

Updates from the American Society of Hematology 2019 annual meeting: practice-changing studies in treatment-naïve chronic lymphocytic leukemia

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ABSTRACT

The 2019 annual meeting of the American Society of Hematology took place 7–10 December in Orlando, Florida. At the meeting, results from key studies in treatment-naïve chronic lymphocytic leukemia (CLL) were presented. Of those studies, phase III oral presentations focused on the efficacy and safety of therapy with inhibitors of Bruton tyrosine kinase (BTK) and Bcl-2.

One presentation reported updated results of the Eastern Cooperative Oncology Group 1912 trial comparing the efficacy and safety of ibrutinib–rituximab with that of fludarabine–cyclophosphamide–rituximab in patients less than 70 years of age with CLL. A second presentation reported interim results of the ELEVATE TN trial, which is investigating the efficacy and safety of acalabrutinib–obinutuzumab or acalabrutinib monotherapy compared with chlorambucil–obinutuzumab. A third presentation reported on the single-agent zanubrutinib arm of the SEQUOIA trial in patients with del(17p). The final presentation constituted a data update from the CLL14 trial, which is evaluating fixed-duration venetoclax–obinutuzumab compared with chlorambucil–obinutuzumab, including the association of minimal residual disease status with progression-free survival.

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 Chronic lymphocytic leukemia, untreated disease, treatment-naïve disease

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BACKGROUND

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia, with an incidence in Canada of approximately 2400 cases per year according to the 2016 Canadian cancer statistics^{1–3}. Based on data from a population-based cohort study of patients diagnosed with CLL in Manitoba between 1998 and 2003, the estimated 5-year survival rate is 80% in men and 85% in women⁴. Despite a promising prognosis, most patients with CLL are older and have other comorbidities that limit treatment options⁵. The median age of patients with CLL is 72 years, and 75% are 65 years of age or older, with at least 3 other comorbidities^{5,6}.

For younger patients without del(17p) or a *TP53* mutation, the recommended frontline treatment is fludarabine–cyclophosphamide–rituximab (FCR).² However, FCR is associated with significant toxicities and is

therefore suitable only for patients who are medically fit⁵. For patients more than 65 years of age without del(17p) or *TP53* mutation, bendamustine–rituximab (BR) is recommended because it is associated with an improved safety profile compared with FCR². For patients who are unable to tolerate FCR and do not have del(17p) or a *TP53* mutation, chlorambucil–obinutuzumab or ibrutinib monotherapy is recommended². Finally, for patients with del(17p) or a *TP53* mutation, ibrutinib monotherapy is recommended based on data showing high efficacy in that high-risk population^{2,7,8}. Given that most patients with CLL are elderly or have a number of comorbidities, more effective treatments that are well-tolerated are needed for that patient group.

This year, key studies in the frontline treatment of CLL presented at the American Society of Hematology (ASH) 2019 meeting focused on novel agents such as ibrutinib, acalabrutinib, and zanubrutinib [which target Bruton tyrosine

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kinase (BTK) and venetoclax (which targets the apoptosis regulator Bcl-2). A member of the Tec protein–tyrosine kinase family, BTK is expressed in B cells, myeloid cells, mast cells, and platelets. It is a key component of the B cell antigen receptor signalling cascade^{9–11}. Given its role in all aspects of B cell development, including proliferation, maturation, differentiation, apoptosis, and cell migration, BTK is critical in the progression of B cell lymphoproliferative disorders, making it an attractive treatment target. Bcl-2 is the first member of a family of apoptosis-regulating proteins that are characterized by the presence of at least one Bcl-2 homology domain^{12,13}. Investigation of Bcl-2 inhibitors in CLL was initially driven by evidence showing the key role of apoptosis resistance in the progression of lymphoid malignancies and the frequent overexpression of Bcl-2 in CLL cells^{14,15}.

Ibrutinib is a first-in-class once-daily oral BTK inhibitor that binds covalently to a cysteine residue (Cys481) in the active site of the ATP-binding domain of BTK, inhibiting B cell receptor signalling and thereby reducing cell growth, proliferation, survival, adhesion, and migration¹⁶. In Canada, ibrutinib is approved by Health Canada for the treatment of previously untreated CLL, including in patients with del(17p)¹⁷, based on results of the phase III RESONATE-2 (PCYC-1115) trial⁷, which compared ibrutinib with chlorambucil in patients 65 years of age or older. Data from RESONATE-2 showed that ibrutinib was associated with significantly prolonged progression-free survival (PFS) after a median follow-up of 18.4 months [median PFS: not reached for ibrutinib vs. 18.9 months for chlorambucil; 95% confidence interval (CI): 14.1 months to 22.0 months]. Ibrutinib was also associated with significantly prolonged overall survival (OS)—the estimated survival rate at 24 months being 98% with ibrutinib compared with 85% with chlorambucil.

The most frequent grade 3 or greater adverse events (AEs) with ibrutinib are neutropenia (12%), anemia (7%), and hypertension (5%)¹⁸. A signal of elevated cardiac toxicities has been observed, with real-world data demonstrating a rate of 25% for cardiac toxicities, including atrial fibrillation and reports of ventricular arrhythmias and sudden death^{19,20}. Moreover, dose reductions are required in more than half of treated patients²¹. Ongoing trials in untreated CLL examining ibrutinib combined with other molecules are now providing preliminary data.

With the success of ibrutinib, novel BTK inhibitors were developed to improve on the safety and efficacy of treatment. Acalabrutinib is a potent second-generation orally bioavailable 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 cells²². However, acalabrutinib is more highly selective than ibrutinib, resulting in less off-target activity; it therefore is predicted to have fewer adverse effects. In November 2019, acalabrutinib was reviewed and approved simultaneously by Health Canada, the U.S. Food and Drug Administration, and the Australian Therapeutic Goods Administration in an accelerated timeline for the first-line treatment of patients with CLL in combination with obinutuzumab or as monotherapy^{23,24}. It is also approved as monotherapy for patients in the relapsed setting of CLL and mantle cell lymphoma. Regulatory approval of

acalabrutinib in Canada and the United States for patients with previously untreated CLL was based on results of the ELEVATE TN trial, which showed improved PFS with acalabrutinib alone or in combination with obinutuzumab compared with chlorambucil in that population²⁵.

Zanubrutinib is a third BTK inhibitor that is potent, specific, and also more highly selective than ibrutinib²⁶. In November 2019, the U.S. Food and Drug Administration approved zanubrutinib for the treatment of adults with mantle cell lymphoma who have received at least 1 prior therapy; however, it is not yet approved for the treatment of CLL²⁷. Zanubrutinib monotherapy is currently being examined in the phase III SEQUOIA trial for patients with untreated CLL, where it is being compared with BR in patients without del(17p) and being examined as monotherapy or in combination with venetoclax in patients with del(17p).

Venetoclax is another novel agent with high activity in CLL. It is an orally bioavailable selective antagonist of Bcl-2 that promotes apoptosis in primary CLL cells by mimicking the BH3 domain of the natural antagonists of Bcl-2 and subsequently inhibiting the antiapoptotic function of Bcl-2¹³. Currently in Canada, venetoclax is indicated, in combination with rituximab, for fixed-duration therapy of up to 2 years in the treatment of patients with CLL who have received at least 1 prior therapy²⁸. It was also issued a Health Canada Notice of Compliance with Conditions as continuous monotherapy in the same setting for patients with either del(17p) or with no other available treatment options. Approval of venetoclax–rituximab in relapsed or refractory CLL was based on results of the MURANO study, which showed a significant PFS benefit for the combination compared with BR [hazard ratio (HR): 0.17; 95% CI: 0.11 to 0.25; $p < 0.001$]²⁹. It appeared to be well-tolerated, with the most common grade 3 or greater AE being neutropenia (57.7%). Clinical trials investigating fixed-duration venetoclax in combination with CD20 antibodies and BTK inhibitors in the first-line and relapsed settings are ongoing.

At the ASH 2019 meeting, several oral presentations reported results from phase III clinical trials that evaluated BTK inhibitors or venetoclax as monotherapy or in combination with CD20 antibodies. In the present report, we summarize the key data presented from those trials, commentaries from study investigators, and Canadian perspectives from hematologists on how the data could affect clinical practice.

METHODS

The first official ASH meeting was held in 1958, and ASH is now the world's largest professional society with a focus on hematologic malignancies. The 2019 ASH annual meeting took place in Orlando, Florida, 7–10 December, attracting 30,024 attendees, including 940 from Canada. Of 5978 abstracts accepted, 930 were chosen for oral presentations because of the high quality of their design and their potential effect on practice. To determine the abstracts most likely to make an impact in the setting of frontline therapy for CLL, only oral presentations under the program category “642. CLL: Therapy, Excluding Transplantation,” which reported on phase III studies, were considered. The three oral abstract sessions that were identified as a result

included eighteen abstract presentations. Of those oral presentations, ten were excluded because they focused on the relapsed or refractory setting or were not specific to first-line therapy. An additional four presentations that reported on single-arm phase II trials were also excluded.

The remaining four oral abstracts that met the inclusion criteria (phase III studies in treatment-naïve CLL) were included. The first abstract reported updated results from the Eastern Cooperative Oncology Group E1912 trial comparing ibrutinib–rituximab (IR) with FCR for efficacy and safety in patients 70 years of age or less with CLL³⁰. The second abstract reported interim results of the ELEVATE TN trial, which is investigating the efficacy and safety of acalabrutinib–obinutuzumab or acalabrutinib monotherapy compared with chlorambucil–obinutuzumab³¹. The third abstract reported on the single-agent zanubrutinib arm of the SEQUOIA trial in patients with del(17p)³². The final abstract reported updated data from the CLL14 trial, which is comparing fixed-duration venetoclax–obinutuzumab with chlorambucil–obinutuzumab, including the association of minimal residual disease (MRD) with PFS³³.

RESULTS

Ibrutinib and Rituximab Provides Superior Clinical Outcome Compared to FCR in Younger Patients with Chronic Lymphocytic Leukemia: Extended Follow-Up from the E1912 Trial (abstract 33)

Objectives: To present updated results from the E1912 trial comparing IR with FCR in patients 70 years of age or less with treatment-naïve CLL.

Methods: In a phase III trial, patients were randomly assigned in a 2:1 ratio to receive IR or intravenous FCR (Figure 1). Patients with del(17p) were excluded from the trial.

Results: After a median follow-up of 48 months, 257 of 354 patients randomized to IR (73%) remain on treatment. Compared with FCR, IR resulted in superior PFS (HR: 0.39; 95% CI: 0.26 to 0.57; $p < 0.0001$). When stratified by *IGHV* mutation status, the PFS with IR was superior to that with FCR

in unmutated *IGHV* disease (HR: 0.28; 95% CI: 0.17 to 0.48; $p < 0.0001$), but not in mutated *IGHV* disease (Figure 2). With the extended follow-up, IR was also associated with improved OS (HR: 0.34; 95% CI: 0.15 to 0.79; $p = 0.009$; Figure 3). Overall, 7% of patients treated with ibrutinib progressed while on therapy. For the 72 patients who stopped ibrutinib treatment for reasons other than progression or death, the median PFS after discontinuation was 22.5 months.

Of 95 patients who discontinued ibrutinib overall, 48 (51%) ended treatment as a result of AEs. However, in a multivariate analysis, only score on the Cumulative Illness Rating Scale (CIRS) predicted ibrutinib discontinuation (HR per unit increase: 1.13; 95% CI: 1.03 to 1.23; $p = 0.009$). Grade 3 or greater AEs occurred in 70% of patients receiving IR and in 80% receiving FCR ($p = 0.013$). Grade 3 or greater AEs that occurred significantly more frequently with IR than with FCR included arthralgia (5.1% vs. 0.6%, $p = 0.011$), hypertension (8.5% vs. 1.9%, $p = 0.003$), atrial fibrillation (2.8% vs. 0%, $p = 0.036$), and other cardiac toxicities (3.4% vs. 0%, $p = 0.022$).

Author Conclusions: With extended follow-up, IR, compared with FCR, continues to provide superior PFS and OS in younger patients with previously untreated CLL.

Investigator Commentary: Dr. Neil Kay

The Eastern Cooperative Oncology Group–American College of Radiology Imaging Network research group designed E1912 as a registration trial to address the clinically important question of whether a novel combination therapy such as IR could demonstrate improved efficacy and safety compared with the “gold standard” chemoimmunotherapy regimen, 6 cycles of FCR. In the updated analysis presented at the 2019 ASH annual meeting, with a median follow-up of 48 months, IR continued to demonstrate a robust improvement in PFS, with a highly significant p value. A statistically significant improvement in OS was also again noted; however, with only 23 death events occurring (FCR, $n = 12$; IR, $n = 11$), the data remain immature and longer follow-up is required.

Compared with FCR, the IR regimen also demonstrated superior tolerability, with fewer treatment-related grade 3

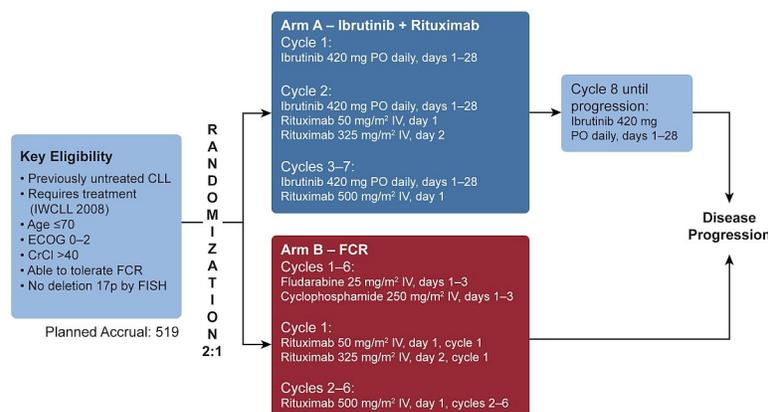


FIGURE 1 E1912 study design. CLL = chronic lymphocytic leukemia; IWCLL = International Workshop on Chronic Lymphocytic Leukemia; ECOG = Eastern Cooperative Oncology Group; CrCl = creatinine clearance; FCR = fludarabine–cyclophosphamide–rituximab; FISH = fluorescence *in situ* hybridization; PO = orally; IV = intravenously.

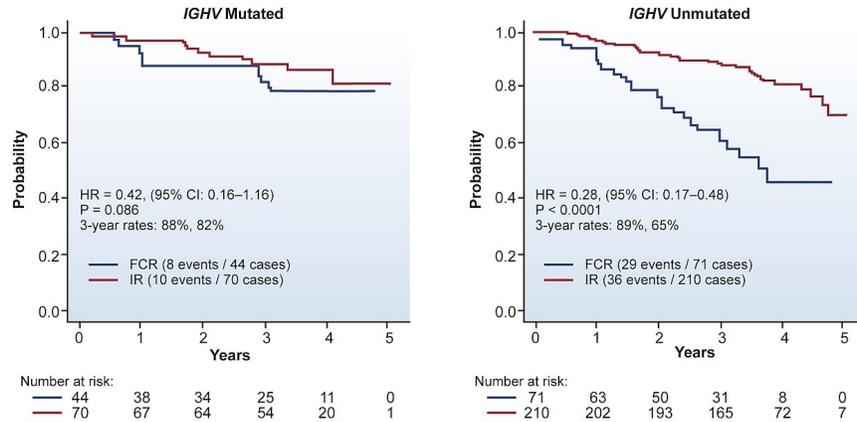


FIGURE 2 Progression-free survival by *IGHV* mutation status. *IGHV* = immunoglobulin heavy chain variable region; HR = hazard ratio; CI = confidence interval; FCR = fludarabine–cyclophosphamide–rituximab; IR = ibrutinib–rituximab.

or greater AEs reported. However, the safety profiles of the two regimens are vastly different, with cytopenias, severe infections, and long-term immune dysfunction being the dominant concerns with FCR, and cardiac toxicities (including atrial fibrillation), hypertension, arthralgias, and diarrhea being the more dominant concerns with IR.

A notable observation in this updated report was that, in patients who discontinued IR for reasons other than progression or death, many continued to be progression-free for a substantial time after therapy was stopped (median PFS: 22.5 months). That observation provides reassurance that, in patients who choose to stop ibrutinib because of financial stress or chronic low-grade AEs, there is a potential for sustained benefit after discontinuation.

The data presented from this trial are practice-changing. They confirm the feasibility of a novel agent combined with an anti-CD20 antibody as an optimal therapy choice compared with FCR for many patients less than 65 years of age with CLL who require first-line therapy—particularly patients in the trial with adverse prognostic markers such

as unmutated *IGHV*, who experienced favourable PFS outcomes with the IR regimen. On the other hand, because no significant difference in PFS for patients with mutated *IGHV* was observed between the treatment arms, FCR—because of its time-limited administration and potential for long-term remission—remains an attractive option in selected patients who are fit, have favourable genetics (including mutated *IGHV*), and no high-risk fluorescence *in situ* hybridization defects. Given that the reported analysis found a higher CIRS score to be the only predictor of ibrutinib discontinuation for reasons other than progression or death, and that, compared with BR, IR did not demonstrate a survival advantage in the companion Alliance trial, some older patients with multiple comorbidities might better tolerate a milder chemoimmunotherapy regimen than IR.

Overall, the robustness of this phase III trial with long-term follow-up allows for a reliable conclusion that IR is superior to FCR in both efficacy and tolerability for younger patients with treatment-naïve CLL, particularly those with unmutated *IGHV*.

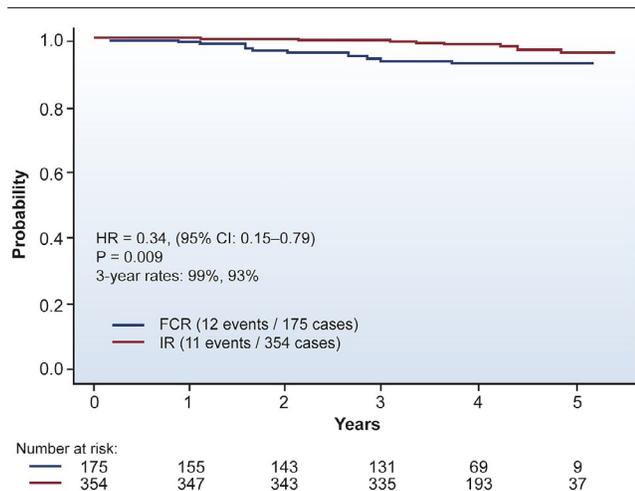


FIGURE 3 Overall survival in the the E1912 trial. HR = hazard ratio; CI = confidence interval; FCR = fludarabine–cyclophosphamide–rituximab; IR = ibrutinib–rituximab.

ELEVATE TN: Phase 3 Study of Acalabrutinib Combined with Obinutuzumab or Alone Vs Obinutuzumab Plus Chlorambucil in Patients with Treatment-Naïve Chronic Lymphocytic Leukemia (abstract 31)

Objectives: To evaluate the efficacy and safety of acalabrutinib–obinutuzumab or acalabrutinib monotherapy compared with obinutuzumab–chlorambucil in patients with treatment-naïve CLL.

Methods: In an open-label multicentre phase III trial, 535 patients were randomized to receive acalabrutinib alone ($n = 179$), acalabrutinib–obinutuzumab ($n = 179$), or obinutuzumab–chlorambucil ($n = 177$, Figure 4). The primary endpoint was the independent review committee-assessed PFS in the comparison of acalabrutinib–obinutuzumab with obinutuzumab–chlorambucil.

Results: Median age of the study participants was 70 years (range: 41–91 years), with 9% of patients having del(17p), 11% having *TP53* mutation, and 63% having unmutated

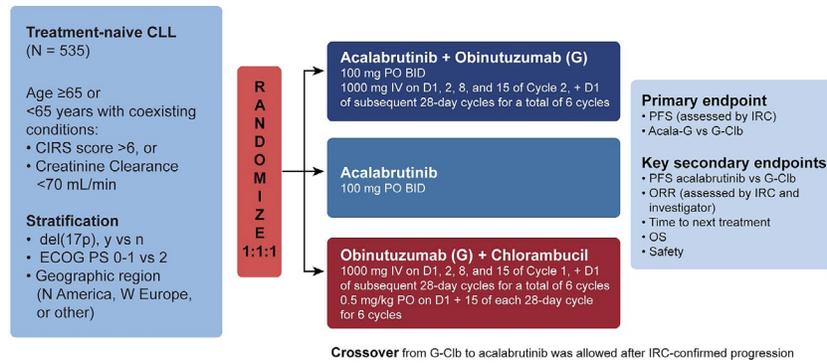


FIGURE 4 Design of the ELEVATE TN study. CLL = chronic lymphocytic leukemia; CIRS = Cumulative Illness Rating Scale; ECOG PS = Eastern Cooperative Oncology Group performance status; PO = orally; BID = twice daily; IV = intravenously; G-Clb = obinutuzumab–chlorambucil; IRC = independent review committee; PFS = progression-free survival; Acala-G = acalabrutinib–obinutuzumab; ORR = objective response rate; OS = overall survival.

IGHV. At a median follow-up of 28.3 months, PFS was significantly longer in the acalabrutinib–obinutuzumab arm than in obinutuzumab–chlorambucil arm (median PFS: not reached vs. 22.6 months; $p < 0.0001$), with a 90% reduction in the risk of progression or death (Figure 5). The PFS was also prolonged with acalabrutinib monotherapy compared with obinutuzumab–chlorambucil (HR: 0.20; $p < 0.0001$). A significant PFS benefit was maintained across patient subgroups for both acalabrutinib arms, with HRS favouring acalabrutinib–obinutuzumab over chlorambucil–obinutuzumab in patients with *IGHV* mutated and unmutated disease alike (mutated HR: 0.15; 95% CI: 0.04 to 0.52; unmutated HR: 0.08; 95% CI: 0.04 to 0.16; Figure 6). Of the 82 patients who progressed on chlorambucil–obinutuzumab, 45 (55%) crossed over to acalabrutinib monotherapy. The estimated 30-month OS rates were 95% for acalabrutinib–obinutuzumab, 94% for acalabrutinib monotherapy, and 90% for obinutuzumab–chlorambucil, showing a potential trend for improvement with acalabrutinib. However, median OS was not reached in any group and requires further follow-up.

The objective response rate was 93.9% for acalabrutinib–obinutuzumab (95% CI: 89.3% to 96.5%), 85.5% for

acalabrutinib monotherapy (95% CI: 79.6% to 89.9%), and 78.5% for obinutuzumab–chlorambucil (95% CI: 71.9% to 83.9%). Moreover, complete response rates were higher with acalabrutinib–obinutuzumab than with chlorambucil–obinutuzumab (13% vs. 5%), with 1% of the patients achieving a complete response in the monotherapy group.

Discontinuation of treatment because of AEs occurred in 20 patients (11%) receiving acalabrutinib–obinutuzumab; 16 (9%) receiving acalabrutinib monotherapy; and 25 (14%) receiving obinutuzumab–chlorambucil. With more than 2 years’ follow-up, 79.3% of the patients in both acalabrutinib-containing arms remain on single-agent acalabrutinib. The most frequent any-grade AEs in the acalabrutinib–obinutuzumab, acalabrutinib monotherapy, and obinutuzumab–chlorambucil groups included headache (39.9%, 36.9%, and 11.8% respectively), diarrhea (38.8%, 34.6%, 21.3%), and neutropenia (31.5%, 10.6%, 45.0%). The AEs of interest were atrial fibrillation (any grade: 3%, 4%, 1% respectively), bleeding (any-grade/grade 3 or greater: 43%/2%, 39%/2%, 12%/0%), hypertension (grade 3 or greater: 3%, 2%, 3%), and infection (grade 3 or greater: 21%, 14%, 8%). No ventricular tachyarrhythmia events were reported.

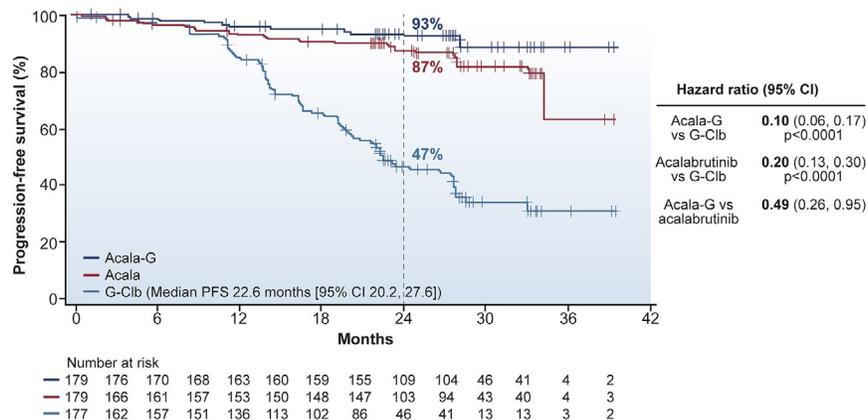


FIGURE 5 Independent review committee–assessed progression-free survival (PFS) in the ELEVATE TN study. Acala-G = acalabrutinib–obinutuzumab; G-Clb = obinutuzumab–chlorambucil; CI = confidence interval.

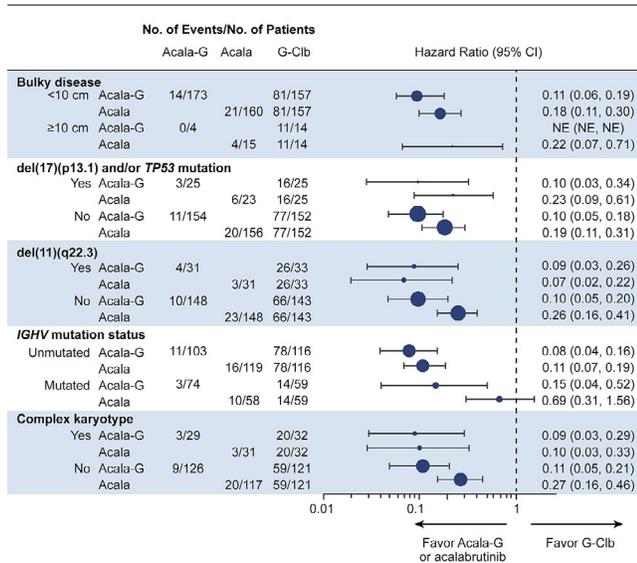


FIGURE 6 Independent review committee–assessed progression-free survival by subgroup in the ELEVATE TN study. Acala-G = acalabrutinib–obinutuzumab; G-Clb = obinutuzumab–chlorambucil; CI = confidence interval; NE = not evaluable.

Author Conclusions: Compared with obinutuzumab–chlorambucil, acalabrutinib (as monotherapy or combined with obinutuzumab) was associated with significantly improved PFS and a tolerable safety profile. Despite cross-over in the obinutuzumab–chlorambucil arm because of disease progression, a trend toward improved OS in both acalabrutinib-containing arms was observed.

Investigator Commentary: Dr. Versha Banerji

Acalabrutinib is a second-generation BTK inhibitor that has demonstrated good efficacy as a single agent in the relapsed and refractory setting, and compared with ibrutinib, with a potentially better rate of toxicity in specific events of concern, including sudden deaths and ventricular tachyarrhythmias. For that reason, the ELEVATE TN study was designed to investigate the performance of acalabrutinib in combination with a CD20 antibody or as a single agent in the frontline setting for patients with CLL who were either 65 years of age or older or less than 65 years of age with coexisting conditions.

Chlorambucil–obinutuzumab was chosen as the comparator because, at the time the trial was designed, that regimen was considered to be the standard of care for this patient population. Obinutuzumab was the CD20 antibody selected to be combined with acalabrutinib because of its demonstrated superiority to rituximab in the CLL11 trial and its ability to enhance depth of remission through clearance of CLL cells in bone marrow. Combining acalabrutinib with obinutuzumab also allowed the study arms to be closely matched.

The protocol specified the administration of obinutuzumab in cycle 2, after 1 prior cycle of acalabrutinib monotherapy so as to debulk the disease before the CD20 antibody was introduced. That approach had been used in other studies to reduce the number of infusion-related reactions experienced with obinutuzumab, and it held true

in the ELEVATE TN study, with 40% of patients experiencing any-grade infusion-related reactions in the control arm and only 14% experiencing such reactions in the acalabrutinib–obinutuzumab arm.

With respect to the primary endpoint of the study, acalabrutinib–obinutuzumab, compared with the chlorambucil-based arm, was associated with a 90% reduction in the risk of progression or death, with a highly significant *p* value. Acalabrutinib monotherapy was associated with a similar improvement in PFS; unfortunately, however, the study was not powered to assess a difference in PFS between acalabrutinib monotherapy and combination therapy. In terms of OS, the HR for survival favoured acalabrutinib–obinutuzumab, although the finding was not statistically significant. Patients in the control arm who crossed over were not censored (45 patients, 55% of those who progressed on the control arm), which might have contributed to the lack of a significant result. However, longer follow-up is also likely required to detect a difference in OS.

Acalabrutinib given as monotherapy or in combination with obinutuzumab appears to be well-tolerated, with a median exposure of 27.7 months. The AEs that are specific to BTK inhibitors were similar or fewer than those seen in past studies with ibrutinib (atrial fibrillation, 3%–4%; hypertension, 5%–7%; bleeding, 39%–43%; major bleeding, 2%–3%). Importantly, no events of ventricular tachyarrhythmia or sudden death were observed.

The ELEVATE TN study confirms that acalabrutinib-based treatments are effective and tolerable in older patients with CLL in the frontline setting, especially patients with high-risk disease. Based on those efficacy and safety results, acalabrutinib with or without obinutuzumab should be considered a frontline option for this population of patients.

Efficacy and Safety of Zanubrutinib in Patients with Treatment-Naïve Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma with del(17p): Initial Results from Arm C of the SEQUOIA (BGB-3111-304) Trial (abstract 499)

Objectives: To evaluate the efficacy and safety of zanubrutinib in treatment-naïve patients 65 years of age or older with del(17p) CLL or small lymphocytic leukemia.

Methods: In an open-label multicentre phase III trial, 109 patients enrolled in a nonrandomized cohort (arm C) were treated with zanubrutinib (Figure 7).

Results: Median age in the cohort was 70.0 years (range: 42–86 years), with 104 patients remaining on treatment at a median follow-up of 10 months. The investigator-assessed objective response rate was 92.7% (95% CI: 86% to 96.8%), with consistent responses across all subgroups. Two patients achieved a complete response, and 95% of patients experienced a duration of response of 6 months or more. Four patients experienced disease progression, and one patient died from grade 5 pneumonia (Figure 8).

The most frequently reported AEs of any grade occurring in more than 10% of the patients were contusion, upper respiratory tract infection, rash, diarrhea, nausea, constipation, and back pain (all occurring in less than 20% of patients). Grade 3 or greater AEs were reported in

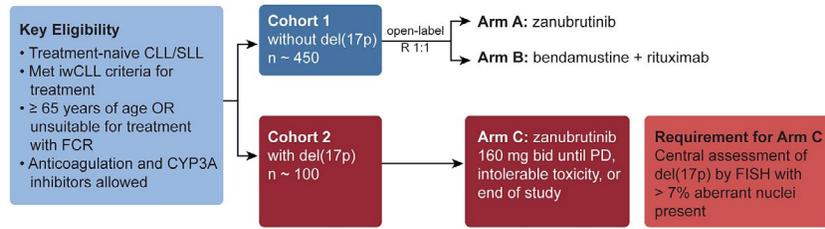


FIGURE 7 Design of the SEQUOIA trial. CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma; iwCLL = International Workshop on Chronic Lymphocytic Leukemia; FCR = fludarabine–cyclophosphamide–rituximab; bid = twice daily; PD = progressive disease; FISH = fluorescence *in situ* hybridization.

40 patients (36.7%). Grade 3 or greater AEs that occurred in more than 2 patients included neutropenia ($n = 11$), pneumonia ($n = 4$), and hypertension ($n = 3$). Figure 9 presents the AEs of interest, the most frequently reported being infections, bruising, and minor bleeding. Treatment was discontinued in 1 patient because of AEs.

Author Conclusions: Preliminary results suggest that zanubrutinib is active and generally well tolerated.

Investigator Commentary: Dr. Constantine Tam

The main improvement of second-generation BTK inhibitors compared with ibrutinib is their specificity. The second-generation molecules such as acalabrutinib and zanubrutinib are more targeted toward BTK, with less off-target inhibition of other Tec family kinases and epidermal growth factor receptor. The improved selectivity of zanubrutinib allowed for an increased dose in the phase I study, with drug exposure that was 8–10 times that of ibrutinib. Notably, at drug trough levels, patients were able to achieve 100% BTK inhibition in lymph nodes. In contrast, ibrutinib is known, through animal models, to have poor lymph node saturation.

Because zanubrutinib is more targeted and bioavailable, the hope is that total body BTK inhibition can be achieved, resulting in improved clinical efficacy with a better safety profile than that seen with ibrutinib. The main safety concerns with ibrutinib are bleeding and atrial fibrillation. However, the most concerning toxicity—although rare—is ventricular tachycardia and sudden death, which is suspected to reside on the same spectrum of cardiotoxicity as atrial fibrillation. Compared with ibrutinib, both acalabrutinib and zanubrutinib have been reported to carry

a lower risk of atrial fibrillation; the hope is therefore that the risk of ventricular tachycardia will be reduced with the newer BTK inhibitors. Another issue with ibrutinib is that patients complain of muscular cramps, arthralgias, and general malaise, which seem to be less of a concern with the second-generation BTK inhibitors.

At ASH, we presented results from the nonrandomized second cohort of the phase III SEQUOIA trial, which includes patients with del(17p) who were given zanubrutinib as first-line therapy. With 109 patients enrolled, SEQUOIA is investigating one of the largest prospective cohorts of patients with treatment-naïve del(17p) CLL. After 10 months of follow-up, the main AEs observed were bleeding and bruising in approximately 25% of patients, which is lower than rates reported with ibrutinib. Infections were commonly reported, but were mostly assessed as grades 1–2. Grade 3 atrial fibrillation was very uncommon, occurring in 0.9% of patients. In addition, only 1 patient discontinued treatment because of an AE. Zanubrutinib was therefore very well tolerated, and the data suggest that, although the spectrum of side effects is similar to that with ibrutinib, zanubrutinib has a better safety profile.

Because of short follow-up, efficacy outcomes focused on response rates. The objective response rate with zanubrutinib was 92.7%, with only 1 patient progressing, suggesting high activity in this patient population—activity that was maintained in all adverse subgroups studied. Further follow-up is required to adequately assess PFS, but the data thus far are highly favourable, with the 12-month PFS for zanubrutinib projected to be greater than 90%.

Ibrutinib is currently the frontline treatment of choice for patients with CLL having del(17p); however, acalabrutinib can now be pre-emptively chosen in certain patients with a high risk for bleeding or cardiovascular events. Given that the side effects with zanubrutinib are very similar to those

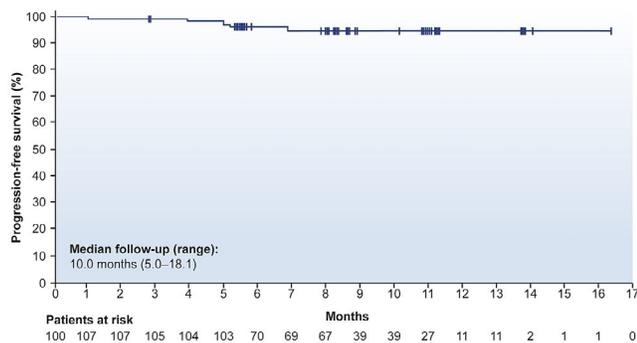


FIGURE 8 Investigator-assessed progression-free survival in the SEQUOIA trial.

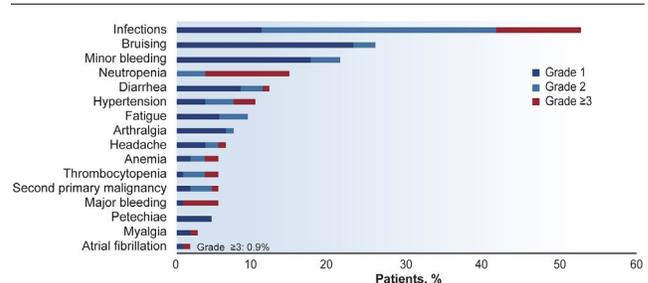


FIGURE 9 Adverse events of interest in the SEQUOIA trial.

with acalabrutinib, we anticipate that the two head-to-head studies comparing zanubrutinib with ibrutinib will report superior safety and potentially superior efficacy outcomes for zanubrutinib, which, for this population, will shift preference among BTK inhibitors to zanubrutinib in the future.

Quantitative Analysis of Minimal Residual Disease Shows High Rates of Undetectable Minimal Residual Disease After Fixed-Duration Chemotherapy-Free Treatment and Serves As Surrogate Marker for Progression-Free Survival: A Prospective Analysis of the Randomized CLL14 Trial (abstract 36)

Objectives: To investigate the prognostic value of MRD after fixed-duration treatment with venetoclax–obinutuzumab in treatment-naïve CLL.

Methods: In a multinational open-label phase III trial, 432 patients were randomized to receive chlorambucil–obinutuzumab or venetoclax–obinutuzumab (Figure 10). The primary endpoint was investigator-assessed PFS. Peripheral blood samples for MRD were taken at cycles 7, 9, and 12, and then serially every 3 months. In patients with a treatment response, MRD in bone marrow was assessed at cycle 9 and at 3 months after the end of treatment. Analysis of MRD was performed by quantitative immunoglobulin allele-specific real-time polymerase chain reaction and by next-generation sequencing.

Results: Median age in the cohort was 71.5 years, and patients had a median CIRS score of 8.5. After a median of 39.6 months' follow-up, PFS was superior with venetoclax–

obinutuzumab (HR: 0.31; 95% CI: 0.22 to 0.44; $p < 0.0001$). The improved PFS was seen in *IGHV* (Figure 11) and *TP53* mutated and unmutated subgroups. No statistically significant difference in OS was observed between the treatment arms.

Undetectable MRD by allele-specific real-time polymerase chain reaction (cut-off: $<10^{-4}$) in peripheral blood and bone marrow was reported in, respectively, 76% and 57% of patients in the venetoclax–obinutuzumab arm and 35% and 17% of patients in the chlorambucil–obinutuzumab arm ($p < 0.0001$). Moreover, undetectable MRD by next-generation sequencing (cut-off: $<10^{-6}$) was observed in 42% of patients receiving venetoclax–obinutuzumab and in 7% of patients receiving chlorambucil–obinutuzumab. In patients with undetectable MRD in peripheral blood, the rate of complete response was higher with venetoclax–obinutuzumab than with chlorambucil–obinutuzumab (42% vs. 14%, $p < 0.001$). An overall concordance of 95.4% between allele-specific real-time polymerase chain reaction and next-generation sequencing methods was observed. Figure 12 depicts the rate of undetectable MRD maintenance at consecutive follow-up times. In patients with undetectable MRD in peripheral blood at the end of treatment, the time to MRD re-detection was longer with venetoclax–obinutuzumab than with chlorambucil–obinutuzumab (median: 17.7 months vs. 7.5 months; HR: 0.19; 95% CI: 0.124 to 0.296). Median PFS was not reached in groups with undetectable MRD. A landmark analysis of PFS by MRD status at the end of treatment showed that undetectable MRD translated into improved PFS from the time of last treatment (Figure 13). The PFS benefit for patients with undetectable MRD was not influenced by clinical response status at the end of treatment.

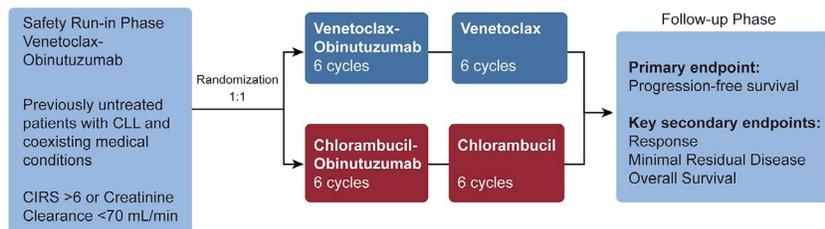


FIGURE 10 Design of the CLL14 study. CLL = chronic lymphocytic leukemia; CIRS = Cumulative Illness Rating Scale.

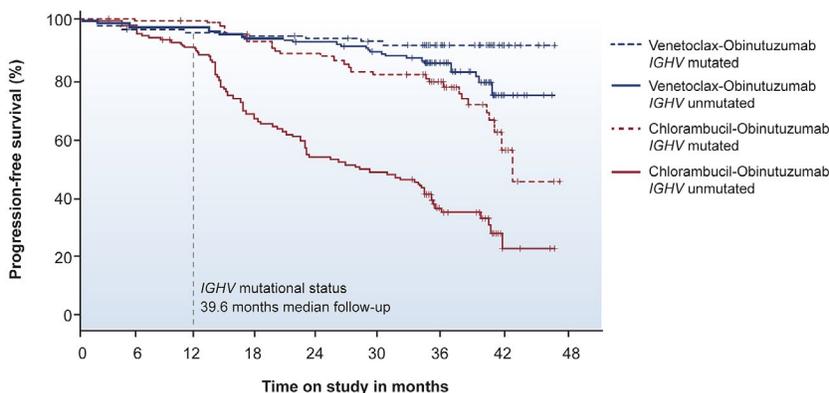


FIGURE 11 Progression-free survival in the CLL14 study by *IGHV* mutation status.

Author Conclusions: Venetoclax–obinutuzumab achieves high and sustainable rates of undetectable MRD in patients with treatment-naïve CLL and coexisting conditions. Findings confirm the prognostic value of MRD for this chemotherapy-free treatment.

CLINICAL IMPACT IN CANADA

Q&A with Drs. Versha Banerji, Peter Anglin, and Pierre Laneuville

Q: What is the current standard of care for patients with untreated CLL in your province?

A (Banerji): In Manitoba, standard of care in the first-line setting is dictated mainly by age and risk status. For patients less than 65 years of age, those with *IGHV* mutation will receive FCR, and those with unmutated *IGHV* or high-risk cytogenetics [such as the presence of del(17p) or *TP53* mutation] are eligible for ibrutinib monotherapy. In patients more than 65 years of age, the standard of care varies by province. In Alberta, patients older than 65 with unmutated *IGHV* are mandated to receive chemoimmunotherapy, whereas in British Columbia, all patients older than 65 are eligible for ibrutinib regardless of risk status. In Manitoba, patients at high risk who have del(17p) or *TP53* mutation generally receive ibrutinib, while those at low risk with mutations generally receive BR or chlorambucil–obinutuzumab

depending on age and fitness. For patients with unmutated *IGHV* [without del(17p)], a discussion of the advantages and disadvantages of chemoimmunotherapy and of ibrutinib is required to help them make an informed decision, because no OS data are available to support a widespread change in treatment. Based on the subgroup analyses of the Alliance A041202 trial, ibrutinib is associated with a longer progression-free interval; however, with chemoimmunotherapy, patients can remain treatment-free for 3–4 years, rather than requiring continuous ibrutinib treatment³⁴.

A (Anglin): In Ontario, any patient with high-risk disease—defined as having unmutated *IGHV* or the presence of del(17p) or *TP53* mutations—has access to ibrutinib monotherapy, accounting for approximately 60% of patients with CLL who require therapy. I believe that many clinicians and patients would like to have access to ibrutinib monotherapy in *IGHV*-mutated cases; however, because data from the Eastern Cooperative Oncology Group 1912 and Alliance trials investigating ibrutinib–rituximab compared with chemoimmunotherapy showed that patients with low-risk or *IGHV*-mutated CLL had similar PFS outcomes regardless of therapy, funding of ibrutinib was restricted in those patients^{34,35}. For most patients with *IGHV*-mutated CLL, the current standard of care is therefore chlorambucil–obinutuzumab or, for patients who are young (<65 years of age) and fit enough, FCR.

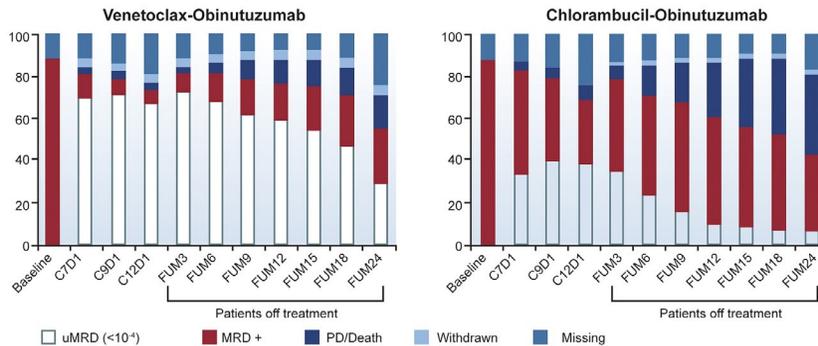


FIGURE 12 Minimal residual disease (MRD) rates over time in the CLL14 study. μ MRD = undetectable minimal residual disease; PD = progressive disease.

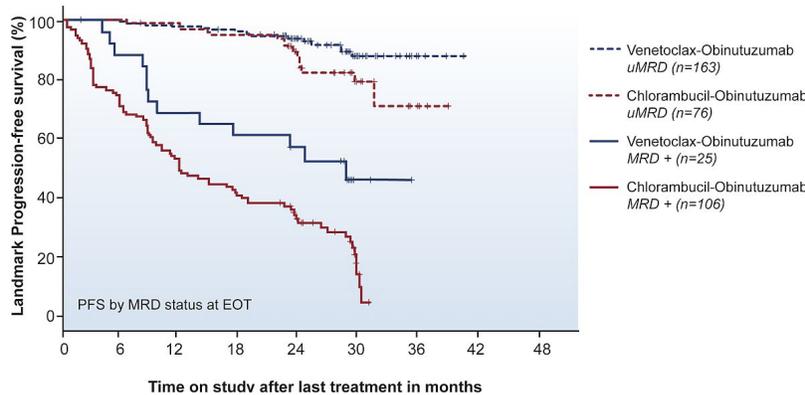


FIGURE 13 Progression-free survival (PFS) in the CLL14 study by minimal residual disease (MRD) status. EOT = end of treatment; μ MRD = undetectable minimal residual disease.

A (Laneville): In Quebec, most institutions have access to cytogenetic testing and sequencing for *TP53* in the frontline setting. That access is important, because all treatment-naïve patients regardless of age or fitness who have loss of *TP53* function, either through deletion on chromosome 17 or an activating mutation, are eligible to receive ibrutinib monotherapy. For the patients with CLL who lack that high-risk factor, treatment eligibility depends on age, fitness, and *IGHV* mutation status. Currently, patients who are young and fit have access to FCR regardless of *IGHV* mutation status, because patients with unmutated *IGHV* do not have a clear funding path to ibrutinib. Chlorambucil–obinutuzumab or ibrutinib monotherapy are the two funded therapies for patients who are unfit or more than 65 years of age, or who have compromised creatinine clearance—with the exception of a few institutions that can get access to BR. Generally, patients and clinicians opt to use ibrutinib in this situation unless there is a strong contraindication (for example, patient on anticoagulation with a high bleeding risk).

Q: What is your impression of the results from the E1912 trial, and what potential clinical implications do those results have in Canada?

A (Banerji): An important takeaway from the trial is that, although IR (compared with FCR) continued to show a PFS benefit for patients with unmutated *IGHV*, no increased benefit was seen in patients with mutated *IGHV*. That finding is in line with our standard of care and suggests that chemoimmunotherapy with FCR remains an excellent time-limited therapy option for these younger patients with low-risk disease, given the chance for cure without the need for bone marrow transplantation. No data yet match those in the phase II MD Anderson study showing a 54% PFS rate at 12.8 years in patients with *IGHV* mutation receiving FCR, with no relapses seen up to 17 years in 14% of patients³⁶. Another study from MD Anderson investigating the correlation of MRD status with PFS outcomes found that undetectable MRD after 3 cycles of FCR was correlated with favourable PFS outcomes, regardless of whether treatment was abbreviated³⁷. For that reason, 3 cycles of FCR with MRD monitoring has been an appealing regimen for many of my young patients with low-risk disease. Abbreviated therapy is particularly attractive because it might lower the risk of myelodysplastic syndrome and bone marrow failure associated with 6 cycles of FCR.

Another important point to take from this updated analysis is that, for the patients who discontinued ibrutinib therapy for reasons other than progression or death, many could still achieve a durable remission after discontinuation (mean: 22.5 months). That durability is something that has been observed in our clinical practice, and it is important to see in the setting of a clinical trial to provide reassurance. The results were particularly impressive given that the study monitored patients every 3 months after discontinuation, highlighting the quality and reliability of the data.

A (Anglin): The results reported in this update of the E1912 study were as expected in the population with unmutated *IGHV*, where, compared with FCR, IR was associated with a significant improvement in PFS. In contrast, patients with

mutated *IGHV* in both treatment arms had similar PFS outcomes. Despite the polarized views concerning which treatment is best in the subgroup with *IGHV* mutation, I believe that these results confirm the reasonability of both ibrutinib-based therapy and chemoimmunotherapy as treatment options for these patients. The long-term follow-up data for FCR are more robust, and the question of ibrutinib-based therapy living up to those long-term results remains unclear. Selection of treatment should therefore be based on the patient's priority: reducing the risk of myelodysplastic syndrome or leukemia (long-term incidence is 3%–5% with FCR) compared with receiving the benefit of a time-limited therapy. Although ibrutinib has been used off-trial for 5 years, and clinicians have gained comfort with its use, this trial provides continued reassurance that ibrutinib-based therapy is effective and tolerable for young patients with CLL in the first-line setting, particularly those with high-risk disease.

A (Laneville): Interpreting the results from the E1912 study poses a couple of challenges. First, IR was shown to be superior to FCR in this group of young fit patients, but given that the Alliance A041202 trial showed that rituximab does not add any benefit to ibrutinib in older patients with CLL³⁴, the indication for ibrutinib in Canada is monotherapy. Thus, if clinicians are willing to adopt a switch to ibrutinib over FCR-based therapy based on the conclusions of the study, they would need to assume that the reported observations extend to monotherapy. Second, there is controversy about how the results will apply to patients with *IGHV*-mutated CLL because, although PFS appeared similar between the study arms for that group of patients, it is unclear whether a PFS plateau and possible cure will be seen, as was observed for FCR in the MD Anderson study³⁶. The answer to that question is many years away, and for conservative clinicians, it could be difficult to deviate from the current standard of care without definitive results. In the meantime, I think that, for older patients who cannot receive FCR, these results provide comfort that ibrutinib is indeed an excellent first-line option regardless of *IGHV* mutation status.

Q: What is your impression of the results from the ELEVATE TN trial, and what potential clinical implications do those results have in Canada?

A (Banerji): The ELEVATE TN trial demonstrated that acalabrutinib alone or in combination with obinutuzumab outperformed chlorambucil–obinutuzumab in patients with CLL who were older than 65 or who had pre-existing conditions. The question of whether acalabrutinib combination therapy is superior to monotherapy is very important clinically, particularly given the results of the Alliance A041202 trial³⁴. Interestingly, the *post hoc* exploratory analysis did show that PFS numerically favoured combination therapy over monotherapy, but unfortunately, the study was not powered to make that comparison. From a Canadian perspective, as we await reimbursement of acalabrutinib, that result could affect which indication we get access to.

This study had design features similar to those in several other recent studies in first-line CLL that used

chemoimmunotherapy as the comparator^{34,35,38}; however, ELEVATE TN was the only study in that group to include patients with del(17p). Chlorambucil–obinutuzumab is not an ideal comparator for patients with this type of high-risk disease because many provinces now have access to ibrutinib for such patients in the first line. However, it is important to note that such access was not the case at the time of study design and that an important feature of the study was the ability to cross over to the acalabrutinib monotherapy arm upon progression in the control arm. That allowance for crossover made the study feasible for our patients, particularly given that testing for high-risk cytogenetics was not available in our province at the time of enrolment. Another important consideration is that the other first-line studies still enrolled patients with high-risk disease: all studies included patients with unmutated *IGHV*, and the E1912 study included patients with *TP53* mutations (approximately 8%).

A (Anglin): The ELEVATE TN study includes a population of patients with CLL representing most patients seen in practice—that is, those who are more than 65 years of age or who have coexisting conditions that make them unfit for FCR. As expected, the trial demonstrated a PFS benefit for acalabrutinib–obinutuzumab compared with chlorambucil–obinutuzumab, with moderate follow-up (median: 28 months). Interestingly, the addition of a CD20 antibody did not appear to have a large incremental benefit over acalabrutinib monotherapy in the trial (24-month PFS: 93% for the combination vs. 87% for monotherapy), echoing the results from the Alliance trial³⁴. Whether the addition of a CD20 antibody adds a significant benefit to acalabrutinib therapy will be an important point to consider, given that the addition of obinutuzumab, compared with acalabrutinib monotherapy, appeared to increase toxicity, particularly neutropenia (32% vs. 11%) and pneumonia (7% vs. 3%). Overall, the trial showed that acalabrutinib-based therapy is tolerable and effective, with an impressive 24-month PFS rate of 93%. In the Canadian context, although those results will not affect treatment choice in the immediate future, they provide reassurance that acalabrutinib is a reasonable alternative to ibrutinib and will allow clinicians to gain comfort with the use of acalabrutinib in the recently opened phase III B study in patients with treatment-naïve and relapsed CLL.

A (Laneville): The result that stands out most from the ELEVATE TN study is that obinutuzumab appears to add a small benefit to acalabrutinib over monotherapy. It will be interesting to see how those data mature, because such a benefit would be a novel finding. However, the indication for which acalabrutinib will gain funding will depend on pharmacoeconomic analyses. There is a particular challenge in Quebec with acalabrutinib combination therapy, because hospitals are required to pay for oral therapy if it is given with parenteral therapy, meaning that hospitals would have to incur significant costs in the first 6 months of therapy, which could affect adoption of this new regimen in practice.

Q: What is your impression of the results from the SEQUOIA trial, and what potential clinical implications do those results have in Canada?

A (All): Given that BTK plays an important role in CLL progression and that inhibition of that kinase has proved to be an effective mechanism in reducing disease, newer agents in this class continue to be of interest. The SEQUOIA trial investigated zanubrutinib, another second-generation BTK inhibitor entering the CLL space. In the analysis of the single-arm cohort of continuous zanubrutinib monotherapy, we so far see good efficacy in the high-risk population of CLL patients with del(17p), with 82% of patients achieving a partial or complete response. In terms of safety, rates of atrial fibrillation and major bleeding appeared to be lower than those reported for ibrutinib; however, the rate of all-grade infections (more than 50%) and rash (approximately 14%) appeared to be higher than expected. With a median follow-up of 10 months, those results are encouraging, but are too early to interpret and will not affect Canadian practice at this time.

Q: How does ibrutinib compare with next-generation BTK inhibitors in terms of efficacy and safety?

A (Banerji): From an efficacy standpoint, acalabrutinib monotherapy has been associated with PFS rates similar to those observed with ibrutinib monotherapy in past studies (24-month PFS: ELEVATE TN, 87%; Alliance, 87%; RESONATE-2, 89%)^{18,34}, and neither ibrutinib or acalabrutinib–obinutuzumab, compared with chlorambucil–obinutuzumab, was associated with a statistically significant OS advantage in older patients with treatment-naïve CLL³⁸.

The most important observation from a safety perspective is that signals of sudden cardiovascular death and ventricular tachyarrhythmia, which have been observed with ibrutinib, have thus far not been observed with acalabrutinib in the approximately 600 patients on trial in the relapsed and refractory or first-line setting. Hypertension and skin events also appear to be less frequent with acalabrutinib; however, those observations must be interpreted with caution given the lack of head-to-head data and shorter follow-up with acalabrutinib. Bleeding events appear to be comparable for the BTK inhibitors, with less extent of bruising and contusion with acalabrutinib. Although the rate of atrial fibrillation originally appeared to be lower with acalabrutinib than with ibrutinib, updated results from clinical trials do not indicate a difference (ILLUMINATE and ELEVATE TN both posted a rate of approximately 5%). Real-world data show a higher rate of atrial fibrillation with ibrutinib than was observed in clinical trials, and data of that type will be needed for acalabrutinib to determine if such rates are also the case for this BTK inhibitor. An AE that is specific to acalabrutinib is headache, with an incidence of 40% in the ELEVATE TN trial and 22% in the ASCEND trial. Fortunately, the headache tends to be transient and can be easily managed with acetaminophen without the need for dose reduction.

A (Anglin, Laneville): With the shorter follow-up in this trial and the lack of a direct comparison, it will be difficult to establish whether acalabrutinib is more effective or has a better safety profile than ibrutinib. In terms of toxicities of interest, acalabrutinib and zanubrutinib both showed potentially lower rates of all-grade atrial fibrillation (approximately 4% and 2% respectively), hypertension

(approximately 7% and 10%), and minor bleeding (approximately 40% and 21%) than had previously been reported with ibrutinib. Although those results are encouraging, follow-up is short; it will therefore be important to monitor whether the frequencies of those AEs increase over time, as was observed with ibrutinib. Long-term safety results of second-generation BTK inhibitors will be of great interest, because robust data showing a more favourable toxicity profile might affect therapy selection in the future, given some of the toxicity challenges with ibrutinib.

Q: How will the differences between BTK inhibitors affect choice of therapy in untreated CLL?

A (Banerji): We are entering an era in which we will have several options in the frontline setting and can tailor treatment by patient preference, treatment goals, and coexisting conditions. Patients can feel empowered in making an educated decision based on the information that is presented to them. In the case of second-generation BTK inhibitors, if acalabrutinib and ibrutinib are equally effective and if acalabrutinib continues to show a similar or more desirable toxicity profile, I owe it to my patients to have it as a frontline option. If acalabrutinib becomes accessible to patients in the frontline setting, I would consider using it in patients with high cardiac risk (for example, known heart failure, use of 3–4 antihypertensive drugs, history of cardiac event within the preceding year) while closely monitoring for cardiac AEs and switching to venetoclax if they occur. There are limitations to that practice as in some provinces; venetoclax cannot be accessed without progression if a patient has been taking ibrutinib for more than 3 months. Such situations are unfortunate, given that toxicities can often occur later in treatment when the disease burden has decreased.

A (Anglin): In the future, making a selection between the different BTK inhibitors will depend on a number of factors, including efficacy, safety, access, ease of administration, and clinician experience. Based on currently available data, we cannot make conclusions about the relative efficacy and safety of the BTK inhibitors. For upcoming BTK inhibitors such as acalabrutinib to be preferred over ibrutinib, it will be important that they are at least as effective and continue to show a more favourable safety profile. If long-term follow-up indicates a decreased incidence of atrial fibrillation, hypertension, and bleeding for the second-generation BTK inhibitors such as acalabrutinib, those agents might be preferentially used in patients with difficult-to-control hypertension or those taking anticoagulants; however, it is premature to make emphatic statements at this time.

Dosing could also play a role in patient and clinician preference for BTK inhibitors, because the second-generation BTK inhibitors are given twice daily as opposed to once daily for ibrutinib. The extra dose might affect the choice of therapy, particularly with an agent that might be given continuously. In terms of experience, ibrutinib has the advantage of being the first BTK inhibitor to market. Its availability has so far allowed Canadian clinicians to gain 5 years of experience with ibrutinib off-study and makes the switch to newer therapies difficult in the absence of compelling long-term or comparative data.

A (Laneville): Because ibrutinib and acalabrutinib might not show large differences in terms of efficacy, safety, and mechanisms of resistance, choice of therapy between those two agents will likely come down to practical considerations such as cost. It will be interesting to see how data for the newer BTK inhibitors—zanubrutinib and LOXO-305—mature, particularly given that the latter has potential activity in CLL cells with C481 BTK mutations³⁹, which are associated with resistance to ibrutinib and acalabrutinib. Looking forward, if these newer BTK inhibitors prove to be safe and effective, there might be an opportunity for sequencing the agents based on BTK mutation status in patients whose disease has progressed, which could extend the role of this class of agents.

Q: What is your impression of the results from the CLL14 trial, and what potential clinical implications do they have in Canada?

A (Banerji): The CLL14 update provides reassurance that a time-limited therapy such as venetoclax–obinutuzumab can prolong PFS in patients with CLL; however, several caveats will challenge its implementation in the Canadian system. First, despite the PFS advantage demonstrated with this novel combination compared with chlorambucil–obinutuzumab, an OS advantage was not seen. The latter observation is of particular concern, because there was no monotherapy arm to permit an evaluation of the incremental benefit of adding obinutuzumab to venetoclax. A cost–benefit analysis would therefore be needed to confirm an advantage of this novel combination regimen in the first line for it to be accepted by our public payer system, particularly given that venetoclax–rituximab is already available at relapse. Second, it is difficult to compare the CLL14 trial with Canadian practice because the comparator arm used 12 cycles of chlorambucil–obinutuzumab (based on the standard of care in the United Kingdom), whereas only 6 cycles are given in Canada. The 12-month time-limited duration of therapy is, however, very attractive.

A (Anglin): In this update of the CLL14 trial, we continue to see impressive efficacy with 1-year fixed-duration venetoclax–obinutuzumab. That efficacy is evidenced by a 36-month PFS rate of 82% and a 76% rate of undetectable MRD in peripheral blood at the end of treatment (42% with complete response). It was encouraging to see that, although some patients who received venetoclax–obinutuzumab became MRD-positive after cessation of treatment, many patients who achieved undetectable MRD had excellent long-term outcomes, with a plateau beginning to be detected on the Kaplan–Meier curve for PFS. It was also interesting to note that patients who achieved undetectable MRD with chlorambucil–obinutuzumab did almost as well as those receiving venetoclax-based therapy, although no current predictors identify the patients who are more likely to achieve undetectable MRD with chemoimmunotherapy. Overall, the MRD results from the CLL14 trial are very interesting and in line with the direction that the CLL treatment paradigm is moving. However, use of MRD-based decision-making in Canada is still several years away.

There could be a few barriers to accessing this time-limited therapy for frontline treatment in CLL, including

lack of OS benefit for venetoclax–obinutuzumab at the current follow-up time. The inclusion of patients based on a CIRS score greater than 6 rather than on age also poses a challenge, because that complicated algorithm makes it difficult to predict the fraction of patients with CLL that this study population represents. Finally, for patients with mutated *IGHV*, those treated with chemoimmunotherapy, compared with those receiving venetoclax–obinutuzumab, appeared to have similar, albeit marginally less favourable, PFS curves. That observation might challenge the ease of access to this novel therapy for patients with low-risk disease, although I am hopeful that this will not be the case, because I feel that venetoclax–obinutuzumab could become another treatment option for patients.

A (Laneville): The CLL14 trial confirms that venetoclax–obinutuzumab is a potent and tolerable fixed-duration regimen for unfit patients in the frontline setting. The current analysis focused on MRD results, which are of great interest to researchers in the field and are likely to play a role in treatment decisions in the future; however, they are not relevant for clinical decisions in Canada at this time.

Q: How do the efficacy results and safety profile of venetoclax compare with those of the BTK inhibitors, and how might they influence choice of treatment?

A (Banerji): Without head-to-head trials, selection between these two novel agent classes is based on the practical considerations of therapy implementation and observation of toxicities over time. The BTK inhibitors and venetoclax both pose challenges in terms of implementation. With venetoclax, the need for a ramp-up schedule and the potential need for hospital admission for patients categorized as high risk for tumour lysis syndrome remains an obstacle. In addition, the monitoring of lab results needed with venetoclax administration can be challenging for physicians who do not have a support network. With BTK inhibitors, baseline electrocardiography, blood pressure, and cardiac and medication history must be taken, and when patients are taking a contraindicated drug, such as warfarin, they must convert to a safer and potentially more expensive anticoagulant. In terms of observation of toxicities, venetoclax is, in my experience, quite tolerable and easy to monitor over time, particularly given that it is a time-limited therapy. Monitoring toxicities with continuous ibrutinib treatment is more challenging: the toxicity profile is greater, with events that are sporadic and variable in grade, and that affect several different organ classes in an unpredictable manner. For that reason, longer-term follow-up with second-generation BTK inhibitors will be important to confirm whether the toxicity profile is improved.

A (Anglin): The Bcl-2 and BTK inhibitor–based therapies both offer better outcomes for patients with high-risk CLL, although how those regimens compare from an efficacy standpoint has not been determined. Compared with ibrutinib, venetoclax–obinutuzumab appears to induce MRD–negativity in a higher percentage of patients. However, whether that effect will translate into a PFS or OS benefit is unclear, and it is important to acknowledge the challenges of comparing fixed-duration with continuous regimens. I

think that there is a desire to use venetoclax in the frontline setting based on its safety profile, which does not include a signal for the major events of concern with BTK inhibitors such as atrial fibrillation and bleeding. Apart from tumour lysis syndrome (which most clinicians have now learned to manage) and some neutropenia and infection, the side-effect profile of venetoclax–obinutuzumab might be more favourable, particularly in the long term.

Some potential caveats to the current use of venetoclax–obinutuzumab in the frontline setting is the lack of knowledge and robust data about the efficacy of ibrutinib-based therapies after relapse on venetoclax-based therapy. There is also a concern that patients who relapse off venetoclax-therapy will have funding constraints for re-treatment with venetoclax. Although those concerns should not prevent the use of venetoclax in the frontline setting, they must be considered when discussing therapy options with patients.

A (Laneville): With no direct comparison available, it is difficult to establish which class of agents will provide the best outcomes for patients in the frontline setting. Based on data from prior studies and those discussed here, we can say that ibrutinib-, acalabrutinib-, and venetoclax-based therapies all look to be very effective for patients with treatment-naïve CLL. I think that there will be interest in using venetoclax–obinutuzumab in the frontline setting for patients with high-risk disease if it meets the threshold for reimbursement in a pharmacoeconomic analysis. The decision to select a Bcl-2 inhibitor–based therapy over a BTK inhibitor–based therapy will likely depend on the patient profile, which will consider factors such as tumour lysis syndrome, cardiovascular and bleeding risk, and desire to have a fixed-duration therapy.

Q: What is the role of novel agents in previously untreated CLL, and what questions remain to be answered?

A (All): It is clear that novel agents are universally accepted as the first-line treatment of choice over chemoimmunotherapy in patients with high-risk disease regardless of age or fitness. Some questions remain to be addressed to better understand the optimal use of novel agents for the treatment of CLL. Those questions include: What is the preferential sequencing of Bcl-2 and BTK inhibitor–based therapies? Which BTK inhibitor will offer the best benefit–risk profile for patients? And will long-term data show a benefit for novel agents compared with chemoimmunotherapy in patients with low-risk disease? To the latter question, if novel agents do show such a benefit, a cost–benefit analysis that considers all treatment-related costs in the Canadian context will be needed to determine the optimal frontline therapy for patients and for the system.

Looking ahead, the CLL landscape is likely moving toward finite treatment with a Bcl-2 inhibitor, BTK inhibitor, and CD20 antibody; however, we are waiting for the related clinical trials to mature. The answers will raise additional questions about how finite therapy will be defined and whether there will be a role for MRD-based decision-making with such regimens. The concepts are very exciting, but their horizon to affect Canadian practice is still several years into the future.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare the following interests: VB has participated on advisory boards or has received research funding from AstraZeneca, AbbVie, Janssen, Roche, Gilead, and Teva Pharmaceuticals. She has received research funding from the Canadian Institutes of Health Research, the Leukemia and Lymphoma Society of Canada, the CancerCare Manitoba Foundation, and Research Manitoba. AC and SD received funding from AstraZeneca for the development of this document. PA has participated in advisory boards or has received honoraria from Janssen, AbbVie, Teva Pharmaceuticals, AstraZeneca, Apotex, and Celgene. PL has participated in advisory boards or has received honoraria from AbbVie, Amgen, ARIAD Pharmaceuticals, Ascentage Pharma, Bristol-Myers Squibb, Celgene, Gilead, Janssen, Lundbeck, Novartis, Paladin, Pfizer, and Roche.

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