Updates from the 2016 American Society of Hematology annual meeting: practice-changing studies in untreated follicular lymphoma

C. Owen MD,* D. MacDonald MD,† A. Aw MD,‡ and A. Christofides MSc RD§

ABSTRACT

The 2016 annual meeting of the American Society of Hematology took place in San Diego, California, 3–6 December. At the meeting, results from key studies on the first-line treatment of follicular lymphoma were presented. Of those studies, key oral presentations included two analyzing data from the GALLIUM study, which evaluated the efficacy and safety of obinutuzumab plus chemotherapy (G-chemo) compared with rituximab plus chemotherapy (R-chemo), followed, in responding patients with follicular lymphoma, by obinutuzumab or rituximab maintenance; results from the SABRINA study, which evaluated the efficacy and safety of subcutaneous compared with intravenous rituximab; results of a cost-effectiveness analysis of first-line treatment with bendamustine and rituximab from a Canadian perspective; and results from the SAKK 35/10 study, which evaluated the safety and efficacy of rituximab plus lenalidomide compared with rituximab monotherapy. Our meeting report describes the foregoing studies and includes interviews with the Canadian investigators, plus commentaries by those investigators about the potential impact on Canadian practice.

Key Words Follicular lymphoma, untreated; front-line treatment; first-line treatment

BACKGROUND

The current standard of care in Canada for the first-line treatment of follicular lymphoma (FL) is bendamustine in combination with rituximab (BR), followed by rituximab maintenance1. Justification for BR as standard therapy is based on results of the phase III STIL-1 trial2, published in 2013, that demonstrated an improvement in progression-free survival (PFS) with BR compared with rituximab plus cyclophosphamide, vincristine, doxorubicin, and prednisolone (R-CHOP) [FL subgroup: not reached vs. 40.9 months respectively; hazard ratio (HR): 0.61; p = 0.0072]. Furthermore, the safety profile was improved with BR, with lower rates of alopecia, hematologic toxicity, and infections than occurred with R-CHOP; however, rates of skin reactions were increased (p < 0.05).

Results from STIL-1 were subsequently confirmed by the BRIGHT study3, which showed that the complete response (CR) rate with BR was statistically noninferior (p = 0.0225) to that with R-CHOP or with rituximab plus cyclophosphamide, vincristine, and prednisolone (R-CVP).

However, given that the BRIGHT study used response rates as a primary outcome, changes in practice were based primarily on PFS data from STIL-1—PFS being is a more appropriate endpoint in this setting.

Based on the foregoing data, BR is now funded for the first-line treatment of FL in all Canadian provinces with the exception of Quebec and can be given to most patients with few restrictions.

Before BR became the standard of care, R-CVP was used in preference to R-CHOP in most centres in Canada, given the potential cardiotoxicity associated with doxorubicin. Because advanced FL is incurable and patients are likely to be exposed to additional treatments over time, it was deemed preferable to save anthracyclines for later in the disease course, especially given the relatively high incidence of transformation to more aggressive disease. Other
countries have taken a different approach, and more recent data—for example, those from the study by Federico et al. demonstrating superior 3-year PFS with R-CHOP compared with R-CVP \((p < 0.05)\)—suggest that R-CHOP should be given in preference to R-CVP in this setting.

In recent years, novel monoclonal antibodies (mAbs), innovative formulations of rituximab, and chemotherapy-free regimens have been developed, with the goal of improving efficacy, administration time, and toxicity associated with treatment. Results of ongoing studies examining those strategies were presented at the 2016 annual meeting of the American Society of Hematology.

**METHODS**

The American Society of Hematology held its first official meeting in 1958, and this professional society is now the world’s largest with a focus on hematologic malignancies. The Society’s 2016 annual meeting took place in San Diego, California, 3–6 December, and attracted 27,380 attendees, the world’s largest with a focus on hematologic malignancies. The Society’s 2016 annual meeting took place in San Diego, California, 3–6 December, and attracted 27,380 attendees, the world’s largest with a focus on hematologic malignancies.

**Methods:** The analysis included 1202 patients 18 years of age or older with untreated FL (grades 1–3a, Eastern Cooperative Oncology Group performance status 0–2) requiring treatment according to Groupe d’Etude des Lymphomes Folliculaires criteria. Patients were given CHOP, CVP, or bendamustine (investigator choice) and were randomized to receive either rituximab 375 mg/m² or obinutuzumab 1000 mg (Figure 1). Patients achieving a complete or partial response received rituximab or obinutuzumab as maintenance every 2 months for 2 years or until disease progression. The primary endpoint was investigator-assessed PFS.

**Results:** Median patient age was 59 years (range: 23–88 years), and baseline characteristics were well balanced between the R-chemo \((n = 601)\) and G-chemo \((n = 601)\) groups. Chemotherapy delivered was bendamustine in 57.1% of patients, CHOP in 33.1%, and CVP in 9.8%. Median follow-up of 34.5 months (range: 0–54.5 months), patients in the G-chemo arm experienced a 34% reduction in the risk of progression or death \((HR: 0.66; 95\% CI 0.51 to 0.85; \ p = 0.0012, Figure 2)\]. The improved PFS with obinutuzumab was consistent across chemotherapy subgroups (Figure 3). Time to next treatment was also superior with G-chemo \((HR: 0.68; p = 0.0094)\]. Among the 696 patients with an available peripheral blood or bone marrow sample at the end of induction, minimal residual disease \((MRD)\) response by real-time quantitative polymerase chain reaction was significantly higher in the G-chemo arm than in the R-chemo arm \((92\% vs. 85\%, p = 0.0041, Table I)\]. At the time of analysis, 35 G-chemo patients (5.5%) and 46 R-chemo patients (8.7%) had died \([HR for overall survival (OS) = 0.75; 95\% CI 0.49 to 1.17; p = 0.210, Table II)\]. Grade 3 or greater adverse events \((AEs)\) and serious AEs were higher with G-chemo \((74.6\% and 46.1\% respectively)\) than with R-chemo \((67.8\% and 39.9\% respectively, Table II)\]. In the absence of disease progression, AEs led to treatment discontinuation in 16.3% of G-chemo patients and 14.2% of R-chemo patients.

**Author Conclusions:** The data support G-chemo becoming a new standard of care in previously untreated patients with FL.

**Investigator Commentary**

**Dr. Carolyn Owen:** Canadian participation in the GALLIUM study was remarkable, with Alberta alone enrolling more patients than any single country outside of Canada, leading to the inclusion of two Canadian authors in this presentation. Overall, Edmonton enrolled the greatest number of patients globally \((n = 52)\), with Calgary having the second-highest enrolment \((n = 49)\). Canadian participation was therefore very high, with few eligible patients deciding against registration. Our centre had great interest in the study given the provision of both obinutuzumab and bendamustine, the broad inclusion criteria, and the small additional burden for patients. The GALLIUM study is a great example of the impact that Canada is able to have within clinical trials, and it confirms our willingness to change practice, especially when experience with new agents is gained through study participation.

At our centre, as was the case at most Canadian sites, bendamustine was chosen as the preferred chemotherapy backbone. Although a few centres used CVP, that choice was most likely made because the stilt-1 data were not yet published when GALLIUM was initiated. In addition, some centres worldwide might still have used CHOP over bendamustine, given that an OS advantage has not yet been demonstrated.
for bendamustine, and experience with CHOP, which also has an infusion time of only 1 day, is greater.

Obinutuzumab was developed to improve on the therapeutic activity of rituximab; but although it might be tempting to think of obinutuzumab as a “beefed up” version of rituximab, the comparison is technically inaccurate. Anti-CD20 mAbs are classified based on their mode of action and CD20 binding properties. In that light, obinutuzumab is a type 2 mAb, which, compared with a type 1 mAb such as rituximab, exerts less complement-dependent cytotoxicity and more direct cell death. Moreover, in preclinical studies, obinutuzumab as monotherapy has, compared with rituximab monotherapy, demonstrated superior efficacy even in patients who are rituximab-refractory.

Patients included in the GALLIUM study were representative of those seen in clinical practice because the exclusion criteria were few. Moreover, the study treatment conformed to our institutional protocol—with the exceptions of additional computed tomography and positron-emission tomography imaging and differences in the maintenance schedule, in which treatment was given every 2 months instead of every 3 months as at our centre.

The study demonstrated an estimated 3-year improvement in PFS with G-chemo, which is a clinically meaningful difference. The improved PFS with G-chemo was seen across all subgroups, and it was encouraging to note that the best results were in the obinutuzumab–bendamustine (gb) group, because that regimen is likely the one we would prefer to use in Canada, given the preference for bendamustine as backbone therapy. The fact that bendamustine and CHOP showed similar efficacy in the rituximab-containing group...
TABLE I  Minimal residual disease by treatment at end of induction in peripheral blood or bone marrow

| Minimal residual disease | Chemotherapy with ... |
|--------------------------|-----------------------|
|                          | Obinutuzumab (n=345)  | Rituximab (n=351)  |

At mid-induction [n (%)]
- Positive: 38 (11.1) vs. 20 (5.7) p Value 0.013
- Negative: 304 (88.9) vs. 328 (94.3)

At end of induction [n (%)]
- Positive: 52 (15.1) vs. 28 (8.0) p Value 0.0041
- Negative: 293 (84.9) vs. 323 (92.0)

TABLE II  Key adverse events

| Adverse event                              | Chemotherapy with ...
|--------------------------------------------|-----------------------|
|                                            | Rituximab (n=597)     | Obinutuzumab (n=595) |

Any adverse event [n (%)]
- 587 (98.3) vs. 592 (99.5)

Grade 3 or greater events [n (%)]
- Neutropenia: 426 (75.0) vs. 457 (78.3)
- Leucopenia: 50 (8.4) vs. 51 (8.6)
- Febrile neutropenia: 29 (4.9) vs. 41 (6.9)
- Infusion-related reactions: 22 (3.7) vs. 40 (6.7)
- Thrombocytopenia: 16 (2.7) vs. 36 (6.1)

Grade 3 or greater events of special interest, by category [n (%)]
- Infections: 93 (15.6) vs. 119 (20.0)
- Infusion-related reactions: 40 (6.7) vs. 74 (12.4)
- Second neoplasms: 16 (2.7) vs. 28 (4.7)

Consequential adverse events [n (%)]
- Classified as serious: 238 (39.9) vs. 274 (46.1)
- Cause of treatment discontinuation: 85 (14.2) vs. 97 (16.3)
- Fatal: 20 (3.4) vs. 24 (4.0)

Change from baseline IgG level at end of induction (g/L)
- Median: –1.46 vs. –1.50
- Range: –16.4 to 9.1 vs. –22.3 to 6.5

was likely a result of the small numbers in those subgroups; those data would not influence our choice of bendamustine as a backbone. Moreover, in Canada, only rituximab is funded for FL. It is also reassuring to see greater MRD negativity in patients given bendamustine, but the number of patients evaluated was small, and it is therefore difficult to use those data for clinical decision-making. It would have been interesting had we changed the maintenance schedule based on the MRD results; however, given that the patients were embarking on maintenance regardless of MRD outcome, the value of those results is unclear. The data concerning OS are premature, because more than 10 years will likely be needed to detect a difference between groups; in contrast, our analysis was based on a median follow-up duration of less than 3 years.

We know of the high incidence of infusion-related reactions (IRR) with obinutuzumab in patients with chronic lymphocytic leukemia, and so it was encouraging that the rate of IRRs in the Gallium study was less than the rate previously reported in such patients. Moreover, no new safety signals with obinutuzumab were observed, and the slight increase in neutropenia and thrombocytopenia reported would not influence my decision to use obinutuzumab over rituximab in these patients. In looking at the raw data with respect to secondary malignancies with bendamustine, the higher rate in the bendamustine group appears somewhat concerning. However, on further investigation, such malignancies are seen to be mainly non-melanoma skin cancers, and whether the higher rate is a true finding is unclear based on the current data. Given that bendamustine has some purine analog-like activity and that purine analogs are associated with an increased risk of secondary malignancies, it is important to closely monitor long-term toxicities to ensure that new malignancies are not a true risk for bendamustine-treated patients.

Efficacy and Safety of Subcutaneous Compared with Intravenous Rituximab [SABRINA (abstract 1103)]

Objectives: To assess the efficacy and safety of SC compared with IV rituximab given as induction with CHOP or CVp, followed by maintenance monotherapy in patients with FL.

Methods: Treatment-naïve patients with CD20+ grades 1–3A FL (n = 410) were randomized to receive IV (n = 205) or SC (n = 205) rituximab, stratified by Follicular Lymphoma International Prognostic Index score, chemotherapy regimen, and region (Figure 4). During maintenance, patients received IV or SC rituximab every 8 weeks for 2 years.

Results: Median patient age was 57 years (range: 28–86 years), and baseline characteristics were equally distributed between the groups. Overall response rate at the end of induction and of maintenance was comparable in the treatment arms (IV: 84.9% and 78.1% respectively; SC: 84.4% and 77.9% respectively; Figure 5). In addition, no differences in response rates were observed in the IV and SC rituximab arms by body surface area (BSA), chemotherapy, or sex subgroup. Moreover, after a median follow-up of 37 months, analyses of PFS (HR: 0.84; 95% CI: 0.57 to 1.23), event-free survival (HR: 0.91; 95% CI: 0.64 to 1.31), and OS (HR: 0.81; 95% CI: 0.42 to 1.57) showed no differences in efficacy for the SC and IV formulations.

Overall, the incidences of 1 or more AE (95% vs. 96%), grade 3 or greater AEs (55% vs. 56%), and serious AEs (34% vs. 37%) were similar for patients receiving IV and SC rituximab (Table III). The AEs reported most frequently overall in the IV and SC rituximab groups were neutropenia...
Overall, no new clinically relevant safety signals were observed with sc rituximab, and the safety profile for the sc formulation was comparable to that for the IV formulation. The approximately 6-minute duration of sc rituximab administration has positive implications for the convenience of patients and health care professionals, as well as for health care resource savings, without compromise to efficacy or safety.

**Investigator Commentary**

Dr. David MacDonald: Rituximab has had an enormous effect on the management of FL, and it is now an integral part of treatment. However, the use of IV rituximab has certain disadvantages, including associated irrs and a long administration time. We are fortunate that, in patients without irrs in the first cycle, we can reduce the infusion time to 90 minutes; however, that time is nonetheless long for patients to undergo treatment. The sc formulation allows for more rapid delivery of the drug, which provides both convenience and reduced chair time, freeing health care resources for other patients.

The aim of the SABRINA study was to measure whether any loss in efficacy occurs for the sc formulation compared with the IV formulation during induction and maintenance in untreated FL. In our study, the first dose was given intravenously because of the risk of irrs related to tumour burden. The IV formulation can be slowed or stopped if reactions occur, but the sc injection is delivered in approximately 6 minutes and is irreversible. For that reason, and because we lack information on the safety of the sc formulation given as a first dose, the first dose must currently be given by the IV route.

**TABLE III**  Key adverse events

| Adverse event type                  | Rituximab administration route | Intravenous (n=210) | Subcutaneous (n=197) |
|-------------------------------------|--------------------------------|---------------------|----------------------|
| Any adverse event                   |                                | 199 (95)            | 189 (96)             |
| Grade 3 or greater events           |                                | 116 (55)            | 111 (56)             |
| Serious events                      |                                | 72 (34)             | 73 (37)              |
| Deaths                              |                                | 22 (10)             | 14 (7)               |
| Adverse events leading to death     |                                | 12 (6)              | 7 (4)                |
| Death from other cause              |                                | 9 (4)               | 7 (4)                |
| Administration-related reactions    |                                | 73 (35)             | 95 (48)              |
| Infections and infestations         |                                | 134 (64)            | 132 (67)             |
| Neutropenia                         |                                | 57 (27)             | 63 (32)              |
| Febrile neutropenia                 |                                | 13 (6)              | 15 (8)               |

(27% vs. 32%), nausea (22% vs. 31%), constipation (26% vs. 25%), cough (13% vs. 23%), and fatigue (18% vs. 20%). Overall, aEs associated with B cell depletion—including neutropenia, febrile neutropenia, and grade 3 or greater infections—were balanced in the sc and IV treatment arms; no differences between the groups by bsa or sex subgroup were observed. The change in route of administration led to an expected higher incidence of local cutaneous reactions in the sc arm (23% vs. 2%), with injection site erythema, injection site pain, and rash being most frequently reported. All reported events, except for 1 ae of injection site rash in the sc arm at cycle 2, were of mild or moderate intensity (grade 2 or less). The incidence of local cutaneous reactions declined in subsequent treatment cycles.
Our study showed that there is no difference in the efficacy of the sc and IV formulations. Safety profiles were also similar between groups, with local reactions such as erythema, injection site pain, and rash being the only AEs reported with a higher frequency in the sc arm; however, those AEs were mostly low-grade, and they were easily managed. There was previously some concern that patients with a low BSA might be over-dosed and that those with a high BSA might be under-dosed, with consequences for both efficacy and safety. However, we found no differences in either the efficacy or the safety of the sc formulation in patients with a low, medium, or high BSA. Overall, the sc formulation showed no difference in efficacy, and the local reactions seen were easily managed. I would therefore use sc over IV rituximab in most patients in this setting.

Efficacy and Safety of Lenalidomide Plus Rituximab Versus Rituximab Monotherapy [SAKK 35/10 (abstract 1099)]

**Objective:** To compare the activity of single-agent rituximab with that of rituximab plus lenalidomide in the first-line treatment of FL.

**Methods:** Patients with untreated grades 1–3a FL were randomized to receive either rituximab monotherapy (n = 77) or rituximab–lenalidomide (n = 77, Figure 6). Treatment was discontinued in patients who did not achieve a 25% or greater reduction in the sum of the products of tumour diameters at week 10. The primary endpoint was the rate of CR or unconfirmed CR (CRu).

**Results:** Median patient age was 62 years (range: 26–85 years), and 47% of patients had a poor-risk score on the Follicular Lymphoma International Prognostic Index. At week 23, the CR/CRu rate was higher in the rituximab–lenalidomide arm than in the rituximab arm (61% vs. 36%). The median duration of CR/CRu was not reached in the rituximab–lenalidomide arm; it was 2.3 years in the rituximab arm (p = 0.04). At a median follow-up of 3.5 years, PFS was longer in the rituximab–lenalidomide arm than in the rituximab arm (not reached vs. 2.3 years, p = 0.03, Figure 7). The OS rates were similar in both arms (93% for rituximab–lenalidomide; 92% for rituximab). Of 77 patients, 11 discontinued lenalidomide because of toxicity. Higher rates of neutropenia (23.4% vs. 6.6%) and thrombocytopenia (3.9% vs. 0%) were reported in the rituximab–lenalidomide arm than in the rituximab arm (Table IV).

**Author Conclusions:** The SAKK 35/10 trial confirmed that the rituximab–lenalidomide regimen is an active and feasible initial treatment for FL patients. Based on the excellent OS in both arms, chemotherapy-free strategies should be further explored in this setting.

**Cost-Effectiveness of BR in Canada (abstract 1186)**

**Objectives:** To assess the cost-effectiveness of BR compared with R–CHOP as frontline treatment for patients with FL in Canada.

**Methodology:** A Markov model was developed to estimate the costs, life expectancy, and quality-adjusted life...
years (qalys) associated with the two regimens, allowing for a determination of the incremental cost–utility ratio. Model parameters were derived from peer-reviewed studies, and cost data were obtained from current funding arrangements under the New Drug Funding Program of Cancer Care Ontario, the Ontario Health Insurance Plan Schedule of Benefits and Fees, and the published literature. Patients were treated with a maximum of 3 lines of salvage therapy (third salvage permitted in age-appropriate patients achieving at least 1 year remission from second-line salvage). Probabilistic analyses were used to account for model variable uncertainty, permitting a Monte Carlo simulation with 5000 replications.

**Results:** The average costs and qalys were $116,811 and 5.86 for r-chop and $121,364 and 6.38 for br. The incremental cost per qaly gained for br with respect to r-chop was $8,812 (Figure 8). Subgroup analyses revealed robust incremental cost–utility ratio results of $27,398 for the fl subgroup. Results were consistent across various indolent nhl subgroups, and sensitivity analyses did not change the interpretation of results.

**Author Conclusions:** The model suggests that, compared with r-chop, br is a cost-effective strategy in the frontline treatment of patients with indolent nhl.

**Investigator Commentary**

**Dr. Andrew Aw:** Cost-effectiveness studies are one tool that can be used by decision-makers to help facilitate evidence-based choices between various interventions or treatments. Because health resource utilization data are not always gathered at the same time that a clinical trial is run, one way to compare the cost-effectiveness of a given treatment with that of another is to develop a model; such a model can be used for health economic evaluation.

Prior studies have confirmed the clinical efficacy of frontline br compared with r-chop or r-cvp in the treatment of indolent nhl, but there was uncertainty about the cost-effectiveness of br. Our study showed that, in a Canadian setting, br is more cost-effective than r-chop. The value of the incremental cost-utility ratio for the fl subgroup was somewhat higher than that for the entire cohort, but still under the willingness-to-pay threshold of $50,000 per qaly gained that is well-accepted in practice.

**CLINICAL IMPACT IN CANADA**

**Question-and-Answer with Drs. Carolyn Owen and David MacDonald**

**Question:** Given the results from the gallium study, what treatment would you give in the frontline setting if all options were available in Canada?

**CO:** Overall, given the clinically meaningful 3-year improvement in pfs observed in the gallium study, I feel that we should aim to replace rituximab with obinutuzumab in the treatment of frontline fl. I would want to use gb as induction, followed by obinutuzumab maintenance in these patients. However, the entry of sc rituximab will change things from a practical point of view. Given that the efficacy of obinutuzumab is superior to that of IV rituximab and that sc rituximab has not proved to be superior to IV rituximab, obinutuzumab is preferred. However, there could be the occasional patient who is elderly or has a lower life expectancy in whom it makes sense to give br (with sc rituximab) over gb.

**DM:** Although the gallium results showed superior pfs for obinutuzumab over rituximab, there was no difference in os. I am not sure that the pfs benefit with obinutuzumab is enough to convince me to switch all patients to obinutuzumab right away. Secondly, we need to consider results from the gadolin trial (NCT01059630) that showed an os benefit for gb compared with bendamustine alone in the relapsed setting. Because we lack data to support the sequencing of therapies, and we know excellent results are achieved with br, I would give br (with sc rituximab) up front and use gb in the relapsed setting. However, if further follow-up from the gallium study shows an os advantage, I would switch to gb up front in these patients.

**Question:** Given the results from the sabrina study, would you give the sc over the IV formulation to all patients if available?

**CO:** The sc formulation will make a big difference in terms of time savings for chemotherapy units and cost savings for cancer centres. Data from the sabrina study should motivate a change in practice from the IV to the sc formulation of rituximab (until obinutuzumab is funded), at least in fl patients.

**DM:** There could be some older patients with a loss of sc integrity or taking anticoagulation therapy who might have a higher risk of bleeding with the sc formulation; in those patients, I would prefer to use the IV formulation. In addition, in patients that present with sc edema, we are not certain how the sc formulation would distribute. Aside from the above circumstances, I would have no concerns about using the sc formulation in most patients with indolent nhl, given the results from our study.

---

**FIGURE 8** Cost-effectiveness acceptability curve. QALY = quality-adjusted life year; RCHOP = rituximab, cyclophosphamide, vincristine, prednisone; BR = bendamustine, rituximab.
**Question:** Do results from the sakk 35/10 trial suggest that use of the rituximab–lenalidomide regimen should be explored further?

**CO:** The addition of lenalidomide to rituximab improves PFS; however, rituximab monotherapy is not a standard treatment for FL in Canada. Although the PFS results are impressive, they do not appear superior to those shown with GA. Concerns about second malignancies and the side effects of chemotherapy are relevant only when chemotherapy-free options are better tolerated. The sakk 35/10 trial showed that the addition of lenalidomide caused a high rate of neutropenia, and concerns about second primary malignancies with the use of this agent are also an issue. To motivate a change in my practice, I would need to see results of a study comparing rituximab–lenalidomide with GA plus obinutuzumab maintenance.

**DM:** With available treatment options such as BR or R-CVP, patients who cannot tolerate standard therapies are few in number. We therefore rarely give rituximab monotherapy to patients, suggesting that the comparator used in the sakk 35/10 study was not relevant to Canadian practice. Furthermore, results showed that lenalidomide was not without significant toxicities, with 1 in 7 patients discontinuing treatment. Results from the RELANCE trial (NCT01476787) comparing rituximab–lenalidomide with rituximab–chemotherapy in the upfront setting will be much more valuable in answering this question.

**Question:** Do results from the BR cost-effectiveness study confirm that BR should be available as a treatment option across Canada?

**CO:** Although not practice-changing (because BR is already the standard of care in Canada), the results from the cost-effectiveness study do confirm that BR should be used in preference to R-CVP in Canada.

**DM:** If this study had been presented several years ago, it would have been very helpful in convincing payers to fund BR. However, BR is now available across Canada in the front-line setting; and in Quebec, it can be accessed on a case-by-case basis. Results from this study therefore reconfirm that we made the right choice in using BR, and it is reassuring that the cost savings resulting from prolongation of remission have made the regimen cost-effective.

**ACKNOWLEDGMENTS**
This document was developed by IMPACT Medicom Inc., with sponsorship provided by Lundbeck Inc.

**CONFLICT OF INTEREST DISCLOSURES**
CO has received honoraria for speaker fees or advisory board participation from Janssen, Roche, Gilead, Abbvie, Celgene, Novartis, and Lundbeck. Her institution has received funding from Roche, Pharmacies Inc, Gilead, Celgene, Novartis, Lundbeck, and Pfizer for trials in which she is a co-investigator. DM has received fees as an advisory board member for Roche, Lundbeck, Gilead, Janssen, Seattle Genetics, and Celgene. DM’s institution receives funding from Roche, Lundbeck, Pharmacies Inc, Pfizer, and Celgene for trials in which he is co-investigator. AA’s institution has received honoraria from Gilead and fees for advisory board membership from Merck and Janssen. AC has received funding for the writing of this document from Lundbeck Inc., Canada.

**REFERENCES**
1. Kuruvilla J, Assouline S, Hodgson D, et al. A Canadian evidence-based guideline for the first-line treatment of follicular lymphoma: joint consensus of the Lymphoma Canada Scientific Advisory Board. Clin Lymphoma Myeloma Leuk 2015;15:59–74.
2. Rummel MJ, Niederle N, Maschmeyer G, et al. on behalf of the Study Group Indolent Lymphomas. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. Lancet 2013;381:1203–10.
3. Flinn IW, van der Jagt R, Kahl BS, et al. Randomized trial of bendamustine–rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. Blood 2014;123:2944–52.
4. Federico M, Luminari S, Dondi A, et al. R-CVP versus R-CHOP versus R-FM for the initial treatment of patients with advanced-stage follicular lymphoma: results of the FOLLO5 trial conducted by the Fondazione Italiana Linfomi. J Clin Oncol 2013;31:1506–13.
5. Marcus RE, Davies AJ, Ando K, et al. Obinutuzumab-based induction and maintenance prolongs progression-free survival (PFS) in patients with previously untreated follicular lymphoma: primary results of the randomized phase 3 GALLIUM study [abstract 3]. Presented at: American Society of Hematology 58th Annual Meeting and Exposition; San Diego, CA; 3–6 December 2016. [Available online at: https://ash.confex.com/ash/2016/webprogram/Paper94744.html; cited 7 January 2017]
6. Pott C, Hoster E, Kehden B, et al. Minimal residual disease in patients with follicular lymphoma treated with obinutuzumab or rituximab as first-line induction immunotherapy and maintenance in the phase 3 GALLIUM study [abstract 613]. Presented at: American Society of Hematology 58th Annual Meeting and Exposition; San Diego, CA; 3–6 December 2016. [Available online at: https://ash.confex.com/ash/2016/webprogram/Paper96473.html; cited 7 January 2017]
7. Davies AJ, Mihaljevic B, Mercadal S, et al. Longer term efficacy and safety of subcutaneous compared with intravenous rituximab: updated results of the phase 3 SARRINA study [abstract 1103]. Presented at: American Society of Hematology 58th Annual Meeting and Exposition; San Diego, CA; 3–6 December 2016. [Available online at: https://ash.confex.com/ash/2016/webprogram/Paper94567.html; cited 7 January 2017]
8. Kimby E, Rondeau S, Vanazzi A, et al. Rituximab plus lenalidomide versus rituximab monotherapy in untreated follicular lymphoma patients in need of therapy: First analysis of survival endpoints of the randomized phase-2 trial SAKK 35/10 [abstract 1099]. Presented at: American Society of Hematology 58th Annual Meeting and Exposition; San Diego, CA; 3–6 December 2016. [Available online at: https://ash.confex.com/ash/2016/webprogram/Paper91021.html; cited 7 January 2017]
9. Aw A, Coyle K, Bence-Bruckler I, Bredeson CN, Coyle D. Bendamustine and rituximab versus conventional chemoimmunotherapy as a frontline treatment for patients with indolent B-cell lymphoma: a cost-effectiveness analysis [abstract 1186]. Presented at: American Society of Hematology 58th Annual Meeting and Exposition; San Diego, CA; 3–6 December 2016. [Available online at: https://ash.confex.com/ash/2016/webprogram/Paper90743.html; cited 7 January 2017]

10. Sehn LH, Goy A, Offner FC, et al. Randomized phase II trial comparing obinutuzumab (GA101) with rituximab in patients with relapsed CD20+ indolent B-cell non-Hodgkin lymphoma: final analysis of the GAUSS study. *J Clin Oncol* 2015;33:3467–74.