CURRENT ONCOLOGY
A Canadian Cancer Research Journal

MEETING REPORT

Updates from the 2017 American Society of Hematology annual meeting: practice-changing studies in relapsed and refractory mantle cell lymphoma

C. Owen MD,* J. Kuruvilla MD,† and A. Christofides MSc RD‡

ABSTRACT

The 2017 annual meeting of the American Society of Hematology took place 9–12 December in Atlanta, Georgia. At the meeting, results from key studies in the treatment of relapsed and refractory mantle cell lymphoma were presented. Of those studies, oral presentations focused on the efficacy and safety of therapy with Bruton tyrosine kinase (BTK) inhibitors. One study presented pooled data from three trials using ibrutinib, with a median follow-up of 3.5 years. A second phase II study presented data on the efficacy and safety of acalabrutinib, a highly selective BTK inhibitor with minimal off-target activity. The final study presented early phase IB data on the efficacy and safety of zanubrutinib, a novel, highly selective BTK inhibitor, in patients with non-Hodgkin lymphoma. Our meeting report describes the foregoing studies and presents interviews with investigators and commentaries by Canadian hematologists about potential effects on Canadian practice.

Key Words Relapsed disease, refractory disease, mantle cell lymphoma

Curr Oncol. 2018 Feb;25(1):83-90 www.current-oncology.com

BACKGROUND

Mantle cell lymphoma (MCL) is a rare and aggressive subtype of non-Hodgkin lymphoma (NHL). Existing data suggest a very poor median overall survival (OS) of 3–5 years[1,2], which has recently improved in the era of novel therapies. In younger (less than 60–65 years) fit patients, standard induction therapy is high-dose chemoimmunotherapy, with consolidation using high-dose therapy, followed by autologous stem-cell transplantation and maintenance rituximab[1,3]. In elderly patients (60–65 years of age and older), or in those ineligible for transplantation, bendamustine–rituximab is the recommended treatment option, followed by rituximab maintenance.

Despite the availability of a number of therapies in the first-line setting, patients inevitably relapse and require additional therapies[1]. Worldwide, four agents are now approved for the treatment of relapsed or refractory (RR) MCL, including bortezomib (Velcade: Takeda Pharmaceutical Company, Osaka, Japan)[4], lenalidomide (Revlimid: Celgene Corporation, Summit, NJ, U.S.A.)[5], and ibrutinib (Imbruvica: Pharmacyclics Sunnyvale, CA, U.S.A.)[6] in the United States, and lenalidomide[5], temsirolimus (Torisel: Pfizer, New York, NY, U.S.A.),[7] and ibrutinib[8] in Europe. In Canada, only two agents are approved in this setting: bortezomib[9] and ibrutinib[10], which have received full marketing approval from Health Canada.

Despite the recent approval of novel therapies, patients with RR MCL generally respond poorly to treatment, with the median OS typically being only 1–2 years[11]. Median progression-free survival (PFS) ranges from 3.9 months to 14.6 months, and overall response rates (ORRS) range from 22% to 72% depending on the type of treatment. Although no current standard of care has been established in the RR setting, ibrutinib shows the most promising single-agent efficacy of the currently approved agents, being associated with a median PFS of 13.6–14.6 months and with ORRS ranging from 54% to 72%[11–13]. In comparison, the reported

Correspondence to: Anna Christofides, IMPACT Medicom Inc., Toronto, Ontario M6S 3K2.
E-mail: anna@impactmedicom.com **DOI:** https://doi.org/10.3747/co.25.4006

median PFS was 9.2 months for bortezomib, 3.9–8.7 months for lenalidomide, and 4.8–6.2 months for temsirolimus.

The oral first-generation once-daily Bruton tyrosine kinase (BTK) inhibitor ibrutinib binds covalently to a cysteine residue (Cys481) in the active site of the ATP-binding domain of BTK, inhibiting B-cell receptor signalling, thereby reducing cell growth, proliferation, survival, adhesion, and migration[11]. With the success of ibrutinib in hematologic malignancies, novel BTK inhibitors designed to improve on its safety and efficacy are being developed. Acalabrutinib (ACP-196) is a potent orally bioavailable novel BTK inhibitor that also binds Cys481 in the BTK active site, inactivating the enzyme and resulting in inhibition of proliferation and survival signals in malignant B-cells[14]. However, acalabrutinib is more highly selective than ibrutinib, resulting in less off-target activity; it is therefore predicted to have fewer adverse effects. During *in vitro* studies comparing acalabrutinib with ibrutinib, acalabrutinib showed more selective BTK inhibition and higher *in vivo* potency[14]. Acalabrutinib was recently granted breakthrough designation for priority review by the U.S. Food and Drug Administration, and on 31 October 2017, it was granted accelerated approval by that agency for the treatment of patients with MCL who have received at least 1 prior therapy[15,16]. In addition, a third BTK inhibitor, zanubrutinib (BGB-3111), is potent and specific, and can also achieve higher selectivity than ibrutinib can[17]. Zanubrutinib is being examined in early clinical trials, with an ongoing phase IB trial examining its efficacy and safety in indolent NHL and aggressive lymphomas.

At the 2017 American Society of Hematology annual meeting, key studies in the treatment of RR MCL focused on BTK inhibitors including ibrutinib, acalabrutinib, and zanubrutinib.

METHODS

The American Society of Hematology held its first official meeting in 1958. Today, it is the world's largest professional society with a focus on hematologic malignancies. The 2017 annual meeting took place 9–12 December in Atlanta, Georgia, attracting 26,640 attendees, including 824 participants from Canada. Of 5730 abstracts accepted, 919 were chosen for oral presentation because of the high quality of their design and their potential effect on practice. To determine the most impactful abstracts in the setting of RR MCL, we searched the oral presentations using the search terms "relapsed," "refractory," and "mantle cell lymphoma." Of 75 abstracts, 18 oral presentations were identified using the search criteria. Of those 18 oral presentations, only studies in phase II and beyond that focused on the efficacy of treatment were included. Three oral presentations met those inclusion criteria.

The first study reported a pooled analysis of a 3.5-year follow-up of ibrutinib treatment in patients with RR MCL from three clinical trials. The second study, ACE-LY-004, examined the efficacy and safety of acalabrutinib in patients with RR MCL. The final study examined the efficacy and safety of zanubrutinib in patients with indolent and aggressive NHL. The section that follows outlines the three studies and presents interviews with investigators and commentaries about potential effects of the studies on Canadian practice.

DISCUSSION

Pooled Analysis of 3.5-Year Follow-Up Data of Ibrutinib in RR MCL—Abstract 151

Objective

To examine the efficacy and safety of ibrutinib in a pooled analysis of three studies—SPARK (NCT01599949), RAY (NCT01646021), and PCYC-1104 (NCT01236391)—after 3.5 years of follow-up[18].

Methods

Patients participating in the SPARK, RAY, and PCYC-1104 trials received oral ibrutinib 560 mg once daily until progression or unacceptable toxicity. Patients participating in SPARK were required to have received both rituximab and bortezomib; in RAY, they had to have already received rituximab. The pooled analysis included only patients on ibrutinib therapy and excluded those who crossed over. The 370 enrolled patients had a median age of 67.5 years, a median duration of follow-up of 41.1 months, and a median treatment exposure of 11.1 months. Patients had received a median of 2 prior therapies before receiving ibrutinib, and 53 patients had a history of atrial fibrillation or arrhythmia at baseline. Responses were assessed using the original International Working Group criteria.

Results

The ORR was 69.7%, with 26.5% of patients achieving a complete response (CR); the response rate was superior in those who had received 1 prior line of therapy (Figure 1). Median PFS was 13.0 months, and 36% and 26% of patients were progression-free at 2 and 3 years respectively. Median OS was 26.7 months, with 53%, 45%, and 37% of patients being alive at 2, 3, and 5 years respectively. Patients who had received only 1 prior line of therapy had the longest PFS and OS: median PFS was 33.6 months, and median OS was not reached in this subgroup of patients (Figure 2).

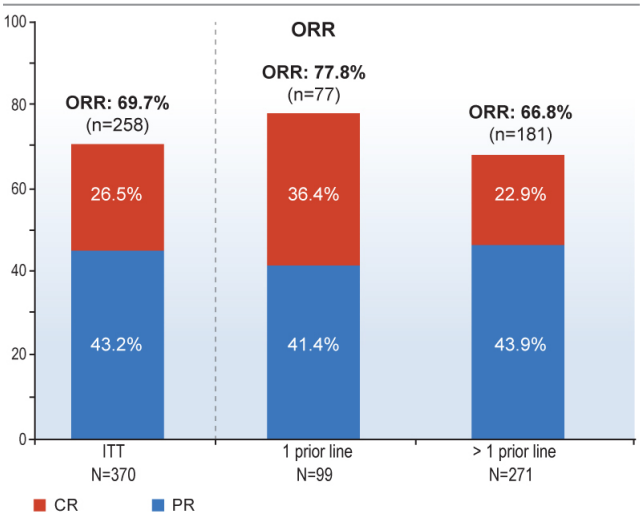

FIGURE 1 Rates of response to ibrutinib by prior line of therapy. ORR = overall response rate; ITT = intention to treat; CR = complete response; PR = partial response.

Median duration of response was 22.2 months overall and 55.7 months in patients achieving a CR. Patients who had received 1 prior line of therapy experienced a median duration of response of 34.4 months. Independent predictors of PFS included Eastern Cooperative Oncology Group performance status, simplified Mantle Cell International Prognostic Index, prior lines of therapy, bulky disease, and blastoid variant.

The most common grade 3 or greater treatment-emergent adverse events (AEs) included neutropenia (17%), thrombocytopenia (12%), and pneumonia (12%). Grade 3 or greater atrial fibrillation and hypertension occurred in 6% and 5% of patients respectively, and grade 3 or greater bleeding occurred in 5.7% of patients. Treatment-related AEs generally declined after the first year of treatment and were less frequent in patients with fewer lines of therapy (Figure 3). Of patients who entered the study with atrial fibrillation or arrhythmia, most (70%) did not experience a recurrence with ibrutinib use. Of the 10% of patients who discontinued treatment because of AEs, none discontinued ibrutinib because of grade 3 or greater atrial fibrillation. Fewer than 2% of patients discontinued ibrutinib or required a dose reduction because of grade 3 or greater bleeding or atrial fibrillation.

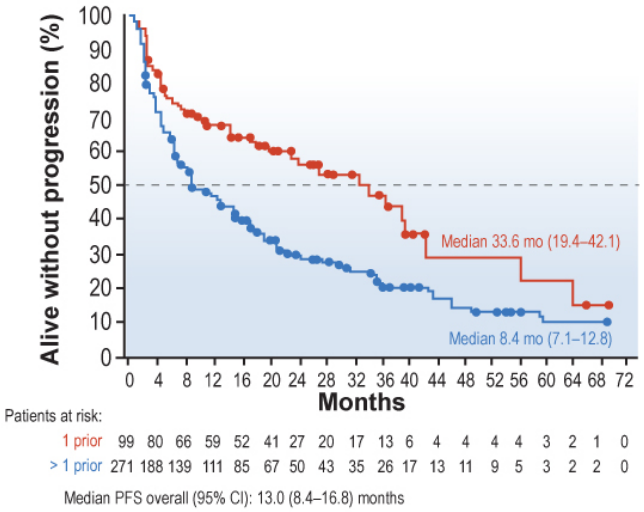

FIGURE 2 Progression-free survival in patients taking ibrutinib, by prior line of therapy. PFS = progression-free survival; CI = confidence interval.

Author Conclusions

In this pooled analysis of ibrutinib-treated patients with RR MCL, more than a quarter of the participants remained progression-free, and almost half were alive at 3 years. Clinical outcomes were best among patients who achieved a CR and among those who were treated with ibrutinib at first relapse or progression. New-onset grade 3 or greater toxicities declined over time.

Acalabrutinib in RR MCL (ACE-LY-004)—Abstract 155

Objective

To examine the efficacy and safety of acalabrutinib, a highly selective oral inhibitor of BTK with minimal off-target activity, in RR MCL[14,19].

Methods

In this phase II study, 124 patients (median age: 68 years) who had received 2 prior therapies were given acalabrutinib 100 mg twice daily in 28-day cycles until disease progression or unacceptable toxicity. The primary endpoint was ORR by investigator assessment, based on the Lugano classification.

Results

At a median follow-up of 15.2 months, 56% of patients remained on therapy. The other 44% of patients discontinued therapy, with 6% discontinuing because of AEs. The most common all-grade AEs (Figure 4) included headache (38%), diarrhea (30%), and fatigue (26%). The most common grade 3 or greater AEs were anemia (12%), neutropenia (11%), and pneumonia (6%). No atrial fibrillation occurred, but 3 grade 3 or greater cardiac AEs were observed. Bleeding events occurred in 31% of patients, all being grade 1 or 2, except for 1 grade 3 gastrointestinal

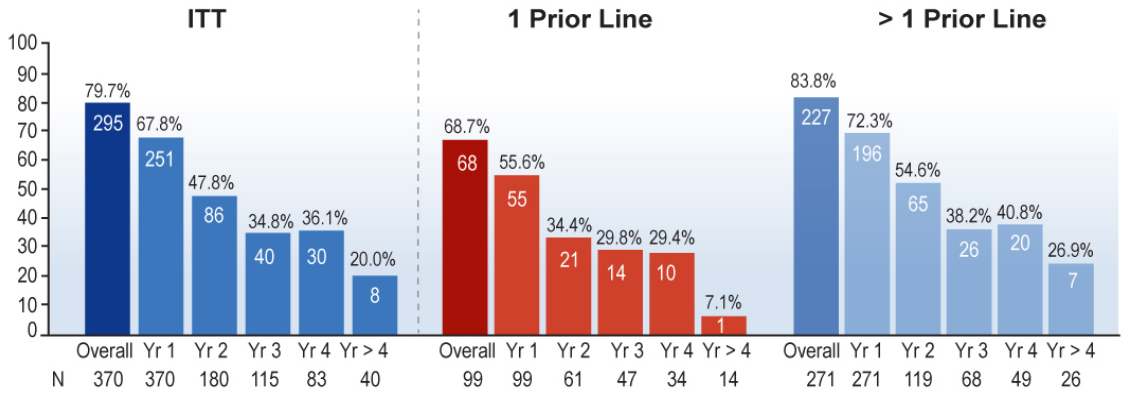

FIGURE 3 Grade 3 or greater treatment-emergent adverse events over time in patients taking ibrutinib, , by prior line of therapy. ITT = intention to treat; Yr = year.

hemorrhage in a patient with a history of gastrointestinal ulcer. Infections of any grade occurred in 53% of patients. The primary endpoint, investigator-assessed ORR, was 81%, with 40% of patients achieving a CR. The ORR was consistent across all pre-specified subgroups, and most patients (94%) experienced a reduction in lymphadenopathy. Median time to response was 1.9 months, and median duration of response had not been reached at the time of writing (Figure 5). The 12-month duration of response rate was 72%. Median PFS and OS had not been reached at the time of writing, with the 12-month PFS and OS rates being 67% and 87% respectively (Figure 6).

Author Conclusions

In patients with RR MCL, treatment with single-agent acalabrutinib resulted in a high ORR and a high CR rate, with durable and clinically meaningful responses. A favourable safety profile was also demonstrated: AEs were low in frequency and severity, and few discontinuations were attributable to AEs. Given the favourable benefit–risk profile, acalabrutinib represents a promising treatment option for RR MCL.

Investigator Commentary by Dr. Simon Rule

The introduction of ibrutinib as an available treatment option for patients with RR MCL has revolutionized outcomes in recent years. However, physicians with experience in using this therapy have noticed that patients with the worst prognostic factors are those who are more likely to come off the drug, resulting in the shortest remissions. By pooling data from three clinical trials, we were able to obtain sufficient data to assess the effect of baseline factors on efficacy outcomes. Our results clearly showed a reduction in PFS and OS when patients were stratified by negative prognostic risk factors such as bulky disease, blastoid variant, simplified Mantle Cell International Prognostic Index, and bone marrow involvement.

Despite the lower efficacy in patients with negative prognostic factors, outcomes with ibrutinib use continue to be dramatic after 3.5 years of follow-up. These results for a single agent are unlike anything we have seen with chemotherapy. Moreover, with extended follow-up, the frequency of AEs declined, with no emerging toxicities. Importantly, patients receiving ibrutinib after 1 prior line of therapy experienced vastly superior outcomes and fewer toxicities than did those receiving ibrutinib in later lines of therapy. That difference in efficacy appears to be greater with ibrutinib than with the use of other regimens earlier in the treatment algorithm. We are therefore now examining ibrutinib–rituximab compared with chemotherapy using bendamustine–rituximab or R-CHOP (rituximab followed by cyclophosphamide, doxorubicin, vincristine, and prednisone) in the front-line setting. For patients with MCL, chemotherapy-free combination therapy including a BTK inhibitor might well be the way of the future.

With the success of ibrutinib, a number of novel BTK inhibitors are now being examined in clinical trials. The newer agents are more highly selective than ibrutinib and appear to have different side effect profiles. In the ACE-LY-004 study, we showed that acalabrutinib was associated with excellent efficacy outcomes that appear to be comparable to those with ibrutinib when considering prior lines of therapy and the criteria used to determine response. However, acalabrutinib appears to be better tolerated, with no signal for atrial fibrillation and lower rates of bleeding and bruising. Given that cardiac toxicities with ibrutinib appear to occur within the first 6 months of treatment, we can assume that those toxicities are not a concern with acalabrutinib. There was, however, a higher rate of headache, which was very mild and appeared to diminish with administration of caffeine.

Within our trial, and in all my experience in using ibrutinib, I have never had to discontinue the drug in patients experiencing atrial fibrillation. What is important is to ensure adequate patient education and to manage expectations to ensure adherence. However, I have found acalabrutinib to be better tolerated than ibrutinib in the 22 patients I have treated with that agent. I would therefore

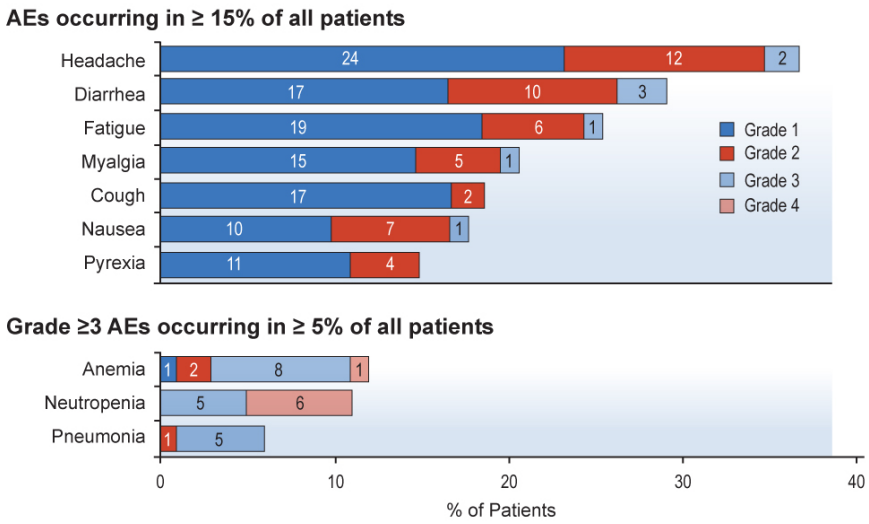

FIGURE 4 Most common adverse events (AEs) in patients taking acalabrutinib.

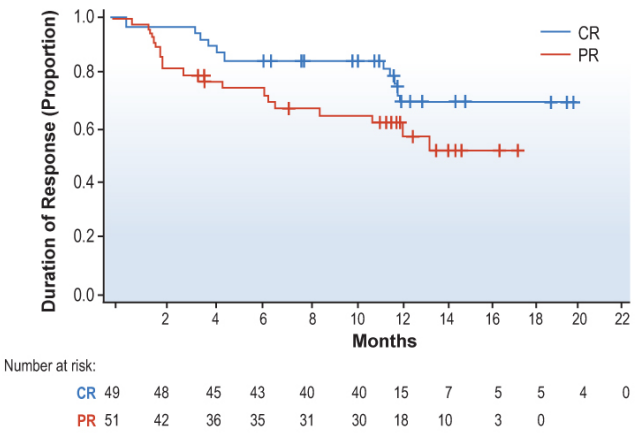

FIGURE 5 Duration of response in patients taking acalabrutinib. CR = complete response; PR = partial response.

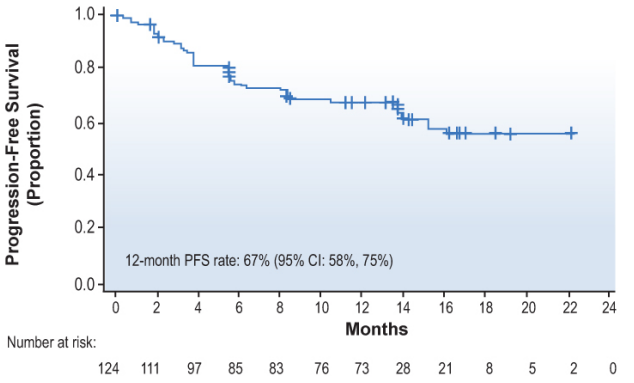

FIGURE 6 Progression-free survival (PFS) in patients taking acalabrutinib. CI = confidence interval.

be interested in using acalabrutinib over ibrutinib, but would like to see longer follow-up to get a better feel for the duration of response. If both agents were available, I would definitely choose to use acalabrutinib in patients with cardiovascular risk factors or bleeding or in those intolerant to ibrutinib. However, I do have some concerns about the twice-daily dosing with respect to the effects of adherence, especially in elderly patients.

As a next step, it would be interesting to see whether acalabrutinib can safely be combined with high-dose chemotherapy. In addition, it remains to be seen whether acalabrutinib crosses the blood–brain barrier and can be used to treat central nervous system disease. Ultimately, a BTK inhibitor with fewer side effects is preferable, but it is likely that the deciding factor will come down to cost.

Zanubrutinib (BGB-3111) in Indolent and Aggressive NHL—Abstract 152

Objective

To examine the efficacy and safety of zanubrutinib, a novel, highly specific, irreversible BTK inhibitor[17].

Methods

This open-label phase IB trial enrolled 99 patients with RR NHL, including 31 with MCL. Dose escalation included patients with RR B-cell malignancies, and the expansion phase enrolled disease-specific cohorts at the recommended phase II dose (320 mg given either once daily or split as 160 mg twice daily). Responses were assessed using the original International Working Group criteria.

Results

Median age in the overall cohort was 68 years, with a median of 2 prior lines of therapy. The most common grade 3 or greater AEs in the aggressive lymphoma cohort included neutropenia (9%), thrombocytopenia (9%), and pneumonia (6%). Treatment discontinuation because of AEs occurred in 12% of patients, with fatal AEs occurring in 6 patients. Atrial fibrillation and hypertension occurred in 3% and 8% of patients with aggressive lymphoma respectively. Severe hemorrhage and petechiae or purpura or contusion occurred in 3% and 25% of patients respectively. Median follow-up was 9.5 months, with the ORR being 88% and the CR rate being 25% in patients with MCL (Figure 7). Figure 8 presents PFS curves by lymphoma subtype.

Author Conclusions

Zanubrutinib is well-tolerated and active as a monotherapy in multiple NHL subtypes. Evaluation of zanubrutinib in NHL, both as monotherapy and in combination with other agents is continuing in phase II trials.

Investigator Commentary by Dr. Judith Trotman

The recent development of the first BTK inhibitor, ibrutinib, revolutionized the treatment of patients with B-cell malignancies. However, ibrutinib is associated with a number of safety concerns, including risk of bleeding and atrial fibrillation. A number of new BTK inhibitors are therefore under development to improve on ibrutinib's efficacy and safety profile. Zanubrutinib (BGB-3111), developed by BeiGene, is a novel BTK inhibitor with greater selectivity than ibrutinib demonstrates. Ongoing preclinical trials have demonstrated greater on-target selectivity in cellular assays, which, when compared with ibrutinib, should translate into improved tolerance in patients.

Our study is an ongoing open-label, multicentre, phase IB trial of zanubrutinib in patients with B-cell malignancies. We included a total of 38 patients with MCL, of whom 32 were evaluable for efficacy. In the subgroup of patients with MCL (all dose levels of treatment), 88% achieved a response (28 of 32), with 25% (8 of 32) achieving a CR. I conjecture that, if positron-emission tomography rather than computed tomography response assessment alone had been mandated in this protocol, we would have seen a higher CR rate. Only 1 patient progressed after a median follow-up of 9.5 months. Based on those results, zanubrutinib could well be at least as effective as ibrutinib; however, we have to exercise caution given the short duration of follow-up in the study.

Early safety results suggest zanubrutinib is well-tolerated, with a very low incidence of bleeding, which contrasts with ibrutinib outcomes, where high rates of bruising are seen. Moreover, rates of atrial fibrillation and diarrhea,

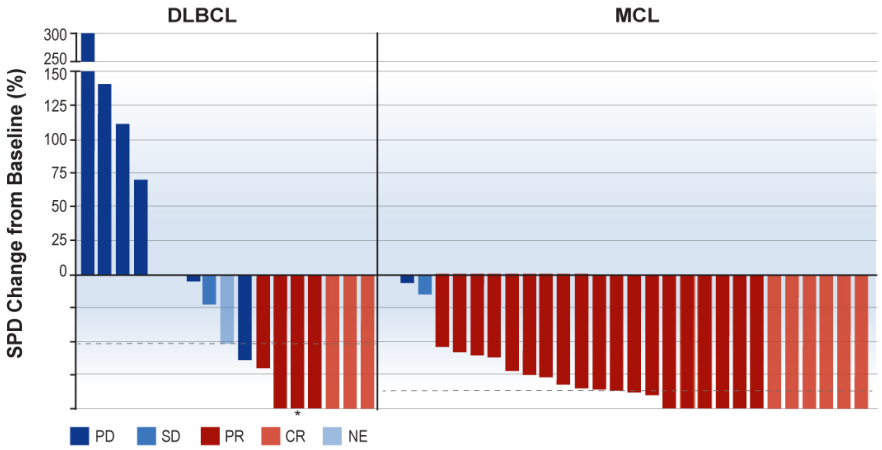

FIGURE 7 Response to zanubrutinib by aggressive lymphoma subtype. At baseline, 4 participants had no measurable lesions; 9 participants had no post-baseline imaging. The dashed lines indicate the median reduction in SPD (sum of the products of lymph node diameters by computed tomography imaging): –53% for diffuse large B-cell lymphoma (DLBCL) and –87% for mantle cell lymphoma (MCL). PD = progressive disease; SD = stable disease; PR = partial response; CR = complete response; NE = not evaluable. *Patients had germinal-centre DLBCL.

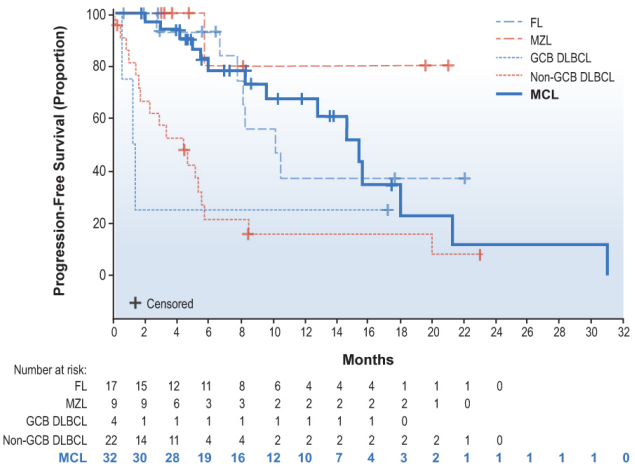

FIGURE 8 Progression-free survival in patients taking zanubrutinib. FL = follicular lymphoma; MZL = marginal zone lymphoma; GCB = germinal centre B-cell; DLBCL = diffuse large B-cell lymphoma; MCL = mantle cell lymphoma.

which are commonly seen with ibrutinib, have been very low. Although approximately 50% of our patients with MCL reported a grade 3 AE in the study, it is unclear whether those AEs were treatment-related. I personally treated 30 patients with B-cell lymphomas using this agent, and only 1 patient discontinued treatment because of toxicity. My personal experience is that, compared with all the other agents I have used in treating lymphoma, zanubrutinib is extremely well-tolerated. Although mature follow-up is needed to examine the efficacy and long-term safety of zanubrutinib, I am very excited about this agent based on our early data, and I hope it will provide an improved treatment option for patients with MCL.

Ongoing studies are also examining the combination of zanubrutinib with other agents. Data in a human MCL xenograft model show that, compared with ibrutinib as monotherapy, the addition of rituximab to ibrutinib did not improve antitumour activity. However, the combination rituximab–zanubrutinib, compared with either agent as monotherapy, demonstrated improved antitumour activity. We believe that that result might translate into better activity when zanubrutinib is combined with rituximab or other antibody-dependent cell-mediated cytotoxicity therapies. Ongoing trials are therefore examining the combination of zanubrutinib with obinutuzumab (NCT02569476) or with the PD-1 inhibitor BGB-A317 (NCT02795182) in patients with B-cell malignancies.

Clinical Impact in Canada

Q&A with Drs. Carolyn Owen and John Kuruvilla

Q Please comment on the impact of the BTK inhibitor ibrutinib for the treatment of RR MCL.

A (Owen) There is currently no cure for patients with RR MCL, and the disease unfortunately remains one with a poor prognosis. New and effective oral therapies such as ibrutinib are therefore a huge gain for these patients. However, physicians in Canada have had access to ibrutinib for only a short time; they have limited experience using this agent for the treatment of MCL. Long-term data such as those from the pooled analysis presented by Rule *et al.* are therefore valuable in confirming the durability of ibrutinib responses in RR MCL.

Although some toxicities are unique to ibrutinib, the therapy is a fairly well tolerated and provides a valuable option for patients with RR MCL. In Canada, we tend to use ibrutinib in the third line, after failure of both chemoimmunotherapy and bortezomib. Based on the results of the pooled analysis, I would prefer to use ibrutinib earlier in the treatment algorithm, and I hope that we can achieve that shift over time. Despite obvious value, it does appear that ibrutinib is less well-tolerated in the real world than in clinical trials. For example, patients experiencing atrial fibrillation while on ibrutinib treatment often wish to discontinue the agent. There is therefore room to improve on the safety of ibrutinib, with the hope of improving quality of life for patients.

A (Kuruvilla) The class of agents known as BTK inhibitors have become the default treatment for patients with MCL in whom primary therapy fails, with ibrutinib being the only such agent available in Canada. The remaining questions surrounding the use of ibrutinib relate to the timing of relapse, exposure to prior therapies, and any contraindications to using the drug. Although ibrutinib is typically well-tolerated, the most concerning toxicities include bleeding and atrial fibrillation. In the case of atrial fibrillation, cardio-oncologists are typically able to control rate and rhythm with the use of other drugs. Moreover, unlike patients with chronic lymphocytic leukemia, who might live decades with their disease, patients with RR MCL tend to have a shorter lifespan. They therefore do not take ibrutinib for very long. Given that, to date, there are no effective alternatives to ibrutinib, we therefore tend to encourage patients to remain on treatment with this agent in the RR setting.

Q How do the novel BTK inhibitors attempt to improve on ibrutinib?

A (Owen) The major difference between ibrutinib and the novel BTK inhibitors such as acalabrutinib and zanubrutinib is an improvement in the specificity of their mechanism of action. The thought is that, by producing fewer off-target effects, fewer toxicities might be associated with the newer agents. However, it does sometimes happen that agents that are more selective might be less effective. Fortunately, a reduction in efficacy with the newer BTK inhibitors is not evident, as shown in the acalabrutinib study by Wang *et al.*[14] and the zanubrutinib study by Tam *et al.*[17], and a reduction in some bothersome AEs is even suggested.

A (Kuruvilla) Acalabrutinib is a novel BTK inhibitor that is "cleaner" and more specific than ibrutinib. Because off-target effects are believed to lead to an increase in toxicity, this agent would be expected to be better tolerated than ibrutinib is. Zanubrutinib is earlier in development, but is also thought to be more selective than ibrutinib.

Q Please comment on the efficacy of the three BTK inhibitors.

A (Owen) Thus far, it appears that all three BTK inhibitors act in a similar way, with a very strong class effect emerging. I am not convinced that acalabrutinib is more effective than ibrutinib once you have accounted for the difference in patient characteristics between the studies. However, it does appear that acalabrutinib has similar efficacy and might therefore be equivalent. Data from an ongoing phase III trial in chronic lymphocytic leukemia should aid in comparing the efficacy of these two BTK inhibitors. Although the data presented by Tam *et al.* concerning zanubrutinib are very early and reflect a small number of patients, it is also possible that this agent will prove to have efficacy similar to that seen with ibrutinib and acalabrutinib.

A (Kuruvilla) The pooled analysis of ibrutinib data included patients from three different trials with a long follow-up duration. Results of the study showed that ibrutinib is more effective when given earlier in the treatment algorithm. It was also nice to see the good durability in the responses to ibrutinib, compared with data reported at about 1 year of follow-up. Although the acalabrutinib study by Wang *et al.* had shorter follow-up, the study still included a reasonable number of patients. The efficacy outcomes with acalabrutinib look similar to what might be expected with ibrutinib. It therefore appears that the efficacy of acalabrutinib is not compromised as a result of its greater selectivity. It is too early to comment on the efficacy results of the zanubrutinib study by Tam *et al.*; we will need to await data from a greater number of patients with longer follow-up.

Q Please comment on the safety profile of the three BTK inhibitors.

A (Owen) The two key toxicities that lead to discontinuation of ibrutinib include atrial fibrillation and bleeding. Based on data from the acalabrutinib study, major bleeding does not seem to be a concern with that agent. Rates of atrial fibrillation also appear to be very low with acalabrutinib, which would be an advantage for patients should that result be confirmed with longer follow-up. Safety data with the use of zanubrutinib look promising at first glance, but we will need to await longer follow-up, given that the results reported so far are very early.

A (Kuruvilla) In the acalabrutinib study, no cases of atrial fibrillation and just 3 grade 3 or greater cardiac AEs occurred, a rate of AEs that appears to be significantly lower than the rates seen with ibrutinib. In theory, cardiac toxicities tend to appear early in the BTK inhibitor treatment course. However, because such toxicities are rarer events, longer follow-up and larger patient numbers might be needed before we start to see some of those toxicities. Safety data for zanubrutinib are too early to draw strong conclusions, and we unfortunately do not have sufficient information about the safety of this agent in the MCL subgroup.

Q Please comment on the potential impact of the novel BTK inhibitors.

A (Owen) The improved side-effect profile of acalabrutinib over ibrutinib offers some value for patients with RR MCL. Although longer follow-up is needed to confirm the acalabrutinib results and to examine the possible toxicities associated with zanubrutinib, access to a safer BTK inhibitor would be beneficial, especially for therapies that must be given long-term. My hope is that increasing the number of BTK inhibitors will provide competition and an eventual reduction in cost. Should ibrutinib and acalabrutinib both be available, I would choose acalabrutinib based on the improved safety profile, and I hope that those results will be confirmed with longer follow-up. It remains to be seen whether zanubrutinib will improve on the safety profile of ibrutinib, but I will feel better able to comment on that agent after 1 more year of follow-up data.

A (Kuruvilla) Overall, there is always an opportunity to improve on first-in-class agents with second-generation

compounds. Some of the cumulative toxicities associated with ibrutinib are troublesome, and acalabrutinib appears to have a favourable safety profile, although large comparative studies are needed. However, longer follow-up is needed to ensure that no new safety signals emerge. Ultimately, the key barrier to the use of BTK inhibitors is cost, and it will be interesting to see whether these newer agents will be priced more competitively.

ACKNOWLEDGMENTS

This document was developed by IMPACT Medicom Inc., with sponsorship provided by AstraZeneca Canada.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: CO has received speaker fees or honoraria for advisory board participation from AstraZeneca, Merck, Janssen, Roche, Gilead, AbbVie, Celgene, Novartis, and Lundbeck. Her institution has received funding from Roche, Pharmacyclics, Gilead, Celgene, Novartis, Lundbeck, and Pfizer for trials in which she is a co-investigator. JK has received speaker fees or honoraria for advisory board participation from AbbVie, AstraZeneca, Bristol–Myers Squibb, Celgene, Gilead, Janssen, Lundbeck, Merck, Roche, and Seattle Genetics; has acted as a consultant for AbbVie, Bristol–Myers Squibb, Gilead, Merck, and Seattle Genetics; and has received research funding from Janssen and Roche.

AUTHOR AFFILIATIONS

*Division of Hematology and Hematological Malignancies, University of Calgary and Foothills Medical Centre, Calgary, AB; †Department of Medicine, University of Toronto, and Princess Margaret Cancer Centre, Toronto, ON; ‡IMPACT Medicom Inc., Toronto, ON.

REFERENCES

1. Dreyling M, Aurer I, Cortelazzo S, *et al.* Treatment for patients with relapsed/refractory mantle cell lymphoma: European-based recommendations. *Leuk Lymphoma* 2017:1–15.
2. Lymphoma Canada. Health Canada Approves Ibrutinib for Mantle Cell Lymphoma [news release]. Mississauga, ON: Lymphoma Canada; 2015. [Available online at: http://www.lymphoma.ca/research/health-canada-approves-ibrutinib-mantle-cell-lymphoma; cited 12 July 2017]
3. Alberta Health Services (AHS). *Lymphoma.* Clinical practice guideline LYHE-002, Ver. 11. Edmonton, AB: AHS; 2017. [Available online at: http://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-lyhe002-lymphoma.pdf; cited 20 December 2017]
4. Takeda Pharmaceutical Company. FDA Approves Velcade (bortezomib) for Injection for Previously Untreated Patients with Mantle Cell Lymphoma [news release]. Osaka, Japan: Takeda Pharmaceutical Company; 2014. [Available online at: https://www.takeda.com/newsroom/newsreleases/2014/fda-approves-velcade-bortezomib-for-injection-for-previously-untreated-patients-with-mantle-cell-lymphoma/; cited 20 December 2017]
5. Celgene Corporation. Revlimid (Lenalidomide) Approved by the European Commission for the Treatment of Relapsed/Refractory Patients with Mantle Cell Lymphoma [news release]. Summit, NJ: Celgene Corporation; 2016. [Available online at: http://ir.celgene.com/releasedetail.cfm?releaseid=979705; cited 20 December 2017]
6. Inman S. FDA Approves Ibrutinib for Mantle Cell Lymphoma [Web article]. Cranbury, NJ: OncLive.com; 2013. [Available at: http://www.onclive.com/web-exclusives/fda-approves-breakthrough-ibrutinib-for-mcl; cited 20 December 2017]
7. European Medicines Agency (EMA). *Public Summary of Opinion on Orphan Designation: Temsirolimus for the Treatment of Mantle Cell Lymphoma.* London, U.K.: EMA; 2011. [Available online at: http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2009/10/WC500005687.pdf; cited 3 January 2018]
8. European Medicines Agency (EMA). *Imbruvica* [European public assessment report]. London, U.K.: EMA; 2017. [Downloadable from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003791/human_med_001801.jsp&mid=WC0b01ac058001d124; cited 12 July 2017]
9. Actavis Pharma. *Act Bortezomib* [product monograph]. Dublin, Ireland: Actavis Pharma; 2016.
10. Janssen. *Imbruvica* [product monograph]. Toronto, ON: Janssen; 2017.
11. Dreyling M, Jurczak W, Jerkeman M, *et al.* Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. *Lancet* 2016;387:770–8.
12. Wang ML, Rule S, Martin P, *et al.* Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *N Engl J Med* 2013;369:507–16.
13. Advani RH, Buggy JJ, Sharman JP, *et al.* Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. *J Clin Oncol* 2013;31:88–94.
14. Wang M, Rule S, Zinzani PL, *et al.* Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. *Lancet* 2017;:[Epub ahead of print].
15. AstraZeneca. Acalabrutinib granted breakthrough therapy designation by US FDA for the treatment of patients with mantle cell lymphoma [news release]. Cambridge, U.K.: AstraZeneca; 2017. [Available online at: https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2017/acalabrutinib-granted-breakthrough-therapy-designation-by-us-fda-for-the-treatment-of-patients-with-mantle-cell-lymphoma-01082017.html; cited 3 August 2017]
16. United States, Department of Health and Human Services, Food and Drug Administration (FDA). FDA approves new treatment for adults with mantle cell lymphoma [news release]. Silver Spring, MD: FDA; 2017. [Available online at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm583076.htm; cited 20 December 2017]
17. Tam CS, Simpson D, Opat S, *et al.* Safety and activity of the highly specific BTK inhibitor BGB-3111 in patients with indolent and aggressive non Hodgkin's lymphoma [abstract 152]. Presented at: American Society of Hematology 59th Annual Meeting and Exposition; Atlanta, GA, U.S.A.; 9–12 December 2017. [Available online at: https://ash.confex.com/ash/2017/webprogram/Paper101647.html; cited 7 January 2018]
18. Rule S, Dreyling M, Goy A, *et al.* Median 3.5-year follow-up of ibrutinib treatment in patients with relapsed/refractory mantle cell lymphoma: a pooled analysis [abstract 151]. *Blood* 2017;130:.
19. Wang M, Rule S, Zinzani PL, *et al.* Efficacy and safety of acalabrutinib monotherapy in patients with relapsed/refractory mantle cell lymphoma in the phase 2 ACE-LY-004 study [abstract 155]. Presented at: American Society of Hematology 59th Annual Meeting and Exposition; Atlanta, GA, U.S.A.; 9–12 December 2017. [Available online at: https://ash.confex.com/ash/2017/webprogram/Paper100664.html; cited 3 January 2018]