

Highlights from ASCO 2020: updates on the treatment of chronic lymphocytic leukemia

S. Dolan MD,* A. Christofides MSc RD,[†] S. Doucette MSc,^{†‡} and M. Shafey MD[‡]

ABSTRACT

Because of the global coronavirus pandemic, the 2020 annual scientific meeting of the American Society of Clinical Oncology took place virtually, 29–30 May. At the meeting, results from key studies about the treatment of chronic lymphocytic leukemia (CLL) were disseminated. Studies examined the efficacy and safety of ibrutinib, acalabrutinib, zanubrutinib, and venetoclax as monotherapy or in combination with novel agents for patients with treatment-naïve and relapsed or refractory CLL. 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, relapsed disease, refractory disease

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BACKGROUND

This year, key studies in the treatment of chronic lymphocytic leukemia (CLL) presented at the American Society of Clinical Oncology (ASCO) 2020 meeting focused on novel agents such as ibrutinib, acalabrutinib, and zanubrutinib [which target Bruton tyrosine 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, and it is a key component of the B cell antigen receptor signalling cascade^{1–3}. 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^{1–3}.

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 migration⁴. In Canada, ibrutinib in combination with obinutuzumab or as monotherapy is approved by Health Canada for the treatment of previously untreated CLL, including in patients with del(17p)⁵.

With the success of ibrutinib, novel BTK inhibitors were developed to improve on the safety and efficacy of treatment. Acalabrutinib (ACP-196) is a potent second-generation orally bioavailable BTK inhibitor that also binds

Cys481 in the BTK active site⁶. However, acalabrutinib is more highly selective than ibrutinib, resulting in less off-target activity; it is therefore predicted to have fewer adverse effects¹. 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^{7,8}. It is also approved as monotherapy for patients in the relapsed setting of CLL and mantle cell lymphoma. Zanubrutinib is a third BTK inhibitor that is potent and specific, and also has a higher selectivity for BTK than ibrutinib does⁹. 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 therapy¹⁰; an approval for the treatment of CLL has not yet been issued.

Bcl-2 is the founding member of a family of apoptosis-regulating proteins that are characterized by the presence of at least one Bcl-2 homology domain^{11,12}. Venetoclax is an orally bioavailable, selective antagonist of Bcl-2 that promotes apoptosis in primary CLL cells by mimicking the Bcl-2 homology domain 3 of Bcl-2's natural antagonists and subsequently inhibiting its antiapoptotic function¹². Currently, venetoclax is indicated in combination with obinutuzumab for the treatment of previously untreated CLL¹³. Venetoclax is also indicated in combination with rituximab for the treatment of patients with CLL who have received at least 1 prior therapy. It is also approved as continuous

Correspondence to: Anna Christofides, IMPACT Medicom Inc., Toronto, Ontario M6S 3K2.
E-mail: anna@impactmedicom.com ■ <https://doi.org/10.3747/co.27.7009>

monotherapy in the same setting for patients with either del(17p) who have received at least 1 prior therapy or in patients without del(17p) who have received at least 1 prior therapy and have no other available treatment options.

The present meeting report summarizes the data presented at the ASCO 2020 virtual meeting that focused on the treatment of CLL with the foregoing novel agents. Also included are commentaries from study investigators and Canadian perspectives from hematologists about how the data might affect clinical practice.

METHODS

The American Society of Clinical Oncology is the world's largest professional society with a focus on malignancies. Because of the coronavirus pandemic, their 2020 annual meeting—Unite and Conquer: Accelerating Progress Together—took place virtually, 29–30 May. A total of 2215 abstracts were accepted by ASCO and were disseminated using their online platform.

The virtual scientific program included 3 sessions on the topic “Hematologic Malignancies—Lymphoma and Chronic Lymphocytic Leukemia,” during which eighty-two abstracts were presented. For the present report, publication-only abstracts, ongoing trials without results, studies in pediatric patients, studies not exclusively focused on CLL, retrospective analyses, and meta-analyses were excluded. Among the abstracts presented orally, five focused on clinical trial results investigating treatments in patients with CLL and were selected for discussion here.

Two presentations examined the efficacy and safety of BTK inhibitors or Bcl-2 inhibitors as monotherapy for the treatment of CLL. The first presentation reported updated results from a phase II study examining the efficacy and safety of acalabrutinib for patients with treatment-naïve CLL¹⁴. The second presentation reported final results from ASCEND, a phase III trial comparing the efficacy and safety of acalabrutinib with those of idelalisib–rituximab or bendamustine–rituximab for the treatment of relapsed or refractory (R/R) CLL¹⁵.

Three presentations examined the efficacy and safety of BTK or Bcl-2 inhibitors in combination with novel agents. The first presentation examined the efficacy and safety of time-limited minimal residual disease (MRD)–driven therapy with zanubrutinib–obinutuzumab–venetoclax in treatment-naïve CLL¹⁶. The second presentation reported

follow-up results from the CLL14 trial on the efficacy and safety of venetoclax–obinutuzumab in treatment-naïve CLL¹⁷. The final presentation reported final results of the phase III GENUINE study, which examined the effect on efficacy outcomes of adding ublituximab to ibrutinib in previously treated high-risk CLL¹⁸.

RESULTS

Acalabrutinib in treatment-naïve CLL: mature results from a phase II study demonstrating durable remissions and long-term tolerability (abstract 8024)

Objective: To examine the long-term safety and efficacy of acalabrutinib monotherapy for patients with treatment-naïve CLL.

Methods: In a phase II trial, 99 patients with treatment-naïve CLL or small lymphocytic lymphoma who were inappropriate for or who declined standard chemotherapy were given acalabrutinib 100 mg twice daily ($n = 62$) or 200 mg once daily ($n = 37$, Figure 1). Per protocol amendment, all patients were subsequently given acalabrutinib 100 mg twice daily. Patients had a median age of 64 years and an Eastern Cooperative Oncology Group performance status of 0–2. Overall, 10% of the patients had deletion mutations [del(17p)], and 62% had unmutated genes of the immunoglobulin heavy chain variable region (*IGHV*). Patients received acalabrutinib until progressive disease or unacceptable toxicity. The primary endpoint was safety.

Results: At a median follow-up of 53 months, 86% of the patients remain on treatment. Most discontinuations were secondary to adverse events [AEs ($n = 6$)] or progressive disease ($n = 3$, 1 with Richter transformation). No patients discontinued treatment because of bleeding, hypertension, or atrial fibrillation. The most common AEs of any grade were diarrhea (52%), headache (45%), upper respiratory tract infection (44%), arthralgia (42%), and contusion (42%). Treatment-related AEs typically decreased over time (Figure 2). Table 1 shows all-grade and grade 3 or greater events of clinical interest. All-grade atrial fibrillation occurred in 5% of patients (incidence: 1% in years 1, 2, 4; 3% in year 3). Serious AEs were reported in 38% of patients; events occurring in more than 2 patients included pneumonia ($n = 4$) and sepsis ($n = 3$). Two non-drug-related grade 5 serious AEs were reported (multi-organ failure in the setting of pneumonia, and cardiac failure).

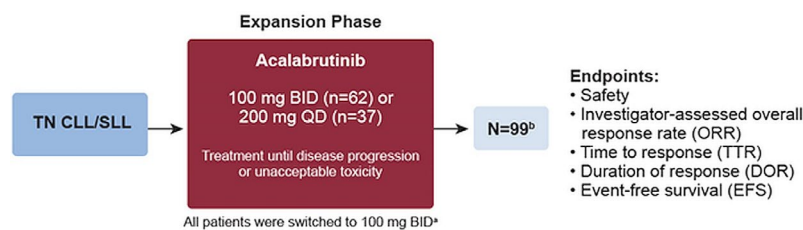


FIGURE 1 Study design. ^aUnder amendment 6 of the protocol (1 May 2015), patients in cohort 7 were switched to 100 mg twice daily, based on the increased Bruton tyrosine kinase (BTK) occupancy seen with the 100 mg twice-daily dose compared with the 200 mg daily dose. ^bAll patients underwent baseline assessment for interphase cytogenetics, *IGHV* (immunoglobulin heavy-chain variable region) gene mutation, β_2 -microglobulin status, and B symptoms. The definition for “complex karyotype” was 3 or more chromosomal abnormalities. TN = treatment-naïve; CLL = chronic lymphocytic leukemia; SLL = small lymphocytic lymphoma; BID = twice daily; QD = once daily.

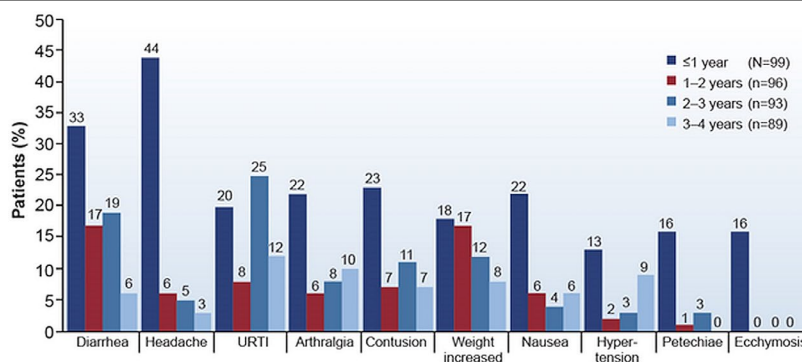


FIGURE 2 Incidence of selected treatment-emergent adverse events over time. URTI = upper respiratory tract infection.

The objective response rate (ORR) was 97% (7% complete responses; 90% partial responses). The ORR was 100% in each high-risk subgroup, including those with unmutated *IGHV*, del(17p), *TP53* mutation, and complex karyotype. Median time to treatment response was 3.7 months (range: 2–22 months). Median duration of response and median event-free survival (EFS) were not reached. The 48-month duration of response rate was 97% [95% confidence interval (CI): 90% to 99%], and the 48-month EFS was 90% (95% CI: 82% to 94%).

Author Conclusions: This study provides the longest safety and efficacy follow-up to date for acalabrutinib monotherapy in symptomatic patients with treatment-naïve CLL. Results support findings from the phase III trials, with no new safety signals.

Investigator Commentary: Dr. Richard Furman

The next-generation BTK inhibitor acalabrutinib is likely as effective as ibrutinib, but with fewer drug–drug interactions and an improved tolerability profile. Given the long-term treatment course required with these BTK inhibitors, establishing long-term safety and efficacy are important. Our study, initiated in August 2015, examined the long-term safety and efficacy of acalabrutinib in patients with treatment-naïve and R/R CLL. At ASCO 2020, we presented results for the population with treatment-naïve disease, representing a median duration of treatment of 52 months.

Overall, our study demonstrated excellent efficacy with acalabrutinib in treatment-naïve CLL, achieving a 97% ORR and an EFS rate of 90% at 48 months. Because EFS includes discontinuations for AEs and other reasons, which were rare with acalabrutinib, the EFS in our study is far superior to that with ibrutinib.

The most frequent AEs reported with ibrutinib include diarrhea and bruising (occurring in approximately 40% of patients), followed by hypertension in approximately 25% of patients, atrial fibrillation in 10%–12% of patients, and arthralgias in 5%^{5,7,19}. Interestingly, hypertension occurs later in treatment, and therefore the current incidence of 25% at 8 years could increase further over time. Additionally, most patients report nail changes, described as the development of brittle, cracked, ridged nails. Overall, 20% of patients discontinue ibrutinib because of AEs. In our study, only 6% of patients discontinued acalabrutinib because of AEs.

TABLE I Adverse events of clinical interest

Event	Grade [n (%)]	
	All	≥3
Cardiac event	20 (20)	4 (4)
Atrial fibrillation	5 (5)	2 (2)
Ventricular tachyarrhythmias	0	0
Anemia	8 (8)	2 (2)
Leucopenia	9 (9)	9 (9)
Neutropenia	9 (9)	9 (9)
Other leucopenia	1 (1)	1 (1)
Thrombocytopenia	3 (3)	1 (1)
Hemorrhage ^a	65 (66)	3 (3)
Major hemorrhage	4 (4)	3 (3)
Hepatotoxicity	4 (4)	2 (2)
Hypertension	22 (22)	11 (11)
Infection ^b	83 (84)	15 (15)
Interstitial lung disease or pneumonitis	1 (1)	0
Second primary malignancy	26 (26)	5 (5)
Non-melanoma skin cancer excluded	11 (11)	5(5)
Tumour lysis syndrome	0	0

^a Most common bleeding events were contusion (42%), petechiae (18%), and ecchymosis (16%).

^b Most common infections were upper respiratory tract infection (44%) and sinusitis (21%). Among patients with opportunistic infections, grade 2 fungal infection, grade 2 coccidioidomycosis, and grade 2 herpes zoster were reported in 1 patient each, and 1 patient experienced both a grade 3 perineal fungal infection and grade 3 herpes zoster.

In general, we see no nail changes with acalabrutinib, far less diarrhea, and less severe bruising. It is important to keep in mind that the already-mentioned studies report any AE without regard for causality. Thus, for AEs that are common in the general population, such as diarrhea, it is not possible to distinguish the cause. Although the reported rate of diarrhea in our study was 51%, the incidences were typically short in duration and not related to medication dosing. For hypertension and atrial fibrillation, the rates seen in our study are much lower than those reported for ibrutinib and are on par with what might be expected in the general population. Interestingly, headaches are a unique AE for acalabrutinib. The headaches occur in approximately 45% of patients and are described as being low-grade,

occurring 1–2 hours after dosing, and being manageable with acetaminophen or caffeine. The headaches usually ameliorate over time, such that by about 4 weeks, they have usually subsided, resulting in very few patients discontinuing treatment. Overall, no new safety signals were seen in our study, and no increased risk of long-term infections with acalabrutinib has been observed, confirming that long-term inhibition of BTK does not result in immune impairment.

Overall, my belief is that BTK inhibition is the most efficacious treatment strategy for CLL. Some physicians recommend fludarabine–cyclophosphamide–rituximab chemoimmunotherapy for their patients with mutated *IGHV*, given the potential for long-term progression-free survival (PFS) without a need for ongoing treatment. I counter that a significant number of patients with mutated *IGHV* will relapse after fludarabine–cyclophosphamide–rituximab or develop a secondary malignancy. For patients who relapse, there is a significant risk of a del(17p) relapse and aggressive disease behaviour. Del(17p) is one predictor of a worse outcome with BTK inhibitor therapy. I therefore prefer BTK inhibitor therapy for all patients in need of therapy for CLL who do not have a contraindication. Currently, acalabrutinib is my preference, based on tolerability. I also do not typically add anti-CD20 monoclonal antibody therapy with BTK inhibitors because I am not convinced that anti-CD20 antibodies improve the long-term efficacy of BTK inhibitors, and the anti-CD20 agent is more likely to be the cause of toxicities.

The next step forward will be to use combination therapy consisting of a B cell receptor antagonist plus venetoclax, taking advantage of the synergy they demonstrate, to achieve very rapid and deep remissions.

Acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed/refractory CLL: ASCEND final results (abstract 8015)

Objectives: To compare the efficacy and safety of acalabrutinib monotherapy (100 mg twice-daily) with those of idelalisib–rituximab or bendamustine–rituximab in 310 patients with R/R CLL.

Methods: In a randomized multicentred phase III open-label study, patients were randomized to acalabrutinib (100 mg twice daily, $n = 155$) or investigator's choice of

idelalisib–rituximab ($n = 119$) or bendamustine–rituximab ($n = 36$) until progression or toxicity (Figure 3). Median age of the patients was 67 years, with 16% having del(17p) and 78% having unmutated *IGHV*.

Results: At a median follow-up of 22.0 months, acalabrutinib was associated with significantly prolonged investigator-assessed PFS when compared with idelalisib–rituximab [hazard ratio (HR): 0.27; $p < 0.0001$] or bendamustine–rituximab (HR: 0.29; $p < 0.0001$; Figure 4). The 18-month PFS rates were 82% for acalabrutinib and 48% for idelalisib–rituximab and bendamustine–rituximab combined. In addition, the PFS for acalabrutinib was significantly prolonged compared with that for idelalisib–rituximab and bendamustine–rituximab combined in patients with del(17p) or *TP53* mutations (HR: 0.11; 95% CI: 0.04 to 0.34) and in those with mutated (HR: 0.30; 95% CI: 0.12 to 0.76) or unmutated *IGHV* (HR: 0.28; 95% CI: 0.18 to 0.43). The estimated 18-month overall survival (OS) rate was 88% for both the acalabrutinib and the investigator's choice arms. The ORR was 80% with acalabrutinib compared with 84% with idelalisib–rituximab or bendamustine–rituximab.

Table II lists the common AEs. An AE led to discontinuation of any drug in 14% of those receiving acalabrutinib; 59% of those receiving idelalisib–rituximab; and 17% of those receiving bendamustine–rituximab. The AEs of interest included atrial fibrillation (all-grade: acalabrutinib, 6%; idelalisib–rituximab or bendamustine–rituximab, 3%), major hemorrhage (all-grade: acalabrutinib, 3%; idelalisib–rituximab or bendamustine–rituximab, 3%), grade 3 or greater infections (acalabrutinib, 20%; idelalisib–rituximab or bendamustine–rituximab, 25%), and second primary malignancies, excluding non-melanoma skin cancer (acalabrutinib, 5%; idelalisib–rituximab or bendamustine–rituximab, 2%). Serious AEs reported in 5% or more of the patients across all groups included pneumonia (acalabrutinib: $n = 9$, 6%; idelalisib–rituximab: $n = 12$, 10%; bendamustine–rituximab: $n = 1$, 3%); diarrhea (acalabrutinib: $n = 1$, 1%; idelalisib–rituximab: $n = 16$, 14%; bendamustine–rituximab: $n = 0$); and pyrexia (acalabrutinib: $n = 2$, 1%; idelalisib–rituximab: $n = 8$, 7%; bendamustine–rituximab: $n = 1$, 3%).

Author Conclusions: Final results of the ASCEND trial confirm earlier findings and support the favourable efficacy

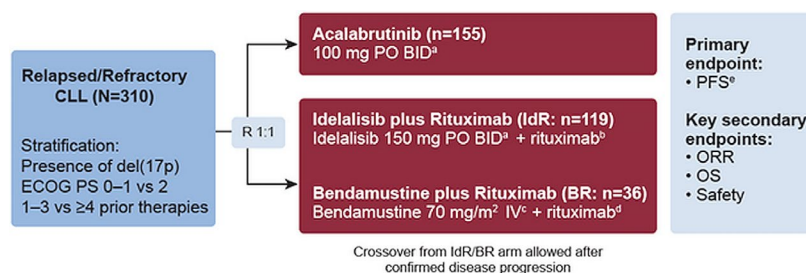


FIGURE 3 ASCEND study design. ^aUntil progression or toxicity. ^b375 mg/m² intravenously (IV) on day 1 of the 1st cycle, and then subsequent doses of 500 mg/m² every 2 weeks for 4 infusions, followed by every 4 weeks for 3 infusions. ^cOn days 1 and 2 of cycles 1–6. ^d375 mg/m² IV on day 1 of the 1st cycle, and then subsequent doses at 500 mg/m² on day 1 of cycles 2–6. ^eProgression-free survival (PFS) was based only on investigator assessment after the interim analysis, when the primary endpoint of independent review committee–assessed PFS was met. CLL = chronic lymphocytic leukemia; ECOG PS = Eastern Cooperative Oncology Group performance status; R1:1 = randomized 1:1; PO = orally; BID = twice-daily; ORR = overall response rate; OS = overall survival.

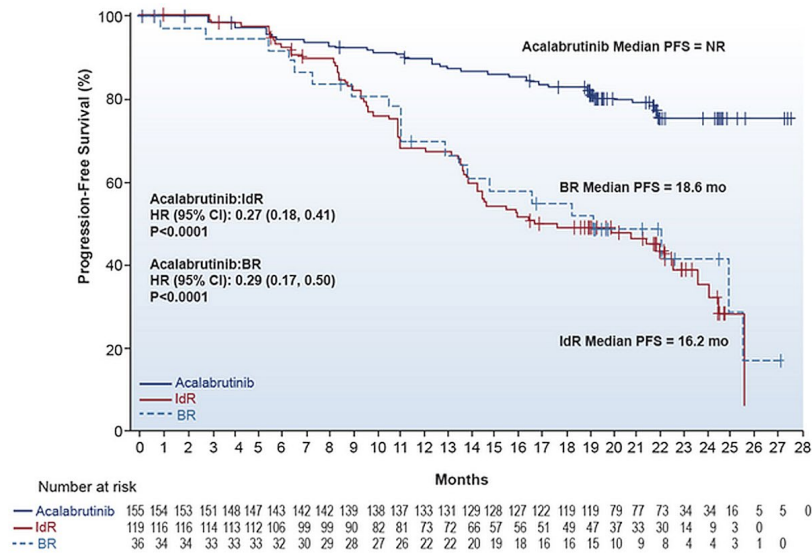


FIGURE 4 Progression-free survival for acalabrutinib compared with bendamustine–rituximab (BR) or idelalisib–rituximab (IdR). HR = hazard ratio; CI = confidence interval; PFS = progression-free survival; NR = not reached.

TABLE II Common adverse events with acalabrutinib, idelalisib–rituximab, and bendamustine–rituximab

Event	Event grade by treatment type [n (%)]					
	Acalabrutinib		Idelalisib–rituximab		Bendamustine–rituximab	
	All	≥3	All	≥3	All	≥3
Headache	34 (22)	1 (1)	7 (6)	0	0	0
Neutropenia	33 (21)	26 (17)	54 (46)	47 (40)	12 (34)	11 (31)
Diarrhea	30 (20)	3 (2)	58 (49)	29 (25)	5 (14)	0
URTI	30 (20)	3 (2)	19 (16)	4 (3)	4 (11)	1 (3)
Cough	25 (16)	0	18 (15)	1 (1)	2 (6)	0
Anemia	24 (16)	19 (12)	11 (9)	8 (7)	4 (11)	3 (9)
Pyrexia	21 (14)	1 (1)	22 (19)	8 (7)	6 (17)	1 (3)
Fatigue	7 (11)	2 (1)	10 (9)	1 (1)	8 (23)	1 (3)
Nausea	11 (7)	0	16 (14)	1 (1)	7 (20)	0
IRR	0	0	9 (8)	2 (2)	8 (23)	1 (3)

URTI = upper respiratory tract infection; IRR = infusion-related reaction.

and safety of acalabrutinib compared with standard-of-care regimens in patients with R/R CLL.

Investigator Commentary: Dr. Sean Dolan

The ASCEND trial compared the efficacy and safety of the second-generation BTK inhibitor acalabrutinib with those of two standard treatment options (idelalisib–rituximab or bendamustine–rituximab). Within the trial, 13 Canadian patients were treated at 6 sites, with 4 patients being treated in our centre at the Saint John Regional Hospital, New Brunswick. Patients included in the study were relatively fit, with no cardiovascular risk factors. Results of our study are now published in the *Journal of Clinical Oncology* and suggest that acalabrutinib is a very effective treatment for CLL, as demonstrated by a superior PFS compared with that for either idelalisib–rituximab or bendamustine–rituximab²⁰.

The safety profile for acalabrutinib was also improved compared with that for idelalisib–rituximab and comparable to that for bendamustine–rituximab. It is worth noting, however, that patients were taking acalabrutinib for a longer duration than they were taking bendamustine–rituximab; a greater number of AES might therefore be expected with acalabrutinib. Although headaches were reported with acalabrutinib, they were easily managed and diminished after a few weeks of treatment.

Though not compared in a head-to-head trial, acalabrutinib appears to have efficacy comparable to that with ibrutinib in trials having similar patient populations. Data, including those from our study, also suggest that cardiovascular toxicities are fewer and that bleeding and bruising are potentially less severe with acalabrutinib than with ibrutinib, making acalabrutinib a more attractive

option for patients with CLL, who tend to be older, with comorbidities. Given the results of our study and others, I would use acalabrutinib, given its improved safety profile, in preference to ibrutinib. I would give acalabrutinib monotherapy to all patients with unmutated *IGHV* and to elderly patients with or without an *IGHV* mutation.

Initial results of a multicentre, investigator-initiated study of MRD-driven time-limited therapy with zanubrutinib, obinutuzumab, and venetoclax (abstract 8006)

Objective: To evaluate the efficacy of time-limited zanubrutinib–obinutuzumab–venetoclax therapy guided by MRD in patients with treatment-naïve CLL.

Methods: In a multicentre, investigator-initiated phase II trial, patients with untreated CLL were given zanubrutinib–obinutuzumab–venetoclax in 28-day cycles (Figure 5). Treatment duration was determined based on MRD levels, with a minimum of 8 cycles. Starting at cycle 7, day 1, and then every 2 cycles thereafter, MRD was assessed in peripheral blood (PB) by flow cytometry (sensitivity > 10⁻⁴). Once undetectable MRD in PB was determined and confirmed in bone marrow, treatment continued for 2 additional cycles. The primary endpoint was frequency of undetectable MRD in PB and marrow.

Results: The study accrued 39 patients with a median age of 59 years. Overall, 28 patients (72%) had unmutated

IGHV, and 6 (15%) had del(17p) or *TP53* mutation. Figure 6 presents the frequency of MRD over time. Overall, 62% of the patients (23 of 37) met the undetectable MRD endpoint and stopped treatment at a median of 8 months. Median time to undetectable MRD in marrow was 6 months (range: 2 to ≥14 months).

The most common treatment-emergent AEs were neutropenia, thrombocytopenia, infusion-related reactions, bruising, and diarrhea (Figure 7). Of special interest, any-grade bleeding, hypertension, and atrial fibrillation occurred in 12.8%, 5.1%, and 2.6% of patients respectively. Lead-in with zanubrutinib–obinutuzumab before venetoclax initiation reduced the proportion of patients with medium and high risk for tumour lysis syndrome to 24% and 5% from 49% and 43% respectively. No patients experienced laboratory or clinical tumour lysis syndrome. Thus far, 10 patients (27%) have discontinued treatment.

Author Conclusions: Zanubrutinib–obinutuzumab–venetoclax is well tolerated and rapidly achieves undetectable MRD.

Investigator Commentary: Dr. Andrew Zelenetz

For a great proportion of systemic regimens in any malignancy, the duration of treatment is based on empirical evidence, which is later refined to develop a standard dosing strategy. An example would be the use of R-CHOP (rituximab, cyclophosphamide–doxorubicin–vincristine–prednisone), whose 8 cycles were based on the dose-limiting toxicity of

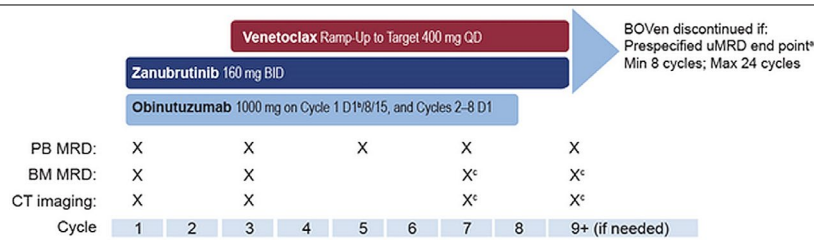


FIGURE 5 Study design. ^aOnce undetectable minimal residual disease (uMRD) is determined in peripheral blood (PB) and confirmed in bone marrow (BM), patients complete 2 additional cycles, followed by confirmatory PB testing for MRD. If PB uMRD_{x2} and BM uMRD_{x1}, therapy is discontinued. ^bObinutuzumab split over days 1 and 2 of cycle 1 if the individual’s absolute lymphocyte count is less than 25,000. ^cBiopsy of BM obtained at screening and at cycle 3, day 1; thereafter, BM is obtained only if disease progresses; uMRD. Computed tomography (CT) imaging is obtained at screening, cycle 3, day 1, cycle 7, day 1, end of treatment, and then every 6 months during post-treatment surveillance. QD = 4 times daily; BID = twice daily; BOVen = venetoclax–zanubrutinib–obinutuzumab.

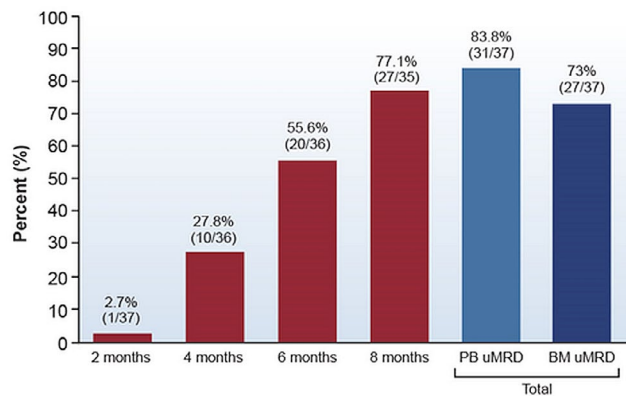


FIGURE 6 Minimal residual disease (MRD) over time. BM = bone marrow; PB = peripheral blood; uMRD = undetectable MRD.

doxorubicin; only much later was the duration reduced to 6 cycles, once it was shown that fewer cycles did not sacrifice the efficacy of treatment.

In our study, we approached the issue of dosing from a different angle, based on the hypothesis that, ideally, therapy for CLL would aim to achieve undetectable MRD, because that endpoint correlates with improved long-term outcome. For patients with undetectable MRD in the PB, we determined whether the result was confirmed in marrow and by computed tomography imaging. One benefit of the approach was that it minimized invasive testing. Patients with undetectable MRD confirmed in marrow received additional months of treatment before stopping therapy. Patients will be eligible for re-treatment with zanubrutinib-venetoclax if relapse is evident. The primary endpoint of the study is the proportion of patients who achieve undetectable MRD.

The initial treatment (2 months of zanubrutinib-obinutuzumab) before the addition of venetoclax increased the percentage of patients with a low risk of tumour lysis syndrome to 70% from 8% at the beginning of the trial. After therapy with zanubrutinib-venetoclax-obinutuzumab, median time to undetectable MRD was 6 months, and more than 50% of patients achieved MRD in marrow at 6 months. The maximum proportion with undetectable MRD has not been reached because some patients remain on therapy. That information will be key to the design of the next study. Overall, the regimen was well tolerated, with grade 3 or greater neutropenia at 15%, lower than we had expected. The use of a second-generation BTK inhibitor with a better safety profile than ibrutinib might explain the lower rates of neutropenia. Our study will provide insight into kinetics and quality of response, and will help to

determine the ideal length of treatment. Our regimen and the acalabrutinib-venetoclax-obinutuzumab regimen are both promising and will aid in determining the value of a triplet combination in CLL.

Fixed-duration venetoclax-obinutuzumab for previously untreated patients with CLL: follow-up of efficacy and safety results from the CLL14 trial (abstract 8027)

Objective: To compare the efficacy and safety of venetoclax-obinutuzumab with those of chlorambucil-obinutuzumab for patients with previously untreated CLL and coexisting conditions.

Methods: In a multinational open-label phase III trial, 432 patients were randomized to receive chlorambucil-obinutuzumab or venetoclax-obinutuzumab (Figure 8). The primary endpoint was investigator-assessed PFS.

Results: After a median follow-up of 39.6 months, PFS continued to be superior for venetoclax-obinutuzumab compared with chlorambucil-obinutuzumab (median: not reached vs. 35.6 months; HR: 0.31; $p < 0.001$). At 3 years, the estimated PFS rate was 81.9% in the venetoclax-obinutuzumab arm and 49.5% in the chlorambucil-obinutuzumab arm. That benefit was consistently observed for all clinical and biologic risk groups, including patients with *TP53* mutation or deletion, and unmutated *IGHV* (Figure 9). No difference in OS was observed between the groups; median OS has not been reached in either group.

At 3 months after treatment completion, a higher rate of undetectable MRD ($<10^{-4}$) in PB by allele-specific oligonucleotide polymerase chain reaction was observed for venetoclax-obinutuzumab than for chlorambucil-obinutuzumab [163

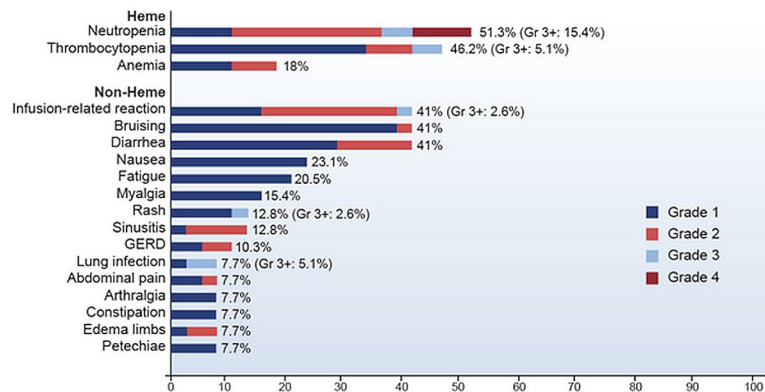


FIGURE 7 Treatment-emergent adverse events (>5% of patients). Heme =hematologic; GERD = gastroesophageal reflux disease.

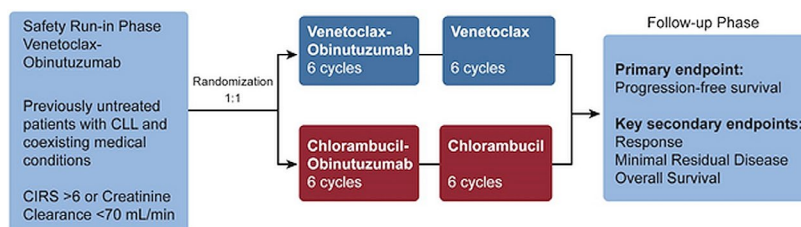


FIGURE 8 Design of the CLL14 trial. CLL = chronic lymphocytic leukemia; CIRS = Cumulative Illness Rating Scale.

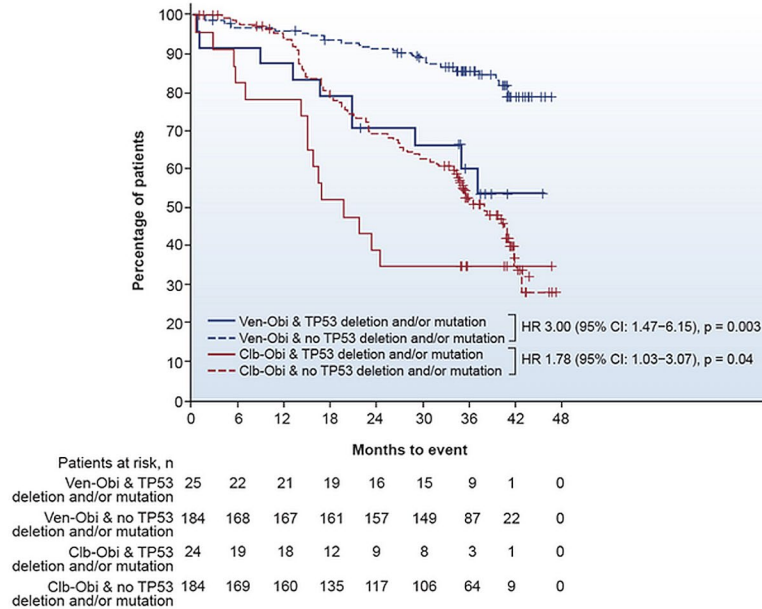


FIGURE 9 Progression-free survival by *TP53* and *IGHV* status. Ven-Obi = venetoclax–obinutuzumab; Clb-Obi = chlorambucil–obinutuzumab; HR = hazard ratio; CI = confidence interval.

of 216 patients (75.5%) vs. 76 of 216 patients (35.2%), $p < 0.001$). Of the patients receiving venetoclax–obinutuzumab, 11 had low MRD ($\geq 10^{-4}$ and $< 10^{-2}$) and 9 had high MRD ($\geq 10^{-2}$) at end of treatment.

Assessment of MRD 18 months after the end of treatment showed that 47.2% of patients in the venetoclax–obinutuzumab arm had undetectable MRD, 13% had low MRD, and 7.9% had high MRD, compared with 7.4% undetectable MRD, 17.1% low MRD, and 26.9% high MRD in the chlorambucil–obinutuzumab arm. Longer PFS was observed in patients with undetectable MRD at the end of treatment than in those with low or high MRD (HR: 0.10; $p < 0.001$). Achievement of complete response compared with partial response did not appear to affect PFS in patients with undetectable MRD. Second primary malignancies were reported in 36 patients in the venetoclax–obinutuzumab arm (17%) and in 22 in the chlorambucil–obinutuzumab arm (10.3%). No new safety signals were observed.

Author Conclusions: The results suggest that the superior efficacy and deep remissions observed after fixed-duration venetoclax–obinutuzumab are maintained during extended follow-up and show the long-term benefits of 12 cycles of venetoclax–obinutuzumab across all known risk categories.

Investigator Commentary: Dr. Othman Al-Sawaf

When the ongoing randomized phase III CLL14 trial in patients with untreated CLL and other pre-existing conditions began at the end of 2015, chlorambucil–obinutuzumab was a standard of care, as shown in the previous CLL11 trial, and it was therefore chosen as the comparator arm. We used a fixed duration of venetoclax–obinutuzumab as the experimental arm. Other trials, such as the recent iLLUMINATE trial, also enrolled unfit patients with treatment-naïve disease;

however, CLL14 enrolled only patients with coexisting conditions or impaired renal function (glomerular filtration rate < 70 mL/min), or both. The iLLUMINATE trial also enrolled fit patients 65 years of age and older²¹. Therefore, with a median score of 8 points on the Cumulative Illness Rating Scale, the patient population in CLL14 carried a considerable burden of comorbidities.

Given that all patients in CLL14 received fixed-duration treatment, it was very important to follow the patients after treatment completion to reach an adequate understanding of the long-term efficacy and safety of the treatments. With a current follow-up of 39.6 months, the 3-year PFS rate is 82% in the venetoclax–obinutuzumab arm. Overall, 21 instances of disease progression were reported, and only 9 of those required a next line of therapy. At the end of treatment, 75% of the patients treated with venetoclax–obinutuzumab had undetectable MRD in PB. At 2 years after treatment completion, approximately half the patients still have undetectable or low MRD.

Overall, the data show that deep and durable MRD levels can be achieved with a fixed-duration approach. Currently, no direct comparison of the two treatment paradigms for CLL is available (that is, fixed-duration compared with continuous approaches). Therefore, for now, it is fair to state that high efficacy is seen with both approaches and that treatment decisions have to be made on an individual basis, depending on patient preferences and comorbidities. Trials such as CLL17 (NCT03701282 at <https://ClinicalTrials.gov/>) will ultimately provide insight into possible differences between the treatment paradigms.

Fixed-duration approaches can be of particular value for patients, because the frequency of toxicities is considerably reduced after treatment completion. Patients with comorbidities who might require several other drugs for treatment of coexisting conditions are especially at risk

for drug interactions. Limiting treatment duration might therefore reduce the chances of interactions between medications. So far, no long-term toxicities, such as late-onset neutropenia, have been observed. We are continuing to follow patients particularly to capture secondary malignancies, which usually require longer follow-up for signal detection.

Because it currently seems that efficacy is comparable for both continuous BTK inhibition and venetoclax-based fixed-duration treatment, the presence of comorbidities and the risk profile of each treatment become even more important for decision-making. For patients with pre-existing heart conditions or a requirement for anti-coagulation therapy, venetoclax–obinutuzumab might be a better option than BTK inhibitors. On the other hand, some patients do not want regular antibody infusions, as required in the venetoclax–obinutuzumab scheme, and they therefore opt for continuous treatment with a BTK inhibitor such as ibrutinib or acalabrutinib.

Currently, it is not totally clear how these treatments might interfere with a possible COVID-19 infection. Society guidelines, such as the ones provided by the American Society of Hematology, generally recommend refraining from the use of CD20 antibodies, because such treatment impairs the humoral immune response, which could ultimately worsen the outcome of COVID-19 infection. Currently, in patients in urgent need of therapy, we prefer to give ibrutinib to reduce the necessity for visits to our clinic

and other medical facilities. If possible, we also try to delay treatment initiation for patients with CLL so as to lower the risk of COVID-19 transmission.

Effect of adding ublituximab to ibrutinib on PFS, ORR, and MRD negativity in previously treated high-risk CLL: final results of the GENUINE phase III study (abstract 8022)

Objective: To evaluate the efficacy and safety of adding ublituximab to ibrutinib in patients with R/R high-risk CLL.

Methods: 117 Patients with one or more of del(17p), del(11q), and TP53 mutations were randomized 1:1 to receive ibrutinib alone or with ublituximab (Figure 10). Median age in the group was 66 years, and patients in each arm had received a median of 1 prior line of therapy (range: 1–5 lines). The primary endpoint was investigator-assessed ORR.

Results: Best ORR and complete response rate were 93% and 20% for ibrutinib–ublituximab and 78% and 5% for ibrutinib alone. At a median follow-up of 42 months, PFS was significantly prolonged for ibrutinib–ublituximab compared with ibrutinib monotherapy (HR: 0.455; $p = 0.016$; Figure 11). For patients with del(11q) mutations, PFS was similar in both the ibrutinib–ublituximab and ibrutinib monotherapy arms. Undetectable MRD (in marrow and PB) was reported for 46% of patients receiving ibrutinib–ublituximab and 7% of those receiving ibrutinib monotherapy. Except for infusion reactions and neutropenia, which

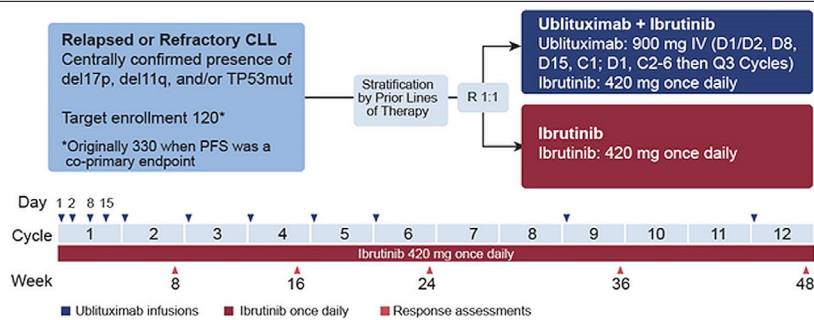


FIGURE 10 GENUINE study design. CLL = chronic lymphocytic leukemia; mut = mutation; PFS = progression-free survival; R1:1 = 1:1 randomization; IV = intravenous; D = day; C = cycle; Q3 = every 3.

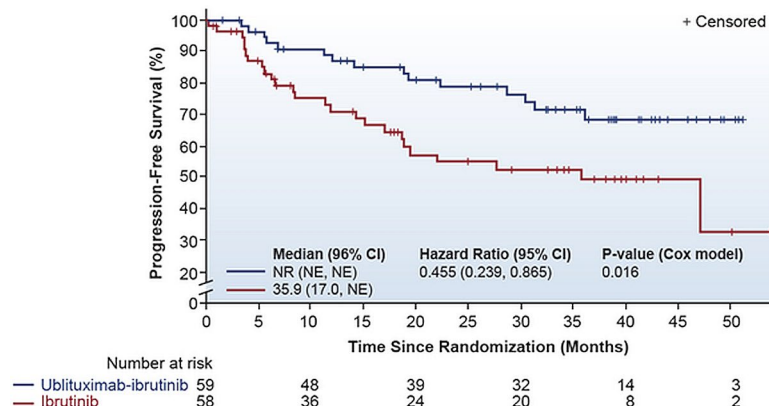


FIGURE 11 Progression-free survival. CI = confidence interval; NR = not reached; NE = not evaluable.

were higher with ibrutinib–ublituximab, AEs were comparable between the study arms (Table III). Of special interest, atrial fibrillation occurred at a rate of 14% in patients treated with ibrutinib–ublituximab and of 7% in those treated with ibrutinib monotherapy; myalgia occurred at rates of 14% and 24% respectively.

Author Conclusions: The GENUINE randomized trial is the first to demonstrate a PFS benefit with the addition of a CD20 molecular antibody to ibrutinib. Increasing depth of response after the first year of treatment supports maintenance therapy with ublituximab.

Investigator Commentary: Dr. Jeff Sharman

Whether combining a CD20 monoclonal antibody with a BTK inhibitor will improve the efficacy of treatment for patients with CLL is currently unknown. Early studies looking at the addition of rituximab to ibrutinib in treatment-naïve or R/R disease did not observe a significant improvement in PFS with the addition of rituximab^{22,23}. Obinutuzumab was added to ibrutinib in the ILLUMINATE study; however, given the study design, the contribution of obinutuzumab could not be determined²¹. Ibrutinib is approved by Health Canada as monotherapy or in combination with obinutuzumab despite the lack of evidence to show that the addition of an anti-CD20 antibody improves efficacy⁵.

The GENUINE study compared ibrutinib monotherapy with ibrutinib–ublituximab in patients with R/R CLL with high-risk molecular characteristics, including either del(17p), TP53 mutation, or del(11q). Our study showed that ORR and PFS were superior for ibrutinib–ublituximab compared with ibrutinib monotherapy. Interestingly, the benefit was seen exclusively among patients with del(17p) or TP53 mutation; no differential benefit was observed in patients with del(11q). The addition of ublituximab resulted in additional toxicities, such as infusion-related reactions and neutropenia, at rates comparable to those reported

in previous studies. The rate of atrial fibrillation was also higher in the combination group, but the small number of events limited the ability to determine whether the effect was causally related.

The biggest limitation of the study was difficulty in identifying sufficient numbers of patients with high-risk features and relapsed disease at the participating centres. As a result, the study design was changed midway through to focus on ORR rather than on PFS as the primary endpoint. That modification will likely prevent registration of the ublituximab–ibrutinib combination in high-risk R/R CLL. Nonetheless, the study follows the recent ELEVATE-TN study²⁴, which demonstrated a benefit of adding obinutuzumab to acalabrutinib in treatment-naïve CLL and presents another clinical circumstance in which adding an anti-CD20 therapy to a BTK inhibitor might provide benefit.

CLINICAL IMPACT IN CANADA

Q&A with Drs. Sean Dolan and Mona Shafey

Q: How do the efficacy and safety profiles of acalabrutinib compare with those of other treatments for CLL?

A (Dolan): The efficacy of acalabrutinib is favourable for an oral therapy and appears comparable to that with ibrutinib. Acalabrutinib is also very effective in high-risk patients, such as those with unmutated *IGHV* or del(17p), suggesting that outcomes can be equally good for patients with adverse prognostic factors. The ASCEND trial showed a vastly superior PFS for acalabrutinib compared with bendamustine–rituximab or idelalisib–rituximab, which is remarkable after a short follow-up of just 1.5 years. In addition, the safety profile of acalabrutinib is very satisfactory, especially when considering the minimal AEs reported in older patients with CLL. The lower rates of atrial fibrillation and hypertension with acalabrutinib are of key importance. Although there is a clear signal for an increase in headaches with acalabrutinib in clinical trials, I have not seen this in my practice, and the headaches reported in clinical trials were easily managed with caffeine or acetaminophen, or both. Acalabrutinib therefore appears to be an excellent treatment choice for patients with CLL.

A (Shafey): The ASCEND trial demonstrated clear superiority in both efficacy and safety for acalabrutinib compared with idelalisib–rituximab, which was the selected comparator in more than 75% of patients on the control arm. Discontinuation rates because of AEs were also significantly higher with idelalisib–rituximab than with acalabrutinib. Despite some differences in patient populations, the efficacy of acalabrutinib appears to be similar to that of ibrutinib. From a safety perspective, the follow-up to date with acalabrutinib shows significantly fewer cardiac events than have been seen with ibrutinib. Even with longer follow-up, it is unlikely that cumulative rates will catch up to those seen with ibrutinib. Other AEs such as bleeding appear to be a class effect of BTK inhibitors, because they have been reported with both ibrutinib and acalabrutinib. Headaches do appear to be a unique AE with acalabrutinib, but in my own experience, those headaches are mild and easily managed with coffee or acetaminophen, and they dissipate after a few weeks.

TABLE III Most common adverse events for ibrutinib with or without ublituximab

Event	Event grade by treatment type (n)			
	Ublituximab–ibrutinib		Ibrutinib	
	All	3–4	All	3–4
Diarrhea	56	10	47	5
Infusion reaction	53	3	0	0
Cough	42	0	31	0
Fatigue	39	3	38	5
Neutropenia	36	19	21	12
Nausea	34	0	33	3
Arthralgia	31	2	21	3
Contusion	31	0	36	2
Insomnia	31	0	17	2
Thrombocytopenia	31	2	21	5
URTI	31	2	28	2

URTI = upper respiratory tract infection.

Q: Is the follow-up long enough to assess the long-term efficacy and safety profile of acalabrutinib?

A (Dolan): The response duration for acalabrutinib appears to exceed 80% after a few years, which is in line with that for ibrutinib. Given the class effect, we would expect both agents to have similar efficacy. However, we may see some improvements with acalabrutinib, because fewer patients are likely to discontinue the drug because of toxicities. We will have to wait a bit longer to give a final comment on the long-term safety of acalabrutinib. However, the data thus far are certainly encouraging, with most side effects dissipating after 6 months to 1 year. In clinical trials and my personal practice alike, patients do seem to tolerate acalabrutinib very well, making it an excellent option for most patients.

A (Shafey): As a threshold, we tend to use 5 years of follow-up to assess long-term safety. For cardiac events such as hypertension, we look at the cumulative effect; atrial fibrillation tends to occur earlier. The average follow-up with acalabrutinib is 54 months, which is pretty reasonable to assess long-term outcomes. Many physicians might be reluctant to change to acalabrutinib from ibrutinib, but the mounting evidence showing lower rates of cardiac events with acalabrutinib justifies the change. If I had the option, I would choose acalabrutinib over ibrutinib for all patients except for those on a proton pump inhibitor, given the drug–drug interactions with that class of antacids. Given the twice-daily dosing with acalabrutinib, a consideration of any compliance issues is important. However, if given the choice, most patients would choose acalabrutinib over ibrutinib because of the reduced cardiac toxicity.

Q: Can the combination of venetoclax–zanubrutinib–obinutuzumab achieve sufficient MRD negativity to justify using this multi-agent combination?

A (Dolan): For younger patients with CLL, we want to improve long-term survival through the use of aggressive multi-agent protocols. The BTK inhibitors provide lengthy remissions, but MRD data are not as strong. A multi-agent regimen is therefore needed to improve OS. The venetoclax–zanubrutinib–obinutuzumab combination is promising, but we will need to see final outcomes to determine whether MRD correlates with an OS advantage. The increase in infection rates seen with monoclonal antibodies are a cause for some concern. It will also be important to determine whether second malignancies increase with this regimen.

A (Shafey): The venetoclax–zanubrutinib–obinutuzumab regimen is a potent group of drugs and should be given only as a fixed-duration therapy. Patients want effective therapies that, to avoid toxicities, do not have to be given long-term. However, there is still much we do not know about MRD, including the length of time that patients achieving MRD negativity can remain off treatment, and whether some patients can be cured. Trying to achieve MRD is an admirable goal if it can translate into an OS advantage. However, more therapies will lead to an increase in toxicity, and so the OS advantage must be weighed against the duration of therapy needed to achieve MRD. The AEs reported with the venetoclax–zanubrutinib–obinutuzumab regimen are as we would expect from the individual agents included, with no surprising toxicities. The higher rates of neutropenia are a

concern, but rates of febrile neutropenia were low and thus did not translate into clinically relevant complications. I would accept the slightly higher toxicity of this regimen if it meant that patients could have improved efficacy, a short duration of treatment, and a longer off-treatment interval.

Q: Based on the CLL14 trial, can the use of venetoclax–obinutuzumab be justified in the first-line setting?

A (Dolan): The MRD results reported in the CLL14 trial are encouraging, especially if MRD can be used as a surrogate for OS. It is clear that we need combination regimens to achieve sufficient MRD, and the combination of a monoclonal antibody with venetoclax appears to provide a synergistic response. However, we have to wait to see if there is an OS advantage before implementing this combination into practice as first-line therapy.

A (Shafey): The CLL14 trial showed a clear PFS advantage for venetoclax–obinutuzumab over chlorambucil–obinutuzumab, regardless of prognostic risk group. There is no question that this combination achieves a deep remission, but there is, unfortunately, no OS advantage to date, which is important when looking at cost-effectiveness of therapies and where they fit into the treatment algorithm. If no OS advantage accrues, it might make more sense to reserve this treatment option for patients with R/R disease. The concerns with greater instances of deaths and second malignancies also have to be assessed further; they might be attributable to the frailer population.

Q: Are we ready for the MRD-driven approach to treatment?

A (Dolan): With the right tools available, MRD data would be valuable in guiding treatment decisions in clinical practice. For example, if we could reduce cycles of chemotherapy in patients achieving MRD negativity, we could tailor treatment in some patients to avoid unnecessary toxicity.

A (Shafey): I do not think we are ready for MRD-guided therapy in clinical practice yet, but I do believe we are headed that way in the future. A number of unknowns with MRD remain—such as, how we define it, how it will be measured in clinical practice, and how we tailor therapy based on results. We also do not know how many months we should continue to treat beyond MRD negativity and whether we can re-treat with the same therapy when patients become MRD-positive. We have to measure MRD in a simple way, such as through PB, using a modality available across labs, such as flow cytometry. We then have to decide how frequently to measure MRD and how to treat patients who remain MRD-positive.

Q: Would you give a monoclonal antibody with a BTK inhibitor?

A (Dolan): I tend to use BTK inhibitors mostly as monotherapy. In the second line, there might be some advantage to adding a monoclonal antibody in terms of providing a sustained response. Based on the GENUINE study, there might also be some value in using the ublituximab–ibrutinib combination in high-risk patients in the first line. However, it is hard to know whether ublituximab is more effective than other monoclonal antibodies such as obinutuzumab. The new monoclonal antibodies appear to be more efficacious than rituximab.

A (Shafey): There is no published advantage of adding rituximab or obinutuzumab to a BTK inhibitor that would justify the additional safety risk. However, the GENUINE

study is the first randomized trial to demonstrate a PFS advantage of adding a monoclonal antibody to a BTK inhibitor. To justify the additional toxicity, we have to wait for longer follow-up to see if there is an OS advantage of adding ublituximab to ibrutinib.

Q: What factors do you consider when determining which treatment to give first-line to patients with CLL? Would you do anything differently during the COVID-19 pandemic?

A (Dolan): The choice of treatment comes down to patient preference, at least in part. Some patients want a fixed duration of treatment; others want to avoid the need for infusions. During the COVID-19 pandemic, we are using less bendamustine to avoid bone marrow suppression. We are also avoiding monoclonal antibodies by using single agents such as BTK inhibitors to minimize the need for infusions and to prevent further immunosuppression. In the future, if available, I would give a triplet therapy such as acalabrutinib–venetoclax–obinutuzumab to achieve a deep remission. In less-fit patients, I would choose acalabrutinib monotherapy, and in the R/R setting, I would give a BTK inhibitor with a monoclonal antibody or venetoclax–obinutuzumab if the patient had previously been given a BTK inhibitor. I do believe that finding the best multi-agent, non-chemotherapy regimen to achieve deep and lasting remissions is the next step in the treatment of CLL.

A (Shafey): Patient preference is a key factor in making treatment decisions. Some patients do not want to visit for intravenous treatment and will choose a BTK inhibitor; others want a fixed duration of treatment and will accept the need for infusions. I tend to offer clinical trials where possible to take advantage of novel treatment options. During the COVID-19 pandemic, I have been delaying the initiation of therapy where possible. However, I still choose the best available treatment option when it is necessary. It is hard to say whether a higher risk of infection is created with a monoclonal antibody than with a BTK inhibitor, given that the disadvantage of prolonged treatment is that experiencing toxicity becomes more likely over time. Future treatment goals should be to achieve MRD negativity with an OS benefit, using the shortest duration of therapy possible to reduce toxicity. Combination therapy is the way of the future, and we will have to determine how best to include MRD as a marker for OS. Chimeric antigen receptor T cell therapy is also promising and could provide a treatment option that is less toxic than stem-cell transplantation.

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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: SD was a primary investigator for the ASCEND and ELEVATE-TN studies, funded by AstraZeneca. AC and SD received funding from AstraZeneca for the development of this document. MS has received honoraria from AstraZeneca, Janssen, AbbVie, Roche, Gilead, and Bristol–Myers Squibb. MS is also involved in clinical trials with AstraZeneca, AbbVie, Roche, and Bristol Myers Squibb.

AUTHOR AFFILIATIONS

*Dalhousie University, St. John, NB; †IMPACT Medicom Inc., Toronto, ON; ‡University of Calgary, Calgary, AB.

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