# A retrospective comparison of venetoclax alone or in combination with an anti-CD20 monoclonal antibody in R/R CLL

Anthony R. Mato,[1,*] Lindsey E. Roeker,[1,*] Toby A. Eyre,[2] Chadi Nabhan,[3] Nicole Lamanna,[4] Brian T. Hill,[5] Danielle M. Brander,[6] Paul M. Barr,[7] Frederick Lansigan,[8] Bruce D. Cheson,[9] Arun K. Singavi,[10] Maryam Sarraf Yazdy,[9] Nirav N. Shah,[10] John N. Allan,[11] Erica B. Bhavsar,[11] Joanna Rhodes,[12] Kaitlin Kennard,[12] Stephen J. Schuster,[12] AnnaLynn M. Williams,[7] Alan P. Skarbnik,[13] Andre H. Goy,[13] Julie M. Goodfriend,[1] Colleen Dorsey,[1] Catherine C. Coombs,[14] Hande Tuncer,[15] Chaitra S. Ujjani,[16] Ryan Jacobs,[17] Allison M. Winter,[5] John M. Pagel,[18] Neil Bailey,[18] Anna Schuh,[2] Mazyar Shadman,[16] Andrea Sitlinger,[6] Hanna Weissbrot,[4] Sivraj Muralikrishnan,[8] Andrew Zelenetz,[1] Amy A. Kirkwood,[19] and Christopher P. Fox[20]

[1]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; [2]Cancer and Haematology Centre, Oxford University Hospitals, NHS Foundation Trust, Oxford, United Kingdom; [3]Aptitude Health, Chicago, IL; [4]Department of Medicine, Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center, New York, NY; [5]Department of Hematology and Medical Oncology, Taussig Cancer Center, Cleveland Clinic, Cleveland, OH; [6]Department of Medicine, Duke University Cancer Center, Durham, NC; [7]Department of Medicine, Wilmot Cancer Institute, University of Rochester, Rochester, NY; [8]Department of Medicine, Norris Cotton Cancer Center, Dartmouth University, Lebanon, NH; [9]Department of Medicine, Lombardi Cancer Center, Georgetown University, Washington, DC; [10]Department of Medicine, Medical College of Wisconsin Cancer Center, Milwaukee, WI; [11]Department of Hematology/Oncology, Weill Cornell Medical Center, New York, NY; [12]Department of Medicine, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; [13]Department of Medicine, John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ; [14]Department of Medicine, University of North Carolina Cancer Center, Chapel Hill, NC; [15]Department of Medicine, Cancer Center, Tufts Medical Center, Boston, MA; [16]Department of Medicine, Fred Hutchinson Cancer Center, University of Washington, Seattle, WA; [17]Levine Cancer Institute, Carolinas Medical Center, Charlotte, NC; [18]Swedish Cancer Center, Seattle, WA; [19]Cancer Research UK & UCL Cancer Trials Centre, University College London, London, United Kingdom; and [20]Nottingham University Hospitals, NHS Foundation Trust, Nottingham, United Kingdom

## Key Points

- Data demonstrate comparable efficacy between VENmono and VEN + CD20 therapy in a heavily pretreated, high-risk CLL cohort.

Venetoclax (VEN) is approved for relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) as monotherapy (VENmono) or in combination with rituximab. Whether VEN plus anti-CD20 (VENcombo) is superior to VENmono is unknown. We conducted a multicenter, retrospective cohort analysis comparing 321 CLL patients treated with VENmono vs VENcombo across the United States and the United Kingdom. We examined demographics, baseline characteristics, dosing, adverse events, response rates, and outcomes. The primary endpoints were progression-free survival (PFS) and overall survival (OS), estimated by Kaplan-Meier method, in patients treated with VENmono vs VENcombo. Univariate and bivariate analyses were performed with COX regression. Three hundred twenty-one CLL patients were included (3 median prior treatments, 78% prior ibrutinib). The overall response rates (ORRs) were similar (VENmono, 81% ORR, 34% complete remission [CR] vs VENcombo, 84% ORR, 32% CR). With a median follow-up of 13.4 months, no differences in PFS and OS were observed between the groups. In unadjusted analyses, the hazard ratios (HRs) for PFS and OS for VENmono vs VENcombo were HR 1.0 (95% confidence interval [CI], 0.6-1.8; $P = .7$) and HR 1.2 (95% CI, 0.6-2.3; $P = .5$), respectively. When adjusting for differences between the cohorts, the addition of an anti-CD20 antibody in combination with VEN did not impact PFS (HR, 1.0; 95% CI, 0.5-2.0; $P = .9$) or OS (HR, 1.1; 95% CI, 0.4-2.6; $P = .8$). We demonstrate comparable efficacy between VENmono and VENcombo in a heavily pretreated, high-risk, retrospective cohort, in terms of both response data and survival outcomes. Prospective studies are needed to validate these findings.

© 2019 by The American Society of Hematology

# Introduction

Venetoclax (VEN) is approved as monotherapy (VENmono) or in combination with rituximab (R) for relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL).[1] Whether VEN-R (VR) is superior to VENmono is unknown and has not been studied and is not planned to be studied in randomized trials.[2-4] Answering this question is now more pressing in view of the accumulating recent data that fail to show a progression-free survival (PFS) benefit to adding R or ublituximab to ibrutinib in front-line and R/R CLL.[5-8] This lack of difference contrasts with the suggested benefit when R or ublituximab and ibrutinib were studied in nonrandomized phase 2 studies.[9,10] In the clinical trial that led to VR approval, patients were not heavily pretreated, with very few (2%; 8/389) exposed to ibrutinib or idelalisib. These characteristics differ from those of patients treated with VEN in other clinical trials or outside of studies.[11] We aimed to compare response and survival outcomes among CLL patients treated with VEN plus an anti-CD20 monoclonal (VENcombo) antibody against patients treated with VENmono in the R/R setting. Therefore, we conducted a multicenter, international study examining the outcomes of 321 CLL patients treated with VEN.

## Methods

We conducted a retrospective cohort study of R/R CLL patients treated with VEN across 24 US and 42 UK academic and community centers in partnership with the UK CLL Forum and the CLL Collaborative Study of Real World Evidence.

To define the study cohort, investigators were asked to identify and collect data on all CLL patients treated with VEN at their center/practice, including those treated on clinical studies. Utilizing a standardized case report form, investigators collected data through medical chart review of CLL patients, including demographics, disease characteristics, VEN dosing, tumor lysis syndrome (TLS) risk and prophylaxis, and adverse events (AEs). Detailed pre-VEN data were collected to confirm that VENmono vs VENcombo groups represented a balanced comparison based on potential confounders.

To understand patterns of VEN use, we collected data on its administration as monotherapy and, if paired, which additional agent was given. Regarding VEN dosing, we collected data on dose reductions, dose interruptions, and duration of interruptions. Regarding VEN combination therapy, investigators were asked if VEN was given as (1) monotherapy or (2) paired with another agent, and if "paired" was selected, they were then asked to select (1) R, (2) obinutuzumab, (3) ibrutinib, or (4) other agent(s). Specific data on "other" combinations were not collected. Patients treated with ibrutinib and VEN were not included in this analysis. Data regarding dose intensity and number of cycles of the paired agent were not collected. For the planned stratified analyses, patients were categorized as VENmono or VENcombo (combination group included patients who were treated with VEN plus either R or obinutuzumab).

TLS risk was defined according to guidance provided in the VEN US Food and Drug Administration package insert as low, medium, or high risk. Investigators were asked to define TLS events by Howard criteria.[12] Response rates were defined by International Workshop on Chronic Lymphocytic Leukemia criteria as complete remission (CR), partial remission, stable disease, and progressive

**Table 1. Baseline characteristics**

| | Number of patients with available data | VEN monotherapy (n = 270) | VEN combination (n = 51; 38 R, 13 obinutuzumab) |
|---|---|---|---|
| Median age VEN start | 321 | 68 (37-91) | 66 (45-88) |
| Median prior therapies | 321 | 3 (0-12) | 2 (0-15) |
| Prior ibrutinib | 319 | 79% | 73% |
| Del17p | 323 | 43% | 44% |
| TP53 mutation | 154 | 37% | 25% |
| IGHV unmutated | 118 | 83% | 82% |
| Complex karyotype | 213 | 43% | 25% |

disease.[13] Because of study design, response assessments and follow-up intervals were not standardized, but time to best response was collected. Because of the relative difficulty in identifying and collecting a comprehensive list of AEs retrospectively, investigators were asked to perform detailed chart reviews to accurately gather data on select grade ≥3 AEs (Common Terminology Criteria for Adverse Events criteria), including neutropenia, thrombocytopenia, diarrhea, and febrile neutropenia. Timing, frequency, causality, and duration of AEs were not collected.

The primary study endpoints were PFS and overall survival (OS) in patients treated with VENmono compared with VEN plus an anti-CD20 antibody. PFS and OS were estimated by the Kaplan-Meier method.[14] To test the association between VEN pairing status and survival outcomes, we used COX regression to perform univariate and bivariate analyses to compare PFS and OS for patients stratified by VENmono vs VENcombo. We adjusted for potential confounders, including chromosome deletion 17p (del17p) status, chromosome deletion 11q (del11q) status, Bruton tyrosine kinase inhibitor exposure in a prior line of therapy, number of lines of prior therapies, patient age at start of VEN, and complex karyotype (3 or more abnormalities). For all regression analyses, hazard ratios (HRs) with 95% confidence intervals (CIs) are reported. All other comparisons were descriptive. Statistical analyses were performed using STATA 10.1 (Stata Statistical Software: released 10, 2007; StataCorp LP, College Station, TX). The study was institutional review board approved.

## Results

### Baseline characteristics

A total of 321 CLL patients were included (VENmono, n = 270; VENcombo, n = 51). A similar proportion of patients was treated in the context of a clinical trial in both groups (n = 7, 16% VENcombo vs n = 32, 12% VENmono). Baseline characteristics stratified by VENmono vs VENcombo are included in Table 1. Patient characteristics were similar except that more patients on VENmono had complex karyotype (≥3 abnormalities, P = .04), and VENmono patients were more heavily pretreated (median 3 prior therapies vs 2, P = .03). Both of these differences might be expected to bias results in favor of the VENcombo group, and therefore, the planned comparison with the study hypothesis was deemed to be appropriate. Moreover, 89% were previously treated with a kinase inhibitor, and 78% received prior ibrutinib (vs 2% reported in the MURANO cohort of VEN plus R).[1] The median time from most recent therapy to starting VEN was 1.1 months.

**Table 2. Adverse events**

| | Number of patients with available data | VEN monotherapy, % | VEN combination, % | P |
|---|---|---|---|---|
| TLS (overall) | 321 | 11.5 | 5.8 | .07 |
| Grade 3 neutropenia | 233 | 40.4 | 34 | .45 |
| Grade 3 thrombocytopenia | 232 | 30.8 | 23 | .27 |
| Neutropenic fever | 232 | 8.6 | 2.3 | .37 |
| Grade 3 diarrhea | 230 | 8.7 | 5.1 | .36 |
| Discontinuation rate | 321 | 41 | 39 | .77 |

## AEs

Available data on AEs stratified by VENmono vs VENcombo are included in Table 2. AEs appeared to be comparable between the VENmono and VENcombo groups. Overall, TLS risk was estimated to be low in 38%, intermediate in 34%, and high in 28%. TLS occurred in 9.7% of patients (9 total clinical events). The overall discontinuation rates for VENmono vs VENcombo were similar at 41% and 39%, respectively.

Following dose escalation, 70% of patients achieved a stable VEN dose of 400 mg daily; 33% required ≥1 dose interruption, and 26% required ≥1 dose reduction. VEN dose interruptions (≥1, 35% vs 29%) and dose reductions (≥1, 28% vs 22%) were comparable between VENmono and VENcombo groups, respectively.

## Response and survival outcomes

For the entire cohort, the overall response rate (ORR) to VEN was 82% (33% CR) and was similar with VENmono (81% ORR, 34% CR) vs VENcombo (84% ORR, 32% CR). The median time to best response was 2.5 months for VENmono and 2.1 months for VENcombo. With a median follow-up of 13.4 months for the entire cohort (VENmono 13.7 vs VENcombo 12.8 months), a total of 91 progression events and 71 deaths were observed. Although the estimated median PFS and OS were not reached, the estimated 12-month PFS and OS were 74% and 82%, respectively, for the entire cohort. In unadjusted analyses, the HRs for PFS and OS for VENmono vs VENcombo were HR 1.0 (95% CI, 0.6-1.8; $P = .7$) and HR 1.2 (95% CI, 0.6-2.3; $P = .5$), respectively. Figure 1 depicts comparable PFS and OS stratified VENmono vs VENcombo in the R/R setting.

Table 3 includes bivariate analyses of VEN pairing status (VENmono vs VENcombo) adjusted for pre-VEN prognostic factors and their impact on HRs for PFS and OS. When adjusting for complex karyotype, number of prior therapies, del17p, del11q, IGHV status, prior ibrutinib exposure, and prior chemoimmunotherapy exposure, PFS and OS remained comparable between the VENmono and VENcombo groups.

When adjusting for observed differences between the cohorts, including both complex karyotype and the number of prior therapies, the addition of an anti-CD20 antibody in combination with VEN did not impact PFS (HR, 1.0; 95% CI, 0.5-2.0; $P = .9$) or OS (HR, 1.1; 95% CI, 0.4-2.6; $P = .8$) as compared with VENmono.

## Discussion

Given the recent broadening of the approval for VEN in R/R CLL, it is important to study whether a clinical benefit exists for VEN plus
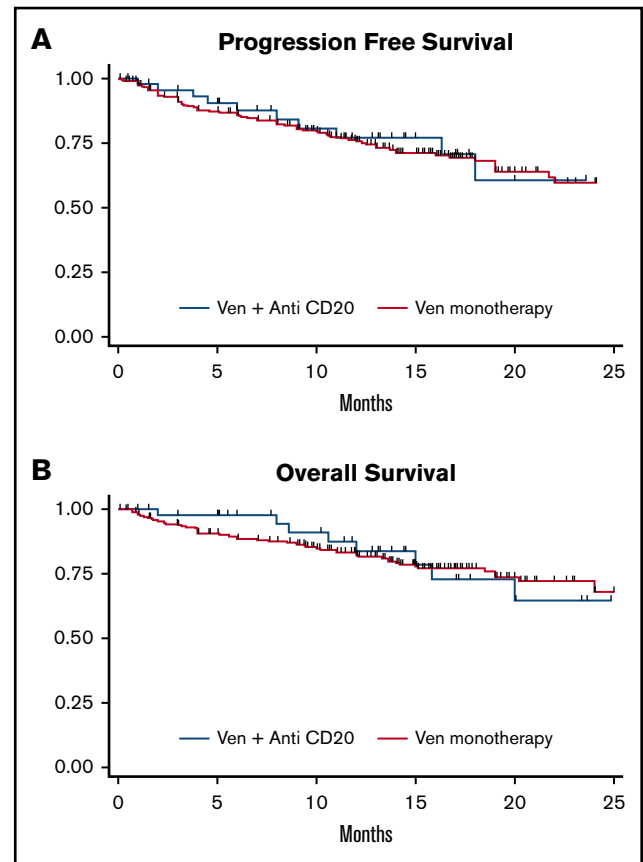


**Figure 1. PFS and OS.** PFS (A) and OS (B) stratified by VEN monotherapy (VENmono) and VEN plus anti-CD20 (VENcombo) in R/R CLL.

anti-CD20 over VENmono.[2-4] With both options available, clinicians may seek guidance in the appropriate selection of these regimens. In the absence of randomized studies, we sought to answer this question by retrospectively analyzing data on patients treated across various centers in the United States and the United Kingdom.

We demonstrate comparable efficacy between VENmono and VEN plus CD20-directed therapy in a heavily pretreated, high-risk cohort, in terms of both response data and survival outcomes. In adjusted and unadjusted models, there were no differences in PFS and OS between these cohorts. PFS and OS were similar between the groups when controlling for complex karyotype, prior ibrutinib exposure, and adjusting for the number of prior therapies. Our findings were particularly surprising because we could not identify a patient population who benefited from the addition of an anti-CD20 antibody to VEN in terms of response and survival outcomes.

Although our analysis is limited by the retrospective design, relatively short follow-up, and small sample size in the VENcombo group, the length of follow-up presented here is comparable to previously published prospective data that led to the approval of VEN.[2-4,15] Longer follow-up of patients receiving VEN may be necessary to understand the depth and durability of response as well as the full impact of VENcombo therapy. There were important differences in our treatment cohorts, with the VENmono group including patients who were more heavily pretreated and more likely to have a complex karyotype. Despite these poor prognostic

**Table 3. Adjusted bivariate analysis**

| | PFS | OS |
|---|---|---|
| Unadjusted VEN combo (vs mono) | HR, 1.0; CI, 0.6-1.8; P = .7 | HR, 1.2; CI, 0.6-2.3; P = .5 |
| VEN combo (vs mono) + number prior therapies | HR, 1.0; CI, 0.6-1.7; P = .9 | HR, 1.2; CI, 0.6-2.2; P = .5 |
| VEN combo (vs mono) + del17p | HR, 1.0; CI, 0.6-1.8; P = .12 | HR, 1.3; CI, 0.7-2.7; P = .4 |
| VEN combo (vs mono) + del11p | HR, 1.4; CI, 0.5-1.5; P = .3 | HR, 1.2; CI, 0.5-2.7; P = .4 |
| VEN combo (vs mono) + complex karyotype | HR, 1.0; CI, 0.5-2.1; P = .9 | HR, 1.1; CI, 0.4-2.6; P = .18 |
| VEN combo (vs mono) + IGHV unmutated | HR, 1.1; CI, 0.5-2.3; P = .8 | HR, 1.0; CI, 0.4-2.5; P = .9 |
| VEN combo (vs mono) + prior ibrutinib | HR, 0.9; CI, 0.5-1.8; P = .9 | HR, 1.1; CI, 0.6-2.2; P = .8 |
| VEN combo (vs mono) + prior chemoimmunotherapy | HR, 1.2; CI, 0.6-2.4; P = .7 | HR, 1.1; CI, 0.5-2.4; P = .8 |

features in VENmono-treated patients,[16-18] the observed survival outcomes were similar in the VENmono and VENcombo groups. Although we collected detailed information on VEN dose reductions and interruptions, we did not have detailed data on the administration schedule and rationale for the anti-CD20 antibody component of the regimen. Thus, we cannot confirm adherence to published combination fixed duration approaches nor have available data on prognostic factors for all patients. Importantly, however, these cohorts do reflect real-world practice across a large number of centers, which addresses an important evidence gap because clinical trial participants are not often representative of routine clinical practice. Regarding response data and survival outcomes, the inclusion of clinical trial participants could potentially introduce bias if imbalanced across comparator groups; however, the proportion of trial participants was similar and were included to capture the entire VEN experience across centers. Although follow-up and response assessments were not standardized due to study design, times to best response were comparable, suggesting these patients were assessed similarly. In addition, we did not confirm all patients with reported CRs had confirmatory bone marrow and computed tomography assessments. With regard to AEs, the retrospective design may make it difficult to capture all events (particularly grade 1 to 2) and therefore underestimates the true VEN toxicity profile. To address this issue, we limited the number of AEs to those of highest clinical importance and note that our AE data are comparable to the incidence of these events reported in clinical trials. Finally, although a few patients treated with VEN plus obinutuzumab were included, we note this comparison did not include enough patients to make conclusions about specific anti-CD20 antibodies or use of VEN plus obinutuzumab in the front-line setting.

Of late, clinical trials in CLL have focused primarily on biologic doublets and triplets.[5,19-26] As multiple studies have demonstrated superior outcomes with the addition of CD20 antibodies to chemotherapy in both CLL and B-cell lymphomas, one would assume the same for small-molecule inhibitors. To date, this finding is not observed with ibrutinib in randomized comparisons. Burger et al demonstrated the lack of improved survival outcomes with the addition of R to ibrutinib in a 2-arm study of treatment-naive and relapsed CLL.[6,9] These results were confirmed in the front-line ALLIANCE study comparing ibrutinib, R plus ibrutinib, and bendamustine plus R, which demonstrated a nearly identical 2-year PFS in the 2 ibrutinib-containing arms.[7,8] Prior to reporting these randomized data, single-arm studies of ibrutinib plus anti CD20 strongly supported the idea that anti-CD20 therapy would improve depth of response and survival outcomes, particularly in high-risk

patients.[9] Although we note different mechanisms of action between ibrutinib and VEN, these data highlight that hypotheses generated from nonrandomized phase 2 data are not always confirmed in randomized studies.[10,27]

Unlike patients included in the MURANO trial (BR vs VR in R/R CLL) with 1 median prior therapy, essentially ibrutinib naive (2.6% B-cell receptor inhibitor exposure) and 27% del17p, our cohort was more heavily pretreated (median 3 prior therapies; 78% previously treated with ibrutinib) and higher risk (43% del17p).[1,28] We hypothesize that our cohort, which may reflect current VEN use in clinical practice, likely contains a higher proportion of anti-CD20 refractory patients. This may explain the observed lack of benefit for the anti-CD20–containing combination over VENmono. This analysis provides a hypothesis that adding anti-CD20 antibodies to VEN in heavily pretreated patients may not improve clinically relevant outcomes.

These findings need to be confirmed and validated in future randomized studies examining (1) VEN monotherapy vs combinations and (2) treat to progression vs fixed duration/retreatment schedules. Unfortunately, we were not able to identify an ongoing or planned clinical study that compares a VEN-based combination to VEN monotherapy. Given the increasing financial burden of novel therapies, the lack of data on how to sequence after novel-novel combinations fail, and the potential for increased toxicity, our results demonstrate that it is imperative to include monotherapy control arms as we continue to investigate the incremental clinical benefit of novel agent combinations for patients with CLL.[29]

## Authorship

ORCID profiles: T.A.E., 0000-0002-6631-9749; F.L., 0000-0001-6027-3359; A.K.S., 0000-0002-5634-5951; M.S.Y., 0000-0003-2787-3867; J.N.A., 0000-0002-2088-0899; A.M.W., 0000-0002-7042-5851; H.T., 0000-0001-8458-9649; A. Sitlinger, 0000-0002-2231-5527; S.M., 0000-0001-5465-9562; A.Z., 0000-0003-1403-6883; C.P.F., 0000-0002-6322-9254.

Correspondence: Anthony Mato, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 1065; e-mail: matoa@mskcc.org.

# References

1.  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.

2.  Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2016;374(4):311-322.

3.  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.

4.  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. *J Clin Oncol*. 2018;36(19):1973-1980.

5.  Sharman J, Brander DM, Mato A, et al. Ublituximab and ibrutinib for previously treated genetically high-risk chronic lymphocytic leukemia: Results of the GENUINE phase 3 study [abstract]. *J Clin Oncol*. 2017;35(suppl). Abstract 7504.

6.  Burger JA, Sivina M, Ferrajoli A, et al. Randomized trial of ibrutinib versus ibrutinib plus rituximab (Ib+R) in patients with chronic lymphocytic leukemia (CLL) [abstract]. *Blood*. 2017;130(suppl 1). Abstract 427.

7.  Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib alone or in combination with rituximab produces superior progression free survival (PFS) compared with bendamustine plus rituximab in untreated older patients with chronic lymphocytic leukemia (CLL): results of Alliance North American Intergroup Study A041202 [abstract]. *Blood*. 2018;132(suppl 1). Abstract 6.

8.  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.

9.  Burger JA, Keating MJ, Wierda WG, et al. Safety and activity of ibrutinib plus rituximab for patients with high-risk chronic lymphocytic leukaemia: a single-arm, phase 2 study. *Lancet Oncol*. 2014;15(10):1090-1099.

10. Sharman JP, Farber CM, Mahadevan D, et al. Ublituximab (TG-1101), a novel glycoengineered anti-CD20 antibody, in combination with ibrutinib is safe and highly active in patients with relapsed and/or refractory chronic lymphocytic leukaemia: results of a phase 2 trial. *Br J Haematol*. 2017;176(3): 412-420.

11. Mato AR, Thompson M, Allan JN, et al. Real world outcomes and management strategies for venetoclax-treated chronic lymphocytic leukemia patients in the United States. *Haematologica*. 2018;103(9):1511-1517.

12. Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. *N Engl J Med*. 2011;364(19):1844-1854.

13. Hallek M, Cheson BD, Catovsky D, et al; International Workshop on Chronic Lymphocytic Leukemia. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood*. 2008;111(12):5446-5456.

14. Bland JM, Altman DG. Survival probabilities (the Kaplan-Meier method). *BMJ*. 1998;317(7172):1572-1580.

15. Coutre S, Choi M, Furman RR, et al. Venetoclax for patients with chronic lymphocytic leukemia who progressed during or after idelalisib therapy. *Blood*. 2018;131(15):1704-1711.

16. Lew T, Anderson MA, Tam CS, et al. Long term outcomes of venetoclax therapy for complex karyotype relapsed/refractory chronic lymphocytic leukemia [abstract]. *Blood*. 2018;132(suppl 1). Abstract 4431.

17. Wierda WG, Seymour JF, Roberts AW, et al. Impact of number of prior therapies and bulk of disease on outcomes with venetoclax (VEN) monotherapy for relapsed/refractory chronic lymphocytic leukemia (CLL) [abstract]. *Blood*. 2017;130(suppl 1). Abstract 4329.

18. Anderson MA, Tam C, Lew TE, et al. Clinico-pathological features and outcomes of progression of CLL on the BCL2 inhibitor venetoclax. *Blood*. 2017; 129(25):3362-3370.

19. Woyach J, Awan FT, Jianfar M, et al. Acalabrutinib with obinutuzumab in relapsed/refractory and treatment-naive patients with chronic lymphocytic leukemia: the phase 1b/2 ACE-CL-003 Study [abstract]. *Blood*. 2017;130(suppl 1). Abstract 432.

20. Esteves IT, Dumontet C, Herveau S, et al. LFB-R603, a third-generation monoclonal anti-CD20 antibody displays an additive antitumor activity with antileukemic chemotherapeutic agents in mouse xenograft models [abstract]. *Blood*. 2011;118(21). Abstract 1660.

21. Flinn I, Gribben J, Dyer MJ, et al. Safety, efficacy and MRD negativity of a combination of venetoclax and obinutuzumab in patients with previously untreated chronic lymphocytic leukemia—results from a phase 1b study (GP28331) [abstract]. *Blood*. 2017;130(suppl 1). Abstract 430.

22. Fischer K, Al-Sawaf O, Fink AM, et al. Venetoclax and obinutuzumab in chronic lymphocytic leukemia. *Blood*. 2017;129(19):2702-2705.

23. Fischer K, Fink AM, Bishop H, et al. Results of the safety run-in phase of CLL14 (BO25323): a prospective, open-label, multicenter randomized phase III trial to compare the efficacy and safety of obinutuzumab and venetoclax (GDC-0199/ABT-199) with obinutuzumab and chlorambucil in patients with previously untreated CLL and coexisting medical conditions [abstract]. *Blood*. 2015;126(23). Abstract 496.

24. Cramer P, von Tresckow J, Bahlo J, et al. Bendamustine followed by obinutuzumab and venetoclax in chronic lymphocytic leukaemia (CLL2-BAG): primary endpoint analysis of a multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2018;19(9):1215-1228.

25. Wierda W, Siddiqi T, Flinn I, et al. Phase 2 CAPTIVATE results of ibrutinib (IBR) plus venetoclax (VEN) in first-line chronic lymphocytic leukemia (CLL) [abstract]. *J Clin Oncol*. 2018;36(suppl). Abstract 7502.

26. Rogers KA, Huang Y, Ruppert AS, et al. Phase 1b study of obinutuzumab, ibrutinib, and venetoclax in relapsed and refractory chronic lymphocytic leukemia. *Blood*. 2018;132(15):1568-1572.

27. Burger JA, Keating MJ, Wierda WG, et al. Safety and activity of ibrutinib plus rituximab for patients with high-risk chronic lymphocytic leukaemia: a single-arm, phase 2 study. *Lancet Oncol*. 2014;15(10):1090-1099.

28. Seymour JF, Kipps TJ, Eichhorst BF, et al. Venetoclax plus rituximab is superior to bendamustine plus rituximab in patients with relapsed/refractory chronic lymphocytic leukemia—results from pre-planned interim analysis of the randomized phase 3 Murano Study [abstract]. *Blood*. 2017;130(suppl 1). Abstract LBA-2.

29. Sarraf Yazdy M, Mato AR, Cheson BD. Combinations or sequences of targeted agents in CLL: is the whole greater than the sum of its parts (Aristotle, 360 BC)? *Blood*. 2018;133(2):121-129.