blood advances

COUNTERPOINT Is BTKi or BCL2i preferable as first novel therapy in patients with CLL? The case for BCL2i

John F. Seymour[1]

Peter MacCallum Cancer Centre, Royal Melbourne Hospital and University of Melbourne, Melbourne, VIC, Australia

This article has a companion Point by Brem and O'Brien.

We are fortunate to have a number of highly effective and generally well-tolerated treatment options for patients with chronic lymphocytic leukemia (CLL).[1,2] These novel targeted agents have contributed greatly to the improvement in overall survival (OS) observed in population-based registries.[3] Critically, in the frontline context where early treatment has no proven long-term benefits, but also in the relapse context, the initiation of treatment should be guided by the presence of active disease, as well defined by the iwCLL guidelines.[4]

Although there has been an appropriate profound shift toward the preferential use of targeted agents over chemoimmunotherapy, it remains important to identify the modest subset of patients for whom frontline FCR (fludarabine, cyclophosphamide, rituximab) chemoimmunotherapy is deliverable with acceptable safety and has a substantial likelihood of achieving cure; these patients have IGHV mutation but no *TP53* aberrations, are aged <65 years with a low comorbidity score (CIRS <6), and have adequate renal function (creatinine clearance [CrCl] >50-70 mL/min).[5-7] In my practice, and supported by the recently updated 2021 European Society of Medical Oncology (ESMO) guidelines,[5] the first consideration to be discussed with the patient is whether cure is potentially achievable with frontline FCR given their specific biologic risk profile, and, if so, after detailed discussions, including the potential risk of secondary myelodysplasia or treatment-related acute myeloid leukemia (t-MDS/AML)[8] whether they wish to pursue that option.

There is still a small cohort of patients with very late relapses many years after well-tolerated frontline chemoimmunotherapy, where retesting shows that *TP53* aberrations are absent, for whom repeat chemoimmunotherapy is a potential consideration.[5] This is a very small subset of patients, and the outcome for most patients with repeat exposure to chemoimmunotherapy is relatively poor.[9] Repeat exposure to DNA-damaging genotoxic therapies will also increase the risk of development of t-MDS/AML in the long term.[8] Thus, I do not support such an approach and strongly recommend treatment with one of the targeted-agent approaches in all patients with disease relapsing after chemoimmunotherapy.

In the current context of COVD-19, regardless of planned treatment, but especially if an anti-CD20 antibody is incorporated, ensuring that the patient is fully vaccination is critical.[10,11] However, I take time to convey the suboptimal efficacy of vaccination responses in patients with CLL and reinforce the ongoing need for behavioral risk-minimization strategies, including encouraging all family members and close contacts to also be vaccinated.[10]

Despite the above considerations, most patients will be unsuitable for chemoimmunotherapy.[5] Thus, the major choice to be confronted is the preferred initial targeted agent approach; in most jurisdictions this is continuous single-agent BTK inhibitor (BTKi), predominantly ibrutinib (RESONATE and RESONATE-2),[12-15] or a time-limited combination of venetoclax and anti-CD20 antibody (24 months of treatment with rituximab [MURANO study] or 12 months of treatment using obinutuzumab [CLL14 study; Ven-Obi]).[16-20] Unfortunately, there are no head-to-head comparisons for these approaches in the frontline or relapsed-disease context. In the frontline setting, there are 3 indirect cross-trial comparisons but they reported conflicting results: one did not find any difference in progression-free survival (PFS) between ibrutinib-rituximab and Ven-Obi,[21] one found that ibrutinib was inferior to Ven-Obi,[22] and the third, which also included acalabrutinib-based treatment, found that acalabrutinib-obinutuzumab was superior to Ven-Obi or ibrutinib-obinutuzumab.[23] However, methodologic flaws and the imbalance of baseline factors across trials make these indirect comparisons of questionable value.[24] In the setting of relapsed disease, one "real-world" comparison suggested a longer PFS with venetoclax compared with ibrutinib as first targeted agent,[25] whereas a network meta-analysis reported no difference in PFS or OS for venetoclax compared with an ibrutinib-based approach.[26] Given this inconclusive evidence base regarding the

superior efficacy of either approach, our considerations should include additional factors, such as tolerability, long-term toxicity, societal cost, and options for effective subsequent treatments.

Because BTKi's were approved earlier, the duration of follow-up of clinical trial data are longer, and many clinicians will have greater and longer experiences with this approach. The major supporting data for their use in the frontline setting come from the RESONATE-2 trial in which patients aged ≥65 years without del(17p) were randomized to ibrutinib, 420 mg daily indefinitely, or the questionable "standard of care," single-agent chlorambucil.[14,15] The median age was 73 years, and 31% of patients had a Cumulative Illness Rating Scale (CIRS) score >6. Response rates were high, but conventional complete remissions were rare. Although ibrutinib was unequivocally superior to the weak standard arm, our focus now is on the long-term outcomes: efficacy and toxicity. Recent long-term follow-up data describe a 61% PFS rate at 6.5 years with no apparent impact of IGHV mutational status.[15] Although with currently shorter follow-up, these favorable outcomes were supported by the ALLIANCE trial, which also included patients aged ≥65 years, but with del(17p) allowed (although present in just 6%); the 2-year PFS rate was 87% overall, and it was 74% in those with *TP53* aberrancy.[27] There are also additional data supporting the efficacy of ibrutinib, albeit in combination with rituximab, in a younger population aged <70 years; the 3-year PFS rate was 89%.[28]

A gap in the disease spectrum of CLL is the lack of inclusion of patients with *TP53* aberrancy in meaningful numbers in these frontline studies. This has been addressed, in part, by a retrospective aggregated analysis of 89 patients with del(17p) or *TP53mut* from four trials (some combination with anti-CD20 antibody); the 4-year PFS rate was 79%,[29] and two small single-arm trials each reported 6-year PFS rates ∼60%.[30,31] Although ibrutinib, as well as other targeted agents, are definitively superior to chemoimmunotherapy for treating *TP53*-aberrant disease, this genomic abnormality still carries an adverse prognostic impact, as do treatment after failure of multiple prior lines of therapy and a complex karyotype (≥3 aberrations).[32]

Despite this favorable efficacy, a number of concerning issues are related to the widespread application of continuous BTKi therapy with ibrutinib. In the context of the carefully selected patient populations in prospective clinical trials, the ibrutinib cessation rate due to toxicity was reported to be 15% to 30% at 3 to 5 years.[13-15,32] However in the "real-world" setting, cessation rates vary, with some reports replicating clinical trial data up to 6 months of follow-up,[33] and others finding much higher cessation rates, up to 42% at a median follow-up of 17 months.[34] Discontinuation rates are also higher in patients with greater comorbidity burden, contributing to inferior outcomes in such patients.[35] This is an important consideration when comparing outcomes with those reported with Ven-Obi in the CLL14 patient population; comorbidity burden was much higher than in the RESONATE-2 population.

Although an infrequent cause for drug cessation, atrial fibrillation (AF) is a concerning adverse effect that occurs in up to 15% of unselected ibrutinib-treated patients within the first 3 to 5 years,[32,36] with higher rates in those with a history of AF or the presence of risk factors, such as male sex, age >75 years, valvular heart disease, or concomitant hypertension, all of which are common in patients with CLL.[36-38] AF is inconvenient and creates management complexities, including difficult decision making regarding anticoagulation in the context of the established antiplatelet effects of BTKi's and the inherent 5% to 10% risk of major bleeding.[39-41] However, ventricular arrhythmias are usually fatal, and the risk of documented ventricular arrhythmias, cardiac arrest, or sudden cardiac death may be increased more than fourfold with ibrutinib treatment.[42,43] These cardiovascular adverse events continue to occur throughout the treatment period; thus, cumulative rates over the full expected treatment duration for patients treated in the frontline will be higher still where the median duration of drug exposure potentially exceeds 10 years. This cumulative cardiovascular morbidity burden is especially concerning for hypertension, with grade ≥3 toxicity reported in 32% of patients in the frontline setting and in 25% of those treated at relapse with 5-year follow-up.[32] Development of these cardiovascular adverse events is associated with an increased mortality risk.[43]

Beyond the morbidity burden, there is a huge personal and societal cost associated with the widespread utilization of the continuous therapy paradigm, with projections for US per-patient out-of-pocket costs to reach $57 000, lifetime treatment costs to reach $604 000, and overall annual societal costs for CLL management to reach $5.13 billion by 2025.[44] The preferential use of Ven-Obi over ibrutinib would reduce the total societal cost of care by $300 942 per patient over the first 3 years of treatment.[45]

Although all of the above issues are real and manifest, there are also theoretical biological reasons to avoid a continuous treatment paradigm that does not achieve deep remissions, leaving a substantial persisting measurable disease burden. Serial analyses of the persisting disease and its underlying clonal genomic composition during ibrutinib treatment showed ongoing clonal instability and acquisition of additional mutations.[46,47] This mutational rate was highest among cases that carried *TP53* aberrations.[46] This may have implications for the likelihood of acquisition of BTK-resistance mutations, such as C481S or PLCG2,[48] because the presence of an *TP53* aberration is an independent predictor for the acquisition of such mutations, along with elevated levels of β_2-microglobulin and lactate dehydrogenase, and relapsed disease status.[49] In this so-called "4-factor" model, even in the frontline setting, patients with three of these risk factors have a predicted 50% likelihood of developing an ibrutinib-resistance mutation within the first 4 years of treatment.[49]

Some of these cardiovascular toxicities may be ameliorated by the preferential use of better-tolerated, but at least as effective (as shown in the relapsed/refractory [R/R] setting in direct randomized comparisons), and more selective second-generation covalent BTKi's, such as acalabrutinib[50] or zanubrutinib.[51] However, the broader issues arising from the continuous therapy paradigm persist.

The data supporting the frontline approval of Ven-Obi are from the CLL14 study, in which patients with a CIRS score >6 or CrCl <70 mL/min but ≥30 mL/min were randomized to Ven-Obi (time-limited total treatment duration of 12 months for all patients, regardless of the depth of response) or the same duration of chlorambucil-obinutuzumab.[18] The eligibility criteria resulted in a population with a median age of 72 years (identical to the RESONATE-2 ibrutinib population) but with a very high comorbidity burden; the median CIRS score was 9, and 86% had a CIRS score >6. Also, del(17p) was not an exclusion criterion, and 14% of patients in the study had *TP53* aberrancy. As with RESONATE-2, the investigational arm (here Ven-Obi) was superior to the standard of care for PFS, but the major focus was on the outcomes of patients treated with Ven-Obi. Follow-up was

shorter than for the RESONATE-2 cohort; median 52.4-month follow-up data were reported recently.[20,52] Although overall response rates were similar to those seen with ibrutinib, complete remissions were confirmed in 49.5%, and many responses were very deep; undetectable minimal residual disease (MRD) at the conventional 10^{-4} level was attained in 76% in the peripheral blood (PB), including a 70% PB undetectable MRD rate for those with del(17p). Highly sensitive next-generation sequencing assays revealed that 40% of Ven-Obi–treated patients achieved MRD levels of $<10^{-6}$ at 3 months after completion of therapy in PB analysis.[20] The depth of remission (using the conventional 10^{-4} threshold) is strongly predictive of the durability of remission after time-limited venetoclax combination therapy.[17,20]

The reported PFS rates at key time points for the entire Ven-Obi–treated frontline cohort are 88% at two years and 74% at four years.[19,20] In contrast to the ibrutinib data, IGHV mutational status retains prognostic relevance with time-limited venetoclax treatment; those with unmutated disease have a greater risk for PFS events (hazard ratio [HR], 2.14) attributable to more rapid re-emergence of MRD and disease regrowth. Concordant with the ibrutinib analyses, outcomes for patients with disease carrying del(17p) were also inferior, with a median PFS of 49.0 months (HR, 3.19; 95% confidence interval, 1.66-6.14). However, disease resistance on therapy was rare, and a number of these PFS events were due to unrelated deaths,[53] as may be expected in an elderly and comorbid population. Preclinical studies have shown that venetoclax's mechanism of action is independent of TP53,[54] and continuous single-agent clinical data from a less comorbid, but heavily pretreated, R/R population showed durable disease control[55,56] despite del(17p). Nevertheless, although not affecting the overall response rate (HR, 1.3) or complete remission rate (HR, 1.2), *TP53* aberrancy retains an adverse prognostic impact on PFS in multivariate analyses of single-agent treatment in the R/R setting (HR, 2.2).[57] This might be mitigated when combination therapy is applied; *TP53mut* status had only a modest and nonstatistically significant adverse impact on PFS outcome when venetoclax-rituximab was given using a 2-year time-limited treatment schedule.[17] When prognostic factors for OS were explored across the range of novel agent classes, including BTKi and BCL2-inhibitors (BCL2i) (here in combination with rituximab from the MURANO study), the same factors impacted outcomes equally with both approaches.[58] Thus, with the exception of IGHV mutational status, it appears that conventional clinical and laboratory adverse prognostic factors are largely shared across BTKi and BCL2i treatments. A key challenge to the field is to analyze genomic and molecular data more deeply with the goal of identifying specific biologic subsets of patients who may be optimally treated with either approach; however, suitable predictive tools are lacking.[59]

The practical, logistical, and morbidity burdens of initiating venetoclax-based treatment with the well-documented issues of the weekly dose ramp-up, tumor lysis syndrome (TLS) prophylaxis and monitoring, the need for IV infusions of antibody, and the potential need for multiple (albeit, usually brief) inpatient admissions are very substantial.[60,61] These concerns are further amplified during the current COVID pandemic by the greater need for patient contact with the health care system, as well as the inherent immunosuppressive effects of the anti-CD20 antibody on serological responses to vaccinations, including COVID-19.[10,11] However, beyond the short-term burdens of the ramp-up period, and the moderate infection risk (15-20% grade 3+) during the combination-therapy period, ongoing toxicity burden is modest.[16,20,62] Initial suggestions of an increased risk for second malignancies have been resolved with longer follow-up.[20] Further, there is strong evidence that patient quality of life actually improves under venetoclax treatment, despite these burdens.[63]

As with the BTKi's, continuous exposure to venetoclax provides a selection pressure for the development of resistance mutations; the best characterized are acquired mutations in *BCL2* that impair venetoclax binding but maintain its antiapoptotic actions.[64-66] Other resistance mechanisms, including upregulation of other antiapoptotic BCL2 family members and metabolic reprogramming, also contribute to acquired resistance.[67,68] Avoidance of the development of such acquired resistance through utilization of combination therapies to attain deep remissions, which then allow time-limited treatment, is a key overarching goal.[69,70] The clinical realization of this goal appears to be possible, because acquisition of these BCL2-resistance mutations among patients with disease progressing after time-limited therapies has not been reported, acknowledging the very small numbers of cases analyzed to date.[20,70]

Retention of venetoclax sensitivity at disease recurrence after time-limited therapy has two major implications: retreatment with reattainment of disease control is feasible, and conventionally defined PFS may not be the appropriate means to measure the duration of benefit of venetoclax or the best comparator to assess efficacy relative to continuous BTKi's. The potential for effective retreatment was established in a phase 1b combination study,[70] as well as in the MURANO cohort, with some patients attaining second undetectable MRD responses.[71] Given this retained efficacy with venetoclax retreatment, even in just a proportion of cases, a better measure of efficacy may be the "time to venetoclax failure," which incorporates the clinical benefit of these subsequent responses.[70]

The question of effective treatment sequencing using these drug classes is a potential consideration. Prospective trials and "real-world" data sets have established the efficacy of venetoclax following failure of a BTKi.[33,72,73] The ability to treat effectively using the opposite sequence has been established, with two recent reports describing high response rates and a median PFS of 32 and 34 months for BTKi after venetoclax failure.[74,75] Thus, there are equally strong data supporting the use of these largely non–cross-resistant drug classes in either sequence.[76]

In summary, we are fortunate to have both of these highly effective treatment options for patients with CLL: continuous BTKi and time-limited BCL2i. In the absence of direct phase 3 comparative data, neither approach has clear evidence of superior efficacy, as measured by PFS (time to first disease progression), with the exception of perhaps those with unmutated IGHV status or *TP53* aberrancy in the frontline setting, where BTKi appears to achieve longer initial disease control. However, this may be mitigated by the capacity to retreat with venetoclax-based therapies, acknowledging that the regulatory and funding status of this approach will likely vary across jurisdictions. There will be individual patients with specific organ function impairment or comorbidities for whom one approach may be strongly preferred (eg, BTKi in those with severe renal failure and venetoclax in those with a high risk for cardiac arrhythmias). In the short term, particularly over the first three to six months of therapy, initiation of BTKi therapy is far more logistically straightforward and less burdensome for patients; these considerations may hold sway during the current COVID-pandemic, although BTKi therapy itself also impairs the serological response to COVID-19 vaccination.[77] However, when we return to normal circumstances, for most

patients in whom the expected duration of time on a BTKi would be beyond two to three years, the cumulative toxicity and cost burden of continuous BTKi's, especially the cardiovascular risk profile, persuade me that time-limited BCL2i is the generally preferred approach. Patients and prescribers can be confident that most patients will achieve deep remissions, with undetectable MRD status predicting prolonged disease control, and know that retreatment with venetoclax at progression or class switch to a BTKi will deliver prolonged disease control. The major unmet need is the development of effective therapies for patients with disease that is resistant to both novel drug classes and for whom outcomes are truly dismal.[78]

Authorship

Contribution: J.F.S. wrote the manuscript.

Conflict-of-interest disclosure: J.F.S. is a member of the board of directors or advisory committee for AbbVie, AstraZeneca, Bristol Myers Squibb, F. Hoffmann-La Roche Ltd., Gilead, Janssen, Mei Pharma, MorphoSys, and Sunesis; is a member of the speaker's bureau for AbbVie, Celgene, and F. Hoffmann-La Roche Ltd; has received honoraria from AbbVie, AstraZeneca, Bristol Myers Squibb, F. Hoffmann-La Roche Ltd, Gilead, Janssen, Mei Pharma, MorphoSys, and Sunesis; has received research funding from AbbVie, Celgene, F. Hoffmann-La Roche Ltd, and Janssen; and has acted as a consultant for Celgene and F. Hoffmann-La Roche Ltd.

ORCID Profile: J.F.S., 0000-0003-2188-6835.

Correspondence: John F. Seymour, Department of Haematology, Peter MacCallum Cancer Centre, 305 Grattan St, Melbourne, VIC 3000, Australia; e-mail: john.seymour@petermac.org.

References

1. Morabito F, Gentile M, Seymour JF, Polliack A. Ibrutinib, idelalisib and obinutuzumab for the treatment of patients with chronic lymphocytic leukemia: three new arrows aiming at the target. *Leuk Lymphoma.* 2015;56(12):3250-3256.
2. Burger JA. Integrating new therapies for chronic lymphocytic leukemia. *Cancer J.* 2021;27(4):275-285.
3. Alrawashdh N, Sweasy J, Erstad B, McBride A, Persky DO, Abraham I. Survival trends in chronic lymphocytic leukemia across treatment eras: US SEER database analysis (1985-2017). *Ann Hematol.* 2021;100(10):2501-2512.
4. Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood.* 2018;131(25):2745-2760.
5. Eichhorst B, Robak T, Montserrat E, et al; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2021;32(1):23-33.
6. Thompson PA, Tam CS, O'Brien SM, et al. Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated chronic lymphocytic leukemia. *Blood.* 2016;127(3):303-309.
7. Fischer K, Bahlo J, Fink AM, et al. Long-term remissions after FCR chemoimmunotherapy in previously untreated patients with CLL: updated results of the CLL8 trial. *Blood.* 2016;127(2):208-215.
8. Carney DA, Westerman DA, Tam CS, et al. Therapy-related myelodysplastic syndrome and acute myeloid leukemia following fludarabine combination chemotherapy. *Leukemia.* 2010;24(12):2056-2062.
9. Tam CS, O'Brien S, Plunkett W, et al. Long-term results of first salvage treatment in CLL patients treated initially with FCR (fludarabine, cyclophosphamide, rituximab). *Blood.* 2014;124(20):3059-3064.
10. Chatzikonstantinou T, Herishanu Y, Montserrat E, et al. COVID-19 and chronic lymphocytic leukemia: where we stand now. *Cancer J.* 2021;27(4):328-333.
11. Teh BW, Tam CS. Between a rock and a hard place: COVID-19 vaccination and patients on rituximab therapy. *Leuk Lymphoma.* 2021;62(12):2820-2822.
12. Byrd JC, Brown JR, O'Brien S, et al; RESONATE Investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med.* 2014;371(3):213-223.
13. Munir T, Brown JR, O'Brien S, et al. Final analysis from RESONATE: up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *Am J Hematol.* 2019;94(12):1353-1363.
14. Burger JA, Tedeschi A, Barr PM, et al; RESONATE-2 Investigators. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med.* 2015;373(25):2425-2437.
15. Barr P, Owen C, Robak T, et al. Up to seven years of follow-up in the RESONATE-2 study of first-line ibrutinib treatment for patients with chronic lymphocytic leukemia. *J Clin Oncol.* 2021;39(15_suppl):7523.
16. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med.* 2018;378(12):1107-1120.
17. Kater AP, Wu JQ, Kipps T, et al. Venetoclax plus rituximab in relapsed chronic lymphocytic leukemia: 4-year results and evaluation of impact of genomic complexity and gene mutations from the MURANO phase III study. *J Clin Oncol.* 2020;38(34):4042-4054.
18. Fischer K, Al-Sawaf O, Bahlo J, et al. Venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med.* 2019;380(23):2225-2236.
19. Al-Sawaf O, Zhang C, Tandon M, et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 2020;21(9):1188-1200.
20. Al-Sawaf O, Zhang C, Lu T, et al. Minimal residual disease dynamics after venetoclax-obinutuzumab treatment: extended off-treatment follow-up from the randomized CLL14 study. *J Clin Oncol.* 2021;39(36):4049-4060. .
21. Davids M, Moreno C, Cuneo A, et al. Indirect treatment comparison analysis of venetoclax plus obinutuzumab with standard frontline regimens for chronic lymphocytic leukemia [abstract]. *Leuk Lymphoma.* 2020;61(suppl 1):188-189. Abstract 2101.
22. Sudhapalli P, Piena M, Palaka A, et al. Systematic literature review and network meta-analysis comparing therapies for treatment naïve patients with chronic lymphocytic leukemia [abstract]. *HemaSphere.* 2020;4(suppl 1):320. Abstract EP725.
23. Molica S, Giannarelli D, Montserrat E. Comparison between venetoclax-based and Bruton tyrosine kinase inhibitor-based therapy as upfront treatment of chronic lymphocytic leukemia (CLL): a systemic review and network meta-analysis. *Clin Lymphoma Myeloma Leuk.* 2021;21(4):216-223.

24. Seymour JF. The tools to choose: applying indirect treatment comparisons to the selection of frontline targeted therapy for CLL. *Leuk Lymphoma.* 2021;62(10):2299-2302.

25. Eyre TA, Lamanna N, Roeker LE, et al. Comparative analysis of targeted novel therapies in relapsed, refractory chronic lymphocytic leukaemia. *Haematologica.* 2021;106(1):284-287.

26. Molica S, Giannarelli D, Mirabelli R, Levato L, Shanafelt TD. The magnitude of improvement in progression-free survival with targeted therapy in relapsed/refractory chronic lymphocytic leukemia based on prognostic risk category: a systematic review and meta-analysis. *Leuk Lymphoma.* 2019;60(7):1644-1649.

27. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. *N Engl J Med.* 2018;379(26):2517-2528.

28. Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. *N Engl J Med.* 2019;381(5):432-443.

29. Allan JN, Shanafelt T, Wiestner A, et al. Long-term efficacy of first-line ibrutinib treatment for chronic lymphocytic leukemia (CLL) with 4 years of follow-up in patients with TP53 aberrations (del(17p) or TP53 mutation): a pooled analysis from 4 clinical trials [abstract]. *Blood.* 2020;136(suppl 1):2219. Abstract 2219.

30. Ahn IE, Tian X, Wiestner A. Ibrutinib for chronic lymphocytic leukemia with *TP53* alterations. *N Engl J Med.* 2020;383(5):498-500.

31. Sivina M, Kim E, Wierda WG, et al. Ibrutinib induces durable remissions in treatment-naïve patients with CLL and 17p deletion and/or TP53 mutations. *Blood.* 2021;138(24):2589-2592.

32. O'Brien S, Furman RR, Coutre S, et al. Single-agent ibrutinib in treatment-naïve and relapsed/refractory chronic lymphocytic leukemia: a 5-year experience. *Blood.* 2018;131(17):1910-1919.

33. Hillmen P, Diels J, Healy N, Iraqi W, Aschan J, Wildgust M. Ibrutinib for chronic lymphocytic leukemia: international experience from a named patient program. *Haematologica.* 2018;103(5):e204-e206.

34. Mato AR, Nabhan C, Thompson MC, et al. Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: a real-world analysis. *Haematologica.* 2018;103(5):874-879.

35. Gordon MJ, Kaempf A, Sitlinger A, et al. The chronic lymphocytic leukemia comorbidity index (CLL-CI): a three-factor comorbidity model. *Clin Cancer Res.* 2021;27(17);4814-4824.

36. Archibald WJ, Rabe KG, Kabat BF, et al. Atrial fibrillation in patients with chronic lymphocytic leukemia (CLL) treated with ibrutinib: risk prediction, management, and clinical outcomes. *Ann Hematol.* 2021;100(1):143-155.

37. Brown JR, Moslehi J, O'Brien S, et al. Characterization of atrial fibrillation adverse events reported in ibrutinib randomized controlled registration trials. *Haematologica.* 2017;102(10):1796-1805.

38. Wiczer TE, Levine LB, Brumbaugh J, et al. Cumulative incidence, risk factors, and management of atrial fibrillation in patients receiving ibrutinib. *Blood Adv.* 2017;1(20):1739-1748.

39. Kamel S, Horton L, Ysebaert L, et al. Ibrutinib inhibits collagen-mediated but not ADP-mediated platelet aggregation. *Leukemia.* 2015;29(4):783-787.

40. Wang J, Zhao A, Zhou H, Zhu J, Niu T. Risk of bleeding associated with ibrutinib in patients with B-cell malignancies: a systematic review and meta-analysis of randomized controlled trials. *Front Pharmacol.* 2020;11:580622.

41. Chai KL, Rowan G, Seymour JF, Burbury K, Carney D, Tam CS. Practical recommendations for the choice of anticoagulants in the management of patients with atrial fibrillation on ibrutinib. *Leuk Lymphoma.* 2017;58(12):2811-2814.

42. Lampson BL, Yu L, Glynn RJ, et al. Ventricular arrhythmias and sudden death in patients taking ibrutinib. *Blood.* 2017;129(18):2581-2584.

43. Salem JE, Manouchehri A, Bretagne M, et al. Cardiovascular toxicities associated with ibrutinib. *J Am Coll Cardiol.* 2019;74(13):1667-1678.

44. Chen Q, Jain N, Ayer T, et al. Economic burden of chronic lymphocytic leukemia in the era of oral targeted therapies in the United States. *J Clin Oncol.* 2017;35(2):166-174.

45. Cho SK, Manzoor BS, Sail KR, et al. Budget impact of 12-month fixed treatment duration venetoclax in combination with obinutuzumab in previously untreated chronic lymphocytic leukemia patients in the United States. *PharmacoEconomics.* 2020;38(9):941-951.

46. Landau DA, Sun C, Rosebrock D, et al. The evolutionary landscape of chronic lymphocytic leukemia treated with ibrutinib targeted therapy. *Nat Commun.* 2017;8(1):2185.

47. Burger JA, Landau DA, Taylor-Weiner A, et al. Clonal evolution in patients with chronic lymphocytic leukaemia developing resistance to BTK inhibition. *Nat Commun.* 2016;7(1):11589.

48. Woyach JA. Mechanisms of resistance to BTK inhibitors in patients with chronic lymphocytic leukemia. *Clin Adv Hematol Oncol.* 2021;19(7):436-438.

49. Ahn IE, Tian X, Ipe D, et al. Prediction of outcome in patients with chronic lymphocytic leukemia treated with ibrutinib: development and validation of a four-factor prognostic model. *J Clin Oncol.* 2021;39(6):576-585.

50. Byrd JC, Hillmen P, Ghia P, et al. Acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia: results of the first randomized phase III trial. *J Clin Oncol.* 2021;39(31):3441-3452.

51. Hillmen P, Brown JR, Eichhorst BF, et al. ALPINE: zanubrutinib versus ibrutinib in relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma. *Future Oncol.* 2020;16(10):517-523.

52. Tausch E, Schneider C, Yosifov D, et al. Genetic markers and outcome in front line obinutuzumab plus chlorambucil or venetoclax – updated analysis of the CLL14 trial [abstract]. *HemaSphere.* 2021;5(suppl 2):26. Abstract S144.

53. Seymour JF. Venetoclax plus obinutuzumab therapy for front-line treatment of chronic lymphocytic leukaemia. *Lancet Oncol.* 2020;21(9):1128-1130.

54. Anderson MA, Deng J, Seymour JF, et al. The BCL2 selective inhibitor venetoclax induces rapid onset apoptosis of CLL cells in patients via a *TP53*-independent mechanism. *Blood.* 2016;127(25):3215-3224.

55. Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. *Lancet Oncol.* 2016;17(6):768-778.

56. Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax for patients with chronic lymphocytic leukemia with 17p deletion: results from the full population of a phase II pivotal trial [published correction appears in *J Clin Oncol.* 2019;37(25):2299]. *J Clin Oncol.* 2018;36(19):1973-1980.

57. Roberts AW, Ma S, Kipps TJ, et al. Efficacy of venetoclax in relapsed chronic lymphocytic leukemia is influenced by disease and response variables. *Blood.* 2019;134(2):111-122.

58. Soumerai JD, Ni A, Darif M, et al. Prognostic risk score for patients with relapsed or refractory chronic lymphocytic leukaemia treated with targeted therapies or chemoimmunotherapy: a retrospective, pooled cohort study with external validations. *Lancet Haematol.* 2019;6(7):e366-e374.

59. Rossi D. Quest of biomarkers for venetoclax-treated CLL. *Blood.* 2019;134(2):97-98.

60. Tambaro FP, Wierda WG. Tumour lysis syndrome in patients with chronic lymphocytic leukaemia treated with BCL-2 inhibitors: risk factors, prophylaxis, and treatment recommendations. *Lancet Haematol.* 2020;7(2):e168-e176.

61. Wierda WG, Tambaro FP. How I manage CLL with venetoclax-based treatments. *Blood.* 2020;135(17):1421-1427.

62. Davids MS, Hallek M, Wierda W, et al. Comprehensive safety analysis of venetoclax monotherapy for patients with relapsed/refractory chronic lymphocytic leukemia. *Clin Cancer Res.* 2018; 24(18):4371-4379.

63. Cochrane T, Enrico A, Gomez-Almaguer D, et al. Impact of venetoclax monotherapy on the quality of life of patients with relapsed or refractory chronic lymphocytic leukemia: results from the phase 3b VENICE II trial [published online ahead of print 11 Oct 2021]. *Leuk Lymphoma.*

64. Blombery P, Anderson MA, Gong JN, et al. Acquisition of the recurrent Gly101Val mutation in BCL2 confers resistance to venetoclax in patients with progressive chronic lymphocytic leukemia. *Cancer Discov.* 2019;9(3):342-353.

65. Blombery P, Thompson ER, Nguyen T, et al. Multiple BCL2 mutations cooccurring with Gly101Val emerge in chronic lymphocytic leukemia progression on venetoclax. *Blood.* 2020; 135(10):773-777.

66. Tausch E, Close W, Dolnik A, et al. Venetoclax resistance and acquired *BCL2* mutations in chronic lymphocytic leukemia. *Haematologica.* 2019;104(9):e434-e437.

67. Guièze R, Liu VM, Rosebrock D, et al. Mitochondrial reprogramming underlies resistance to BCL-2 inhibition in lymphoid malignancies. *Cancer Cell.* 2019;36(4):369-384.e13.

68. Blombery P. Mechanisms of intrinsic and acquired resistance to venetoclax in B-cell lymphoproliferative disease. *Leuk Lymphoma.* 2020;61(2):257-262.

69. Seymour JF, Ma S, Brander DM, et al. Venetoclax plus rituximab in relapsed or refractory chronic lymphocytic leukaemia: a phase 1b study. *Lancet Oncol.* 2017;18(2):230-240.

70. Ma S, Seymour JF, Brander DM, et al. Efficacy of venetoclax plus rituximab for relapsed CLL: 5-year follow-up of continuous or limited-duration therapy. *Blood.* 2021;138(10):836-846.

71. Wu JQ, Seymour JF, Eichhorst B, et al. Impact of unfavorable genetics on minimal residual disease (MRD) response to venetoclax + rituximab retreatment in relapsed or refractory chronic lymphocytic leukemia (R/R CLL): MURANO phase 3 substudy [abstract]. *HemaSphere.* 2021;5(suppl 2):265. Abstract EP599.

72. Jones JA, Mato AR, Wierda WG, et al. Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. *Lancet Oncol.* 2018; 19(1):65-75.

73. Tam CS, Seymour JF. Choosing and sequencing novel drugs in CLL: dealing with an embarrassment of riches? *Ann Oncol.* 2017; 28(5):920-921.

74. Lin VS, Lew TE, Handunnetti SM, et al. BTK inhibitor therapy is effective in patients with CLL resistant to venetoclax. *Blood.* 2020; 135(25):2266-2270.

75. Mato AR, Roeker LE, Jacobs R, et al. Assessment of the efficacy of therapies following venetoclax discontinuation in CLL reveals BTK inhibition as an effective strategy. *Clin Cancer Res.* 2020;26(14): 3589-3596.

76. Lew TE, Tam CS, Seymour JF. How I treat chronic lymphocytic leukemia after venetoclax. *Blood.* 2021;138(5):361-369.

77. Chung DJ, Shah GL, Devlin SM, et al. Disease- and therapy-specific impact on humoral immune responses to COVID-19 vaccination in hematologic malignancies. *Blood Cancer Discov.* 2021;2(6): 568-576.

78. Lew TE, Lin VS, Cliff ER, et al. Outcomes of patients with CLL sequentially resistant to both BCL2 and BTK inhibition. *Blood Adv.* 2021;5(20):4054-4058.

DOI 10.1182/bloodadvances.2019001205