumab, thus making a direct comparison of outcomes between these two trials difficult. In the absence of a direct comparison of maintenance schedules for obinutuzumab, a summary of these two trials, each with a different maintenance schedule, was provided.

Overall, patient baseline characteristics were similar in the trials and similar proportions of patients entered the maintenance phase. Both trials reported PFS rates at three years. Similar proportions of patients experienced grade 3-5 AEs in both the GALLIUM and GAUDI trials. However, reporting of AEs differed between the trials specifically during the maintenance phase; breakdown of grade 3-5 AEs were reported for the GALLIUM trial, however specific types of grade 3-5 AEs were not reported for the GAUDI trial. Instead, the GAUDI trial reported grade 3-4 hematological AEs. Overall, differences in the GALLIUM and GAUDI trials with respect to differences in the study design, sample size, proportion of patients receiving each type of induction therapy, and reporting of outcome data made a naïve comparison difficult. Overall, limited conclusions on the clinical efficacy, safety and therapeutic equivalence of the two maintenance schedules can be drawn from the two trials. It is unclear without a direct comparison of alternate obinutuzumab maintenance schedules whether a three month maintenance schedule is more favourable, less favourable or similar to a two month maintenance schedule.

Table 13: Key efficacy and safety data from the GALLIUM trial and the GAUDI trial[1,10]

Trial	GALLIUM		GAUDI	
	Obinutuzumab + Chemotherapy n=601	Rituximab + Chemotherapy n=601	Obinutuzumab + Bendamustine n=41	Obinutuzumab + CHOP n=40
Median follow-up, months (range)	34.5 (0-54.5)		51.0 (0.3-60)	
Dosing and Patient Disposition				
No. patients who started maintenance therapy	539 (89.7)	527 (87.7)	36 (87.8)	36 (90.0)
No. patients who withdrew from maintenance, (%)	118 (21.9)	132 (25.0)	7 (19.4)	10 (27.8)
No. patients who completed maintenance therapy	361 (66.8)	341 (64.7)	29 (80.6)	26 (72.2)
No. patients with dose interruptions/delays (%)	33/540 (6.1) [a]	35/526 (6.7) [a]	6 (16.7)	2 (5.5)
Cumulative dose during maintenance (mg), mean (range)	12,000 (1000-12,088) [a]	7679 (555-12,000) [a]	7222 (NA)	7222 (NA)
Doses received during maintenance, mean (range)	12 (1-12)	12 (1-12)	NA	NA
Efficacy				
Events of progression, relapse or death, n (%)				
By IRC	93 (15.5)	125 (20.8)	NA	NA
By INV	101 (16.8)	144 (24.0)	NA	NA
PFS				
By IRC % (95% CI)	81.9 (77.9-85.2)	77.9 (73.8-81.4)	NA	NA
	HR=0.71, 95%CI: 0.54-0.93; p=0.001 [b]		NA	
By INV % (95% CI)	80.0 (75.9-83.6)	73.3 (68.8-77.2)	90 (90.80-0.99) [b]	84 (0.72-0.96) [b]
	HR=0.66, 95%CI,0.51-0.85; p=0.001 [b]		NA	
Safety				
All grade AEs during maintenance, n	3002	2578	NA	NA
Patients with ≥1 AE, n (%)				
Any event during maintenance	501/548 (91.4)	458/535 (85.6)	8/36 (22) [c]	0/36 (0) [c]

Trial	GALLIUM		GAUDI	
	Obinutuzumab + Chemotherapy n=601	Rituximab + Chemotherapy n=601	Obinutuzumab + Bendamustine n=41	Obinutuzumab + CHOP n=40
Event of grade 3 to 4 during maintenance	205/548 (37.4) [d]	169/535 (31.6) [d]	6/36 (17) [c]	0/36 (0) [c]
Event of grade 5 during maintenance	10/548 (1.8) [e]	10/535 (1.9) [e]	0	1
Patients with ≥1 serious AE, n (%)	134/548 (24.5%)	110/535 (20.6)	NA	NA

IRC=independent review committee; **INV**=investigator; **AE**=adverse event; **ORR**=Overall Response Rate; **CR**=Complete Response; **PFS**=Progression Free Survival; **HR**=Hazard Ratio; **NA**= not available

[a] Results are provided for the safety population.

[b] Rate of estimated 3-year progression-free survival.

[c] Hematologic adverse events occurring in >5% of patients.

[d] Adverse events were reported for Grades 3 to 5.

[e] Fatal adverse events (grade 5) during induction (which occurred in one patient each unless otherwise specified) were cardiogenic shock, pneumonia (in two), and dehydration in the obinutuzumab group and multi-organ failure, septic shock, and polyneuropathy in the rituximab group. Fatal adverse events that occurred after induction (in one patient each) were cardiogenic shock, gastric hemorrhage, death, pneumonia, staphylococcal bacteremia, acute lymphocytic leukemia, acute myeloid leukemia, hepatic neoplasm, acute lung injury, and respiratory failure in the obinutuzumab group and cardiac arrest, myocardial infarction, death, multi-organ failure, colon cancer, gastric cancer, lung adenocarcinoma, malignant melanoma, neuroendocrine carcinoma of the skin, and encephalopathy in the rituximab group. Fatal adverse events occurring in the follow-up phase were upper gastrointestinal hemorrhage, ill-defined disorder, pneumonia, lower respiratory tract infection, lung infection, respiratory tract infection, sepsis, non-small cell lung cancer, and non-small cell lung cancer of stage IV (in one patient) and *Clostridium difficile* colitis, the myelodysplastic syndrome, and prostate cancer (all in one patient) in the obinutuzumab group; and general physical health deterioration, pneumonia, hypercalcemia, cerebral hematoma, cerebrovascular accident, ischemic stroke and chronic obstructive pulmonary disease (in one patient each) in the rituximab group.

8 COMPARISON WITH OTHER LITERATURE

No comparisons with other literature were included in this pCODR review.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Lymphoma 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 (Gazyva) FL 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. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publically posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report.

The Lymphoma 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 February 2018, Embase 1974 to 2018 March 27, Ovid MEDLINE(R) ALL 1946 to March 27, 2018

#	Searches	Results
1	(Obinutuzumab* or gazyva* or afutuzumab* or R7159 or R 7159 or GA101 or GA 101 or RO5072759 or RO 5072759 or HSDB 8349 or HSDB8349 or huMAB CD20 or huMABCD20 or O43472U9X8 or 949142-50-1 or "949142501").ti,ab,ot,kf,kw,hw,rn,nm.	1947
2	Lymphoma, Follicular/ or Lymphoma, Non-Hodgkin/	65062
3	(lymphom* or lymphogranuloma* or granuloma* or lymphosarcoma* or blastoma* or lymphoid hyperplasia* or lymphoblastoma* or lymphomatos?s).ti,ab,kf,kw.	556335
4	(brill adj2 symmers).ti,ab,kf,kw.	405
5	or/2-4	569669
6	1 and 5	815
7	6 use medall	109
8	6 use cctr	99
9	*obinutuzumab/	447
10	(Obinutuzumab* or gazyva* or afutuzumab* or R7159 or R 7159 or GA101 or GA 101 or RO5072759 or RO 5072759 or HSDB 8349 or HSDB8349 or huMAB CD20 or huMABCD20).ti,ab,kw,dq.	1310
11	9 or 10	1328
12	follicular lymphoma/ or nonhodgkin lymphoma/	74303
13	(lymphom* or lymphogranuloma* or granuloma* or lymphosarcoma* or blastoma* or lymphoid hyperplasia* or lymphoblastoma* or lymphomatos?s).ti,ab,kw,dq.	557865
14	(brill adj2 symmers).ti,ab,kw,dq.	407
15	or/12-14	575521
16	11 and 15	621
17	16 use oemezd	431
18	17 and conference abstract.pt.	244
19	limit 18 to english language	244
20	limit 19 to yr="2013 -Current"	191
21	17 not 18	187
22	7 or 8 or 21	395
23	remove duplicates from 22	291
24	limit 23 to english language	279

25	24 or 20	470

2. Literature search via PubMed

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

Search	Query	Results
#5	Search #3 AND publisher[sb] Filters: English	5
#4	Search #3 AND publisher[sb]	5
#3	Search #1 AND #2	109
#2	Search obinutuzumab [Supplementary Concept] OR O43472U9X8[rn] OR 949142-50-1[rn] OR 949142501[rn] OR obinutuzumab*[tiab] OR Gazyva*[tiab] OR afutuzumab*[tiab] OR R7159[tiab] OR R 7159[tiab] OR GA101[tiab] OR GA 101[tiab] OR RO5072759[tiab] OR RO 5072759[tiab]	327
#1	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] OR lymphomatosis[tiab] OR lymphomatoses[tiab]	243033

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: Gazyva/Gazyvaro/obinutuzumab

Select international agencies including:

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

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

Search: Gazyva/Gazyvaro/obinutuzumab

Conference abstracts:

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

American Society of Hematology (ASH)

http://www.hematology.org/

Search: Gazyva/Gazyvaro/obinutuzumab – last 5 years

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 (1946-2018 Mar 27) with in-process records & daily updates via Ovid; Embase (1974-2018 Mar 27) via Ovid; The Cochrane Central Register of Controlled Trials (Feb 2018) 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 Gazyva, Gazyvaro, obinutuzumab and follicular lymphoma.

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

The search is considered up to date as of August 2, 2018.

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 limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) 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. One member of the pCODR Methods Team independently made the final selection of studies to be included in the review.

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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