Blood First Edition Paper, prepublished online March 12, 2019; DOI 10.1182/blood-2019-01-896290

Phase 1b study of venetoclax-obinutuzumab in previously untreated and relapsed/refractory chronic lymphocytic leukemia

Ian W. Flinn,[1] John G. Gribben,[2] Martin J. S. Dyer,[3] William Wierda,[4] Michael B. Maris,[5] Richard R. Furman,[6] Peter Hillmen,[7] Kerry A. Rogers,[8] Swaminathan Padmanabhan Iyer,[9] Anne Quillet-Mary,[10] Loic Ysebaert,[10] Harriet S. Walter,[3] Maria Verdugo,[11] Christian Klein,[12] Huang Huang,[13] Yanwen Jiang,[14] Gerard Lozanski,[15] Daniela Soriano Pignataro,[16] Kathryn Humphrey,[16] Mehrdad Mobasher,[14] and Thomas J. Kipps[17]

Affiliations: [1]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [2]Barts Cancer Institute, Queen Mary University of London, London, UK; [3]Ernest and Helen Scott Haematological Research Institute, University of Leicester, Leicester, UK; [4]The University of Texas, MD Anderson Cancer Center, Houston, TX, USA; [5]Sarah Cannon Research Institute/Colorado Blood Cancer Institute, Denver, CO, USA; [6]Weill Cornell Medicine, CLL Research Center, New York, NY, USA; [7]St. James University Hospital, Leeds, UK; [8]Division of Hematology, The Ohio State University, Columbus, OH, USA; [9]Houston Methodist Hospital, Houston, TX, USA; [10]Cancer Research Center of Toulouse, Université Toulouse III Paul Sabatier, Toulouse, France; [11]AbbVie, North Chicago, IL, USA; [12]Roche Pharma Research and Early Development, Roche Innovation Center Zurich, Schlieren, Switzerland; [13]F-Hoffmann-La Roche Ltd., Mississauga, ON, Canada; [14]Genentech Inc., South San Francisco, CA, USA; [15]Department of Pathology, The Ohio State University, Columbus, OH, USA; [16]Roche

Products Limited, Welwyn Garden City, UK; and [17]University of California School of Medicine, San Diego, CA, USA

Financial support: Financial support for the study was provided by Genentech Inc. and AbbVie.

Corresponding author: Ian W. Flinn, Sarah Cannon Research Institute/Tennessee Oncology, 250 25th Avenue North, Suite 412, Nashville, TN 37203, USA. Tel. +1 615-986-7600. Fax. +1 615-986-7601. E-mail. iflinn@tnonc.com

Running head: Venetoclax and obinutuzumab in R/R and 1L CLL

Statement of prior presentation: Previous interim analyses of this study were presented at the American Society of Hematology Annual Meeting in 2015 and 2017 (oral presentations).

Text word count: 3999/4000 words max

Abstract word count: 249

Figures and tables: 3 figures / 4 tables

References: 44

Scientific category: Clinical trials and observations

Key points [2 key points maximum, up to 140 characters, including spaces]:

1. Dose finding established venetoclax 400 mg combined with obinutuzumab; this regimen had an acceptable safety profile in R/R and 1L CLL. **[138 ch]**
2. Venetoclax-obinutuzumab elicited high response rates with deep remissions in R/R and 1L CLL, irrespective of cytogenetic risk factors. **[137 ch]**

Abstract

This single-arm, open-label, phase 1b study evaluated the maximum tolerated dose (MTD) of venetoclax when given with obinutuzumab and its safety and tolerability in patients with relapsed/refractory (R/R) or previously untreated (1L) chronic lymphocytic leukemia. Venetoclax dose initially was escalated (100-400 mg) in a 3+3 design to define the MTD combined with standard-dose obinutuzumab. Patients received venetoclax (Schedule A) or obinutuzumab (Schedule B) first to compare safety and determine dose/schedule for expansion. Venetoclax-obinutuzumab was administered for 6 cycles, followed by venetoclax monotherapy until disease progression (R/R) or fixed-duration 1 year of treatment (1L). 50 R/R and 32 1L patients were enrolled. No dose-limiting toxicities were observed. Safety, including incidence of tumor lysis syndrome (TLS), did not differ between schedules (2 laboratory TLS per schedule). Schedule B and 400 mg dose of venetoclax was chosen for expansion. The most common grade 3-4 adverse event was neutropenia (R/R, 58% of patients; 1L, 53%). Rates of grade 3-4 infections were 29% (R/R) and 13% (1L); no fatal infections occurred in 1L. All infusion-related reactions were grade 1-2, except for 2 grade 3 events. No clinical TLS was observed. Overall best response rate was 95% (CR/CRi, 37%) in R/R and 100% (CR/CRi, 78%) in 1L patients. Rate of undetectable ($<10^{-4}$) minimal residual disease (MRD) in peripheral blood for R/R and 1L patients respectively was 64% and 91% ≥3 months after last obinutuzumab dose. Therapy with venetoclax and obinutuzumab had an acceptable safety profile and elicited durable responses and high rates of undetectable MRD. The study is registered to https://clinicaltrials.gov as NCT01685892.

Introduction

Despite the evolving therapeutic landscape,[1,2] chronic lymphocytic leukemia (CLL) remains incurable; most patients relapse or become treatment refractory.[3-6] Novel targeted agents (B-cell receptor inhibitors; BCRis) are used mainly in high-risk patients, especially where standard chemoimmunotherapy may be unsuitable due to toxicity and short remission durations. While these novel agents improve progression-free survival (PFS), they often require prolonged treatment leading to unique toxicities.[7–9] Further investigation of chemotherapy-free regimens, particularly with a fixed duration of treatment, is warranted in previously untreated (1L) and relapsed/refractory (R/R) CLL.

BCL-2 overexpression allows CLL cells to evade apoptosis by sequestering pro-apoptotic proteins;[10] thereby representing a therapeutic target. Venetoclax, a potent, oral BCL-2 inhibitor,[11] acts independently of *TP53*,[12] and has demonstrated substantial anti-CLL activity as monotherapy[13,14] and with rituximab,[15,16] in R/R CLL patients. Fixed-duration venetoclax-rituximab improved PFS *versus* bendamustine-rituximab (BR) and achieved undetectable minimal residual disease (uMRD) in 62.4% of R/R CLL patients in the phase 3 MURANO study.[16,17]

Obinutuzumab, a type II anti-CD20 antibody,[18] is also active in CLL.[19-21] Preclinically, obinutuzumab mediates superior B-cell depletion *versus* rituximab in whole blood from CLL patients, independent of prognostic markers.[18,22] Clinically, obinutuzumab-chlorambucil was associated with a PFS and overall survival benefit over rituximab-

chlorambucil in the phase 3 CLL11 trial,[20,23] leading to the approval of obinutuzumab-chlorambucil as a frontline therapy for CLL patients with comorbidities.[24]

Preclinical assessments to evaluate venetoclax-obinutuzumab as proof-of-concept showed that reduction of B-cells was significantly higher with venetoclax-obinutuzumab than with venetoclax-rituximab or venetoclax alone (supplemental Table 1, supplemental Figure 1). Here, we report results from a phase 1b study with venetoclax-obinutuzumab in R/R and 1L CLL (NCT01685892).

Patients and methods

Study conduct

This phase 1b, single-arm, open-label study was conducted at 11 sites across the USA and UK. Review boards at all institutions approved the protocol. Patients provided written informed consent.

Patients

Eligible patients (supplemental Table 2) were aged ≥18 years with CLL in need of therapy by International Workshop on CLL (iwCLL) 2008 criteria[25] and had: an Eastern Cooperative Oncology Group performance status 0-1; adequate hematologic function unless directly attributable to underlying CLL; and adequate organ function, including creatinine clearance ≥30 mL/min. Patients with R/R CLL must have received 1-3 prior chemotherapy-containing regimens, patients with 17p deletion (del[17p]) and/or *TP53*

mutation could have received at least 1 line of prior therapy with alemtuzumab-containing treatment or a BCRi (ibrutinib or idelalisib).

Study design and treatment

The study comprised 2 phases for each patient population (R/R and 1L): dose-finding and safety-expansion (supplemental Figure 2). Dose-finding was planned to include multiple doses of venetoclax (100-600 mg) combined with standard-dose obinutuzumab (cycle 1: 100 mg day 1, 900 mg day 2, 1000 mg days 8 and 15; cycles 2-6: 1000 mg day 1), in 28-day cycles. Ultimately, the 600 mg dose was not explored after review of the present study and program-wide data, including data review of a phase 1b study in CLL with venetoclax-rituximab, in which the recommended phase 2 dose of venetoclax was 400 mg.[15] To mitigate risk of tumor lysis syndrome (TLS), venetoclax was initiated with a ramp-up period with weekly dose increases to target dose (Figure 1). Prophylactic measures for TLS mitigation included hydration, allopurinol, rasburicase (for TLS high-risk patients with high pre-treatment uric acid levels), and hospitalization for the first venetoclax dose (supplemental Table 3).

The dose-finding stage explored 2 schedules of drug administration during cycle 1 for TLS risk mitigation: Schedule A (venetoclax ramp-up, followed by obinutuzumab) and Schedule B (obinutuzumab loading-dose over 21 days, followed by venetoclax initiation). Dose escalation occurred according to Schedule A in R/R patients before initiating cohorts according to Schedule B or any 1L patients. Standard 3+3 dose-escalation rules were applied, whereby if no dose-limiting toxicity (DLT) was observed in any 3 patients in a given cohort, the next cohort could begin enrollment without further

expansion (supplemental Table 4). Once R/R patients in Schedule A had completed the DLT observation window (supplemental Table 5) for cohort 3 (venetoclax 400 mg) or reached the maximum tolerated dose (MTD), whichever occurred first, an internal monitoring committee (IMC) and external scientific overview committee (SOC, composed of CLL experts) were to provide recommendations for the initial cohort dose of venetoclax for Schedule B in the R/R population and for Schedule A in the 1L population. Subsequent assessment for dose/schedule recommendations were to be provided by the SOC/IMC according to supplemental Figure 2 to determine the venetoclax dose and schedule for safety-expansion. Patients previously enrolled into cohorts with lower target doses of venetoclax than the recommended dose for safety-expansion were to be allowed to increase the venetoclax dose once the safety-expansion phase of the study started.

Venetoclax-obinutuzumab was administered for 6 cycles, followed by venetoclax monotherapy until disease progression (PD), unacceptable toxicity, or death in R/R patients, or completion of a 1-year fixed treatment duration in 1L patients. In 1L patients, venetoclax could be extended beyond 1 year if there was detectable MRD in the bone marrow (BM) or the patient was not in complete response (CR).

Endpoints

Primary endpoints were MTD of venetoclax when combined with obinutuzumab, and safety/tolerability (including incidence/type of protocol pre-defined DLTs, adverse events [AEs] and serious AEs [SAEs], laboratory variables, and vital signs) of the combination

in R/R and 1L patients. DLTs (supplemental Table 5) were defined as grade 4 neutropenia, thrombocytopenia, and infusion-related reactions (IRRs); grade 3-4 febrile neutropenia; clinical TLS; or all other non-hematologic grade 3-5 AEs. Efficacy measures (including CR, overall response rate [ORR; CR + partial response (PR)], duration of response, and PFS) were secondary endpoints. uMRD rate was an exploratory endpoint.

Evaluations

Baseline characteristics including cytogenetic aberrations, mutational analysis of immunoglobulin heavy-chain variable region (*IGHV*) and *TP53* genes, serum beta-2-microglobulin, and CD38 expression were assessed centrally. Measurable lymph node size assessments (by computed tomography/magnetic resonance imaging) were mandatory before treatment initiation to assess TLS risk (supplemental Table 3) and subsequently to confirm response.

AEs were assessed at every visit and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events v4.0. In patients with cytopenias at baseline, hematologic toxicity was graded according to the National Cancer Institute-Sponsored Working Group (NCI-WG)[26] until recovery of peripheral blood (PB) cells following treatment initiation. TLS was classified according to Howard criteria.[27] Response assessments were performed by investigators per iwCLL 2008 criteria,[25] with BM examination and imaging to confirm response, starting from cycle 2 whenever there was clinical indication of response. PB MRD samples were taken at baseline, cycle 4,

any time CR was determined, every 2-3 months after the last obinutuzumab dose (1L and R/R), and every 3 months after the last venetoclax dose (1L). BM MRD samples were taken at CR confirmation, and at 3 months after 1 year of treatment. PB and BM MRD analyses were assessed centrally at The Ohio State University using a 5-color flow cytometry assay (uMRD threshold of 1 CLL cell/10^4 cells in samples with a minimum of 200 000 leukocytes) following the European Research Initiative on CLL principle.[28]

Statistical methods

Planned enrollment was approximately 90 patients: 3-6 for each dose-finding cohort and ≥14 additional patients for each safety-expansion cohort. Safety analyses included all patients receiving ≥1 dose of any study drug. Efficacy analyses included all patients receiving ≥2 cycles of venetoclax-obinutuzumab (as response assessment with BM examination and imaging according to the iwCLL started from end of cycle 2). MRD analyses included all patients who reached the specified landmark timepoint, plus those discontinuing the study earlier because of AEs, PD, or death (if applicable). At each assessment, the first evaluable PB MRD sample after that timepoint was used for analysis. Kaplan-Meier methodology was used for time-to-event analyses.[29]

The first 4 patients with R/R CLL enrolled were subsequently discontinued from the study, shortly after a sponsor-initiated clinical hold in December 2012, due to clinical TLS events in other early-phase venetoclax studies that resulted in extensive changes to all venetoclax CLL protocols, including the present study. Safety data for these

patients were reviewed independently and were not included in the final analyses given the different treatment schedule and limited follow-up available. These data are presented in supplemental Table 6.

Data-sharing statement

Qualified researchers may request access to individual patient-level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx. For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here: https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

Results

Patients

Between May 2013 and March 2016, 46 R/R and 32 1L patients were enrolled; 24 R/R and 12 1L patients during dose-finding and 22 and 20, respectively, during safety-expansion. One patient did not meet the inclusion criteria (QTc interval >470 ms) and discontinued prior to receiving any study drugs. Two patients discontinued treatment due to AEs before completing 2 cycles of combination treatment (1 case each of grade 2 lower respiratory infection and grade 3 ulcerative colitis). The R/R safety and efficacy populations therefore comprised 45 and 43 patients, respectively. All 32 1L patients

were included in the analyses (supplemental Figure 3). During dose-finding, 23 R/R patients and 12 1L patients were safety-evaluable. Among them, 22 (16 R/R; 6 1L) received cycle 1 treatment according to Schedule A, and 13 (7 R/R; 6 1L) according to Schedule B. Data cut-off was May 21, 2018.

Baseline characteristics are reported in Table 1. Fifty-six percent of R/R patients and 71% of 1L patients had creatinine clearance ≥70 mL/min, and 56% and 56%, respectively, were ≤65 years old at screening. In the R/R cohort, median number of prior therapies was 2 (range, 1-6); 79% of patients had received fludarabine-based combinations, 21% Bruton's tyrosine kinase inhibitors (BTKis), and 14% phosphoinositide-3-kinase inhibitors previously. Among patients with samples available for baseline cytogenetic and/or molecular assessment, 77% of R/R and 57% of 1L patients had unmutated *IGHV*; del(17p) and/or *TP53* mutation was present in 55% of R/R and 17% of 1L patients.

Treatment exposure

Eighty percent (36/45) of R/R patients and all 1L patients (32/32) received venetoclax 400 mg/day. Ninety-three percent (42/45) of R/R patients and all 1L patients (32/32) completed 6 cycles of venetoclax-obinutuzumab. Median venetoclax treatment duration was 789 days (range, 8-1516) and 371 days (range, 314-883) in the R/R and 1L populations, respectively. Median relative venetoclax dose intensity (supplemental information) was 100% (range, 31-100) and 100% (range, 53-100) for R/R and 1L

patients, respectively. Twelve 1L patients received venetoclax beyond 1 year (range, 408-883 days).

Safety

During dose-finding, R/R patients were enrolled to either the 100 mg (Schedule A), 200 mg (Schedule A), or 400 mg (Schedule A or B) venetoclax dose cohorts. As the 1L cohorts were initiated after the R/R cohort's safety assessment by the IMC and SOC, all 12 1L patients enrolled during the dose-finding were included in the 400 mg (Schedule A or B) venetoclax dose cohort. No DLTs (including clinical TLS) were observed with either Schedule A or B during dose-finding, and the MTD was not reached.

There were no differences in safety, including rate of TLS events between schedules. During dose-finding, 4 laboratory grade 3 TLS events were observed in 3 patients (all R/R): 2 events each with Schedules A and B. One TLS event with Schedule B occurred after obinutuzumab administration but before introduction of venetoclax. The other 3 events (2 with Schedule A and 1 with Schedule B) occurred during venetoclax ramp-up. Details of TLS events are summarized in supplemental Table 7. After reviewing the safety database of the dose-finding phase and program-wide data, the IMC and SOC recommended Schedule B for obinutuzumab debulking followed by venetoclax, and a venetoclax dose of 400 mg for the safety-expansion phase.

All 77 safety-evaluable patients reported ≥1 AE; mostly grade 1-2 (87%). The most frequent AEs (any grade) were infections, diarrhea, IRRs, nausea, and neutropenia

(Table 2). Infections were mainly low grade and driven by upper respiratory tract infections and sinusitis (Table 2). Overall, 64% (29/45) of R/R and 81% (26/32) of 1L patients received treatment according to Schedule B and all IRR events were grade 1-2 except for 2 grade 3 events observed in the R/R cohort; none led to obinutuzumab discontinuation.

In the R/R and 1L populations, grade 3-4 AEs were reported in 80% and 78% of patients, respectively, most frequently neutropenia (R/R, 58%; 1L, 53%) (Table 2). Grade 3-4 febrile neutropenia was reported in 16% and 13% of R/R and 1L patients, respectively. The overall rate of grade 3-4 infections was 29% in R/R patients and 13% in 1L patients (Table 2). The most common grade 3-4 infection AEs in R/R patients were pulmonary infection (16%; including preferred terms of pneumonia, lower respiratory tract infection, viral lower respiratory tract infection, and lung infection), cellulitis (9%), and urinary tract infection (4%). Grade 3-4 infections reported in 1L patients included 1 case each of appendicitis, diverticulitis, Enterobacter bacteremia, and viral respiratory tract infection. SAEs were reported in 46% of patients (R/R, 60%; 1L, 34%; supplemental Table 8). During the safety-expansion phase of the study, 1 laboratory TLS event occurred in a 1L patient after obinutuzumab and before initiation of venetoclax (supplemental Table 7). No clinical TLS was reported.

Seventy-six percent of R/R and 66% of 1L patients experienced grade 3-4 AEs during the combination treatment period versus 54% and 34%, respectively, during the venetoclax monotherapy period (supplemental Table 9). Grade 3-4 neutropenia

occurred in 48% (R/R, 49%; 1L, 47%) and 24% (R/R, 30%; 1L, 16%) of patients during the combination and monotherapy phases, respectively. In R/R patients, grade 3-4 infections occurred in 18% (8/45) of patients during the combination treatment period compared with 21% (9/43) of patients during the venetoclax monotherapy period. In the 1L population, 6% (2/32) of patients reported grade 3-4 infections in each of the combination and monotherapy periods.

Venetoclax was discontinued due to AEs in 16% (7/45) of R/R patients and 3% (1/32) of 1L patients; most occurred after 1 year of treatment. Obinutuzumab was discontinued due to AEs in 4% (2/45) of R/R patients and no 1L patients (Table 3).

Three patients (7%) in the R/R population had a fatal AE (acute respiratory failure in a patient with suspected Richter's transformation, pneumonia in the context of metastatic squamous cell carcinoma of the lung, and pneumonia reported approximately 3 months following the last venetoclax dose). No deaths were reported in the 1L population.

Efficacy

ORR (best response) was 95% (95% confidence interval [CI], 84-99) and 100% (95% CI, 89-100) in R/R and 1L patients, respectively (Table 4). Thirty-seven percent (95% CI, 23-53) of R/R patients and 78% (95% CI, 60-91) of 1L patients achieved CR/CR with incomplete marrow recovery (CRi) as best response. Responses were similar among patients in the different cytogenetic subgroups (Table 4).

Rates of PB uMRD were 64% (27/42) and 91% (29/32) in R/R and 1L patients, respectively, ≥3 months after last obinutuzumab dose. After a median of 12.0 months (range, 11.1-18.4) from last obinutuzumab dose, PB uMRD rates were sustained at 63% (25/40) in R/R patients (Figure 2A) and 78% (25/32) in 1L patients (Figure 2C). For 1L patients, ≥3 months after completion of all treatment (median, 4.4 months [range, 2.8-8.5] from last venetoclax dose), the rate of PB uMRD was 72% (23/32) (Figure 2D).

In the R/R and 1L populations, 62% (26/42) and 78% (25/32) achieved uMRD in BM, respectively (Figure 2B and 2E). Specifically, 26% (11/42) and 63% (20/32) of R/R and 1L patients, respectively, were in CR/CRi and had uMRD in BM. Concordance between PB and BM MRD from paired post-baseline samples was high and similar across the R/R (79% [19/24]) and 1L (86% [25/29]) populations. Therefore, subsequent analysis of MRD kinetics was based on PB MRD.

Patient-level MRD kinetics are shown in Figure 3. Among R/R patients with PB uMRD ≥3 months after the last obinutuzumab dose, 19% (5/27) converted to detectable MRD (low-level: $\geq 10^{-4}$-$<10^{-2}$ or high-level: $\geq 10^{-2}$) in 2 consecutive assessments; 1 had PD at data cut-off. Among 1L patients with PB uMRD after completion of all treatments (median follow-up 14.4 months [range, 0.5-27.3] post-venetoclax cessation), 34% (10/29) converted to positive MRD in 2 consecutive assessments; 5 maintained low-level MRD, 1 became high-level MRD, and 4 became low-level MRD but returned to uMRD at the last MRD assessment, among whom 1 had confirmed PD at data cut-off. No association was observed between cytogenetics and MRD conversion. Median time

to first MRD conversion was 196 days (range, 91-554) from last venetoclax dose for the 10 1L patients.

After a median follow-up of 29.3 months (range, 3-55) in R/R patients and 26.7 months (range, 16-39) in 1L patients, estimated 24-month PFS was 85.4% (95% CI, 74.5-96.2) and 90.6% (95% CI, 80.5-100), respectively (supplemental Figure 4A and 4B). Median duration of response was 40.9 months (range, 39.9-51.8) and not reached in R/R and 1L patients, respectively. In total, PD occurred in 16 patients (R/R, n = 12; 1L, n = 4). Of the R/R patients who progressed, 7/12 had del(17p)/*TP53* mutation at baseline and 7/12 were on venetoclax at PD. Three of the 4 1L patients who progressed had del(17p)/*TP53* mutation at baseline and 2 were on venetoclax at PD. Richter's transformation occurred in 1 R/R patient (diffuse large B-cell lymphoma [DLBCL]) and 2 1L patients (DLBCL and Hodgkin lymphoma [HL]; the DLBCL case was also MRD-positive for CLL in PB and BM, the HL case was uMRD for CLL in both PB and BM; both events were diagnosed after 1 year on study).

Discussion

The current study established venetoclax 400 mg in combination with obinutuzumab as the dose for the safety-expansion cohorts in the R/R and 1L CLL populations. In both populations, the median age (R/R, 61 years; 1L, 63 years) was lower than that usually associated with the initial diagnosis of CLL (range, 65–70 years).[30–32] Dosing schedules assessed were safe and acceptable, with Schedule B recommended for the safety-expansion. The safety profile of venetoclax-rituximab has recently been established for

rituximab initiation after venetoclax ramp-up, using a dosing schedule akin to Schedule A.[16] Hence, both schedules appear feasible for venetoclax administration with an anti-CD20 antibody.

Venetoclax-obinutuzumab had an acceptable safety profile, with expected and manageable toxicities. Most patients completed the planned treatment regimen. The absence of clinical TLS and low incidence of laboratory TLS with venetoclax supported the effectiveness of the ramp-up and prophylactic management strategy.

In the R/R and 1L populations, most AEs were low grade and, as expected based on the known modes of action and established tolerability profiles of both study drugs,[19,21,33] neutropenia was the most common grade 3-4 AE. Neutropenia was manageable with standard-of-care measures, and did not result in complications. Grade 3-4 neutropenia was more frequent during combination therapy than monotherapy, confirming tolerability of single-agent venetoclax. Rates of grade 3-4 infections were not especially high and were as expected for this combination and patient population, with no increased mortality due to infection. Although the emergence of hematologic toxicities with this regimen was higher than observed with BTKis such as ibrutinib,[34] the incidence of grade 3-4 neutropenia (R/R, 58%; 1L, 53%) was lower than seen with fludarabine-cyclophosphamide plus rituximab (FCR) in 1L patients in the CLL10 trial[35] and similar to that observed with venetoclax-rituximab in the MURANO study (58% in R/R patients).[16] Furthermore, in 1L patients, the incidence of grade 3-4 infections (13%) was lower than seen with chemoimmunotherapy in CLL10 (FCR, 39%; BR, 25%)[35] and

similar to that seen with ibrutinib (13%).[36] In R/R patients, the grade 3-4 infection rate (29%) was higher than seen with venetoclax-rituximab in MURANO (18%)[16] and lower than seen with ibrutinib (51%).[36] However, direct comparisons are difficult given differences in sample sizes, baseline characteristics, treatment duration, and follow-up between studies.

Despite the study population including a high proportion of patients with poor cytogenetics, all patients except 2 with R/R CLL (both with bulky disease and del[17p] or del[11q]) responded to treatment, demonstrating venetoclax-obinutuzumab as an efficacious regimen in R/R and 1L CLL. Importantly, high response rates and deep remissions were observed in most patient subgroups regardless of cytogenetics and/or physical fitness. PFS in both populations was promising but must be viewed in the context of a small phase 1 study. We did not observe any association between cytogenetics and MRD conversion.

uMRD was sustained at 63% ≥1 year from last obinutuzumab dose in R/R patients and at 72% after completion of all treatment in 1L patients. High uMRD rates ≥1 year after cessation of obinutuzumab allays concerns regarding MRD-negative status during obinutuzumab treatment. Furthermore, the high rate of uMRD in BM, and the concordance between BM and PB MRD data, suggest that PB MRD could predict BM MRD status in patients treated with venetoclax-obinutuzumab.

MRD status is a known predictor of PFS with chemoimmunotherapy.[20,23,35,36] The deep remission rates we observed with venetoclax-obinutuzumab have not been reported with previously available CLL treatments, including FCR, which is currently considered the most efficacious regimen with limited-duration therapy.[35,37] MURANO also demonstrated high uMRD rates and the value of uMRD in predicting improved outcome for a fixed-duration, chemotherapy-free regimen with venetoclax-rituximab.[17] Therefore, it is expected the high, sustained rate of uMRD seen with venetoclax-obinutuzumab would lead to improved outcomes.

Re-emergence of MRD positivity, mainly low-level, was observed in 5 R/R and 10 1L patients; of the 1L patients, only 1 had PD, thereby indicating the potential feasibility of time-limited therapy. Longer follow-up and larger trials are needed to explore the predictive value of deep remissions (CR with uMRD) and the impact of MRD conversion on the appearance of clinical progression using time-limited therapy.

Ongoing studies are investigating venetoclax-obinutuzumab and other venetoclax combinations as doublets or triplets in CLL, including a phase 1b/2 study of venetoclax-obinutuzumab-ibrutinib.[38] Preliminary results for 12 patients with R/R CLL showed a high ORR (92%) and deep remissions (all 12 patients became uMRD in PB or BM), consistent with our findings for venetoclax-obinutuzumab; however, longer follow-up is needed to determine longer-term outcomes.[38] Ibrutinib-venetoclax has also shown promising clinical activity in the frontline treatment of CLL in early data from the phase 2 CAPTIVATE study.[39] In the first 30 patients, uMRD in PB was reached by 77%. These

results are consistent with those achieved in our study, which showed similar rates with 1-year limited-duration treatment in 1L patients. Furthermore, although longer follow-up is needed, and with the caveat of the small population size, the CR and uMRD rates observed in our study compare favorably with the results of a phase 3 trial (iLLUMINATE) in the frontline CLL setting with ibrutinib-obinutuzumab,[40] in which CR and uMRD (PB or BM) were achieved by 41% and 35% of patients, respectively.

Different approaches to deliver efficacious venetoclax-obinutuzumab are under investigation. Recently, preliminary results of a phase 2 study with bendamustine debulking followed by venetoclax-obinutuzumab showed high ORRs and deep remissions in all subgroups of CLL patients, regardless of whether patients completed the planned 2 cycles of bendamustine debulking.[41] Bendamustine debulking contributed to normalization of the lymphocyte count so that the risk category for development of TLS could be downgraded before initiation of venetoclax-obinutuzumab. No incidences of clinical TLS were reported. Additionally, preliminary results from the first 30 patients enrolled in the HOVON 139/GIVE trial, in which 2 cycles of obinutuzumab were given for debulking before venetoclax-obinutuzumab, reported no incidences of clinical TLS and only 4 patients had laboratory TLS.[42] This study also demonstrated early signs of efficacy with venetoclax-obinutuzumab (including high rates of uMRD) in 1L unfit patients.[40]

Our results confirm favorable benefit–risk for R/R and 1L CLL patients at the established dose of 400 mg venetoclax together with the standard dose of

obinutuzumab. For 1L fit patients, a phase 3 study of venetoclax-obinutuzumab *versus* chemoimmunotherapy (FCR or BR) *versus* triplet therapy with ibrutinib is ongoing (CLL13; NCT02950051). In 1L unfit CLL, results from the safety run-in of the phase 3 CLL14 study, using venetoclax-obinutuzumab in patients with 1L CLL and coexisting medical conditions, similarly showed an acceptable safety profile, high uMRD rates, and promising PFS.[43] If the primary endpoints of these large-scale trials are met, venetoclax-obinutuzumab may become a new standard treatment option in 1L CLL irrespective of clinical fitness.

Acknowledgments

Special thanks go to the patients and their families, investigators, study coordinators, and support staff, and all Genentech GP28331 study team members. The authors acknowledge Elizabeth A. Punnoose for technical evaluation, and Richa Rajwanshi for safety data interpretation. Venetoclax is being developed in collaboration between Genentech and AbbVie. Genentech and AbbVie provided financial support for the study and participated in the design, study conduct, and data analysis and interpretation. Tara Miller of Envision Pharma Group and Susan Hasmall and Kate Rijnen of Gardiner-Caldwell Communications provided writing and editorial assistance based on specific direction from the authors; this service was funded by F. Hoffmann-La Roche Ltd.

Authorship

IWF: study design, collection and assembly of data, data analysis, data interpretation, writing process, participation in manuscript development and final approval.

JGG: study design, data analysis, data interpretation, writing process, participation in manuscript development and final approval, was a member of the Scientific Overview Committee.

MJSD: collection and assembly of data, data analysis, data interpretation, writing process, participation in manuscript development and final approval.

WW: collection and assembly of data, data analysis, data interpretation, writing process, participation in manuscript development and final approval.

MBM: data analysis, data interpretation, writing process, participation in manuscript development and final approval.

RRF: data analysis, data interpretation, writing process, participation in manuscript development and final approval.

PH: data analysis, data interpretation, writing process, participation in manuscript development and final approval.

KR: data analysis, data interpretation, writing process, participation in manuscript development and final approval.

SPI: data analysis, data interpretation, writing process, participation in manuscript development and final approval.

AQ-M: collection and assembly of data, data analysis, data interpretation, writing process, participation in manuscript development and final approval.

LY: collection and assembly of data, data analysis, data interpretation, writing process, participation in manuscript development and final approval.

HSW: collection and assembly of data, data analysis, data interpretation, writing process, participation in manuscript development and final approval.

MV: data analysis, data interpretation, writing process, participation in manuscript development and final approval.

CK: study design, data analysis, data interpretation, writing process, participation in manuscript development and final approval.

HH: data analysis, data interpretation, writing process, participation in manuscript development and final approval.

YJ: collection and assembly of data, data analysis, data interpretation, writing process, participation in manuscript development and final approval.

GL: generation, collection, interpretation and assembly of CLL MRD data, writing process, participation in manuscript development and final approval.

DSP: data analysis, data interpretation, writing process.

KH: data analysis, data interpretation, writing process, participation in manuscript development and final approval.

MM: generation, collection, interpretation and assembly data, data analysis, data interpretation, writing process, participation in manuscript development and final approval.

TJK: study design, data analysis, data interpretation, writing process, participation in manuscript development and final approval.

Conflict-of-interest disclosure: I.W.F. has received research funding for his institution from AbbVie, Acerta, Agios, ArQule, Beigene, Calithera, Celgene, Constellation, Curis, Forma, Forty Seven, Genentech, Gilead, Incyte, Infinity, Janssen, KITE, Merck, Novartis, Pfizer, Pharmacyclics, Portola, Seattle Genetics, Takeda, TG Therapeutics, Trillium, and Verastem. J.G.G. has received honoraria from Roche, AbbVie, Pharmacyclics, Celgene, and Janssen, and has held a consulting or advisory role for Roche, Acerta, AbbVie, Pharmacyclics, Celgene, and Janssen; he has also received research funding from Celgene, Acerta, and Janssen. M.J.S.D. has received honoraria from, and has held a consulting or advisory role for AbbVie and Roche; his institution has received research funding from Roche and he has received travel, accommodation, or expenses from AbbVie. W.W. has received travel, accommodation, or expenses from AbbVie, Genentech/Roche, Janssen, Pharmacyclics, Gilead, and Pfizer; his institution has received research funding from GSK/Novartis, AbbVie, Genentech, Karyopharm, Pharmacyclics LLC., Acerta, Gilead Sciences, Juno Therapeutics, KITE Pharma, Sunesis, Miragen, Oncternal Therapeutics, Inc., Cyclacel, Loxo Oncology, Janssen, and Xencor. M.B.M. has no conflicts of interest to declare. R.R.F. has received honoraria from Janssen and Genentech, has held a consulting or advisory role for AbbVie, Genentech, Gilead, Janssen, Acerta/AstraZeneca, Pharmacyclics, Sunesis, Loxo Oncology, TG Therapeutics, and Verastem, and has received research funding from Acerta and TG Therapeutics; he has also served on a Data Safety Monitoring Board for Incyte. P.H. has received honoraria from, and participated in Speakers' Bureaus for, Janssen, AbbVie, and Gilead; he has also received travel, accommodation, or expenses from Janssen and AbbVie, and his institution has received research funding from

Pharmacyclics, Janssen, AbbVie, Gilead, and Roche. K.R. has held a consulting or advisory role for Acerta and has received research funding from Genentech. S.P.I. has held a consulting or advisory role for Genentech, Takeda, and BMS, and has received research funding from Genentech, Takeda, Spectrum Pharmaceuticals, Seattle Genetics, BMS, Amgen, and Rhizem. A.Q.-M. has received research funding from Roche and Glycart. L.Y. has held a consulting or advisory role for Janssen, Roche, Gilead, and AbbVie, and has received research funding from Roche and Janssen. H.S.W. has received honoraria from Gilead and AbbVie, has held a consulting or advisory role for AbbVie, and has received travel, accommodation, or expenses from AbbVie and Gilead. M.V. is an employee of AbbVie. C.K. and an immediate family member of C.K. are employees of Roche and own Roche stock; C.K. has a patent or intellectual property interest to declare from Roche. H.H. is an employee of Roche. Y.J. is an employee of Genentech and owns Roche stock. G.L. has research funding to disclose from Genentech, Boehringer Ingelheim, Stemline, Celgene, and BC Pharma. D.S.P. is an employee of Roche and owns Roche stock. K.H. is an employee of Roche and owns Roche stock. M.M. is an employee of Genentech and holds Roche stock. T.J.K. is an employee of UC San Diego Health and Moores Cancer Center, has held a consulting or advisory role for Gilead, Celgene, Roche/Genentech, AbbVie, and Pharmacyclics, has received honoraria from Gilead, AbbVie, Pharmacyclics, Janssen, and Verastem, and has received research funding from Roche/Genentech, AbbVie, Pharmacyclics, and Oncternal.

Correspondence: Ian W. Flinn, Sarah Cannon Research Institute/Tennessee Oncology, 250 25th Avenue North, Suite 412, Nashville, TN 37203, USA; e-mail: iflinn@tnonc.com.

References

1. O'Brien S, Jones JA, Coutre SE, et al. Ibrutinib for patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (RESONATE-17): a phase 2, open-label, multicentre study. *Lancet Oncol*. 2016;17(10):1409-1418.

2. Mato AR, Nabhan C, Barr PM, et al. Outcomes of CLL patients treated with sequential kinase inhibitor therapy: a real world experience. *Blood*. 2016;128(18):2199-2205.

3. Rossi D, Khiabanian H, Spina V, et al. Clinical impact of small TP53 mutated subclones in chronic lymphocytic leukemia. *Blood*. 2014;123(14):2139-2147.

4. Maddocks KJ, Ruppert AS, Lozanski G, et al. Etiology of ibrutinib therapy discontinuation and outcomes in patients with chronic lymphocytic leukemia. *JAMA Oncol*. 2015;1(1):80-87.

5. Shustik C, Bence-Bruckler I, Delage R, Owen CJ, Toze CL, Coutre S. Advances in the treatment of relapsed/refractory chronic lymphocytic leukemia. *Ann Hematol*. 2017;96(7):1185-1196.

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

7. 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.

8. 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.

9. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. *N Engl J Med.* 2014;370(11):997-1007.

10. Lampson BL, Davids MS. The Development and Current Use of BCL-2 Inhibitors for the Treatment of Chronic Lymphocytic Leukemia. *Curr Hematol Malig Rep*. 2017;12(1):11-19.

11. Souers AJ, Leverson JD, Boghaert ER, et al. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. *Nat Med*. 2013;19(2):202-208.

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

13. 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.

14. 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.

15. 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.

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, Seymour JF, Hillmen P, et al. Fixed duration of venetoclax-rituximab in relapsed/refractory chronic lymphocytic leukemia eradicates minimal residual disease and prolongs survival: post-treatment follow-up of the MURANO phase III study. *J Clin Oncol*. 2019;37(4):269-277.

18. Mossner E, Brunker P, Moser S, et al. Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. *Blood*. 2010;115(22):4393-4402.

19. Byrd JC, Flynn JM, Kipps TJ, et al. Randomized phase 2 study of obinutuzumab monotherapy in symptomatic, previously untreated chronic lymphocytic leukemia. *Blood*. 2016;127(1):79-86.

20. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med*. 2014;370(12):1101-1110.

21. Cartron G, de Guibert S, Dilhuydy MS, et al. Obinutuzumab (GA101) in relapsed/refractory chronic lymphocytic leukemia: final data from the phase 1/2 GAUGUIN study. *Blood*. 2014;124(14):2196-2202.

22. Ysebaert L, Laprevotte E, Klein C, Quillet-Mary A. Obinutuzumab (GA101) is highly effective against chronic lymphocytic leukemia cells in ex vivo B-cell depletion irrespective of high-risk prognostic markers. *Blood Cancer J*. 2015;5:e367.

23. Goede V, Fischer K, Dyer MJS, et al. Overall survival benefit of obinutuzumab over rituximab when combined with chlorambucil in patients with chronic lymphocytic

leukemia and comorbidities: final survival analysis of the CLL11 study. Paper presented at 23rd Congress of the European Hematology Association. 14-17 June 2018. Stockholm, Sweden. Abstract S151.

24. Wierda WG, Zelenetz AD, Gordon LI, et al. NCCN guidelines insights: chronic lymphocytic leukemia/small lymphocytic lymphoma, version 1.2017. *J Natl Compr Canc Netw*. 2017;15(3):293-311.

25. Hallek M, Cheson BD, Catovsky D, et al. 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.

26. Cheson BD, Bennett JM, Grever M, et al. National Cancer Institute-Sponsored Working Group guidelines for chronic lymphocytic leukemia: revised guidelines for diagnosis and treatment. *Blood*. 1996;87(12):4990-4997.

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

28. Rawstron AC, Villamor N, Ritgen M, et al. International standardized approach for flow cytometric residual disease monitoring in chronic lymphocytic leukaemia. *Leukemia*. 2007;21(5):956-964.

29. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53(282):457-481.

30. Abrisqueta P, Pereira A, Rozman C, et al. Improving surival in patients with chronic lymphocytic leukemia (1980-2008): the Hospital Clinic of Barcelona experience. *Blood.* 2009;114(10):2044-2050.

31. Brenner H, Gondos A, Pulte D. Trends in long-term survival of patients with chronic lymhpocytic leukemia from the 1980s to the early 21st century. *Blood.* 2008;111(10):4916-4921.

32. Call TG, Phyliky RL, Noël P, et al. Incidence of chronic lymphocytic leukemia in Olmsted County, Minnesota, 1935 through 1989, with emphasis on changes in initial stage at diagnosis. *Mayo Clin Proc.* 1994;69(4):323-328.

33. 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.

34. Robak T. Ibrutinib in chronic lymphocytic leukaemia: alone or in combination? *Lancet Oncol*. 2016;17(2):129-131.

35. Eichhorst B, Fink AM, Bahlo J, et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. *Lancet Oncol*. 2016;17(7):928-942.

36. Byrd JC, Furman RR, Coutre SE, et al. Three-year follow-up of treatment-naïve and previously treated patients with CLL and SLL receiving single-agent ibrutinib. *Blood.* 2015;125(16):2497-2506.

37. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet*. 2010;376(9747):1164-1174.

38. 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.

39. Wierda WG, Siddiqi T, Flinn I, et al. Phase 2 CAPTIVATE results of ibrutinib (ibr) plus venetoclax (ven) in first-line chronic lymphocytic leukemia (CLL). *J Clin Oncol*. 2018;36(15 suppl):7502.

40. Moreno C, Greil R, Demirkan F, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;20(1):43-56.

41. 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.

42. Kater AP, Kersting S, van Norden Y, et al; HOVON CLL study group. Obinutuzumab pretreatment abrogates tumor lysis risk while maintaining undetectable MRD for venetoclax + obinutuzumab in CLL. *Blood Adv.* 2018;2(24):3566-3571.

43. Fischer K, Al-Sawaf O, Fink A-M, et al. Continuing remissions after venetoclax and obinutuzumab in patients with previously untreated chronic lymphocytic leukemia (CLL) and coexisting medical conditions. Paper presented at 23rd Congress of the European Hematology Association. 14-17 June 2018. Stockholm, Sweden. Abstract PF349.

Tables

Table 1. Patient demographics and baseline characteristics for the relapsed/refractory and first-line populations (efficacy population)

Characteristic	R/R (N = 43)	1L (N = 32)
Median age, years (range)	61 (42-80)	63 (47-73)
Male, n (%)	30 (70)	20 (63)
ECOG PS, n (%)		
0	22 (51)	16 (50)
1	21 (49)	16 (50)
2	0	0
Rai stage at screening, n (%)		
0	0	0
I/II	13 (30)	9 (28)
III/IV	28 (65)	18 (56)
Unknown	2 (5)	5 (16)
Creatinine clearance, n/N (%)		
<70 mL/min	19 (44)	9/31 (29)
≥70 mL/min	24 (56)	22/31 (71)
Pre-treatment TLS risk, n (%)*		
Low	10 (23)	2 (6)
Medium	19 (44)	22 (69)
High	14 (33)	8 (25)
Cytogenetics, n/N (%)†		
del(17p)/*TP53* mut‡	23/42 (55)	5/29 (17)
del(11q)	8/42 (19)	6/29 (21)
Trisomy 12	2/42 (5)	6/29 (21)
No abnormalities	3/42 (7)	1/29 (3)
del(13q)	6/42 (14)	11/29 (38)
TP53 mutation, n/N (%)§	18/40 (45)	5/26 (19)
IGHV unmutated, n/N (%)	26/34 (77)	16/28 (57)
Serum beta-2 microglobulin, n (%)		
≥3.5 mg/mL	28 (65)	19 (59)
CD38 positive, n/N (%)¶	19/33 (58)	12/25 (48)
Median previous therapies, n (range)	2 (1-6)	NA

Prior therapies received, n (%)		
Fludarabine-based treatment	34 (79)	NA
Bendamustine or bendamustine plus rituximab	12 (28)	NA
BTKis	9 (21)	NA
PI3Ki	6 (14)	NA

*Low risk if largest node <5 cm diameter AND ALC <25×10^9/L, medium risk if ALC ≥25×10^9/L OR largest nodes ≥5 cm and <10 cm diameter, or high risk if ALC ≥25×10^9/L and largest node ≥5 cm diameter OR largest node ≥10 cm diameter. †Fluorescence in situ hybridization (FISH) cut-offs for positivity: del17p >7%; del11q >6%; del13q >5.5%; trisomy 12 >2.5%. ‡A modified hierarchical model was used to maximize identification of the higher risk population due to missing samples for cytogenetic assessment. The del(17p)/*TP53* mut subgroup included patients with a 17p deletion by FISH and/or *TP53* mutation by NGS. §By NGS. Cut-off for positivity >5%. ¶Cut-off for positivity >30%. 1L indicates first-line; ALC, absolute lymphocyte count; BTKi, Bruton's tyrosine kinase inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; NA, not applicable; NGS, next-generation sequencing; PI3Ki, phosphoinositide 3-kinase inhibitor; R/R, relapsed/refractory; and TLS, tumor lysis syndrome.

Table 2. Treatment-emergent AEs (safety population)

Patients, n (%)	R/R (N = 45)		1L (N = 32)	
	All grade	Grade 3-4	All grade	Grade 3-4
AEs occurring in ≥20% of patients*				
Diarrhea	31 (69)	3 (7)	18 (56)	1 (3)
Infusion-related reaction	29 (64)	2 (4)	22 (69)	0
Neutropenia	29 (64)	26 (58)	21 (66)	17 (53)
Fatigue	24 (53)	1 (2)	14 (44)	1 (3)
Nausea	23 (51)	0	22 (69)	0
Cough	22 (49)	0	11 (34)	0
Pyrexia	20 (44)	0	15 (47)	1 (3)
Anemia	19 (42)	2 (4)	9 (28)	1 (3)
Chills	16 (36)	0	11 (34)	0
Thrombocytopenia	15 (33)	10 (22)	14 (44)	7 (22)
Headache	15 (33)	0	12 (38)	0
Vomiting	14 (31)	1 (2)	11 (34)	0
Dyspnea	12 (27)	0	9 (28)	0
Arthralgia	12 (27)	0	3 (9)	0
Dizziness	10 (22)	0	6 (19)	0
Constipation	9 (20)	0	8 (25)	0
Hyperphosphatemia	9 (20)	1 (2)	2 (6)	0
Rash	8 (18)	0	7 (22)	0
Abdominal pain	6 (13)	0	8 (25)	0
Hypotension	5 (11)	0	7 (22)	0
Flushing	4 (9)	0	10 (31)	0
Chest discomfort	4 (9)	0	7 (22)	0
Dyspepsia	4 (9)	0	7 (22)	0
Infection AEs occurring in >5% of patients*				
Infections and infestations (SOC)	38 (84)	13 (29)	26 (81)	4 (13)
Upper respiratory tract infection	17 (38)	1 (2)	6 (19)	0
Sinusitis	12 (27)	0	5 (16)	0
Pneumonia	7 (16)	5 (11)	1 (3)	0

Lower respiratory tract infection	6 (13)	2 (4)	2 (6)	0
Cellulitis	5 (11)	4 (9)	1 (3)	0
Rhinovirus infection	5 (11)	0	0	0
Urinary tract infection	4 (9)	2 (4)	4 (13)	0
Influenza	4 (9)	1 (2)	2 (6)	0
Herpes zoster	3 (7)	0	1 (3)	0
Diverticulitis	2 (4)	0	2 (6)	1 (3)
Bronchitis	2 (4)	0	3 (9)	0
Skin infection	2 (4)	0	2 (6)	0
Nasopharyngitis	2 (4)	0	2 (6)	0
Respiratory syncytial virus infection	1 (2)	0	2 (6)	0
Fungal skin infection	0	0	2 (6)	0

Data include all investigator-reported AEs, regardless of relationship to study drug. AEs occurring in ≥20% of patients are listed by MedDRA PT. Infection AEs occurring in >5% patients are listed by MedDRA SOC and PT. *In either population. 1L indicates first-line; AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; R/R, relapsed/refractory; and SOC, system organ class.

Table 3. Venetoclax and obinutuzumab discontinuations due to AEs

AEs	Grade	Study day of treatment discontinuation
AEs leading to venetoclax discontinuation		
R/R cohort		
Diarrhea in context of ulcerative colitis*	3	29
Thrombocytopenia	2	652
Lymphopenia	3	
Autoimmune hemolytic anemia	2	954
Pneumonia in context of a metastatic squamous cell carcinoma of the lung†	3	619
Fatigue in context of persistent anemia	2	331
Intermittent long-lasting diarrhea	1	575
Esophageal adenocarcinoma	3	722
1L cohort		
Diarrhea	3	346
AEs leading to obinutuzumab discontinuation		
R/R cohort		
Lower respiratory tract infection	2	29
Ulcerative colitis*	3	43
1L cohort – no discontinuations due to AEs		

1L indicates first line; AE, adverse event; PD, disease progression; and R/R, relapsed/refractory.

*Both AEs occurring in the same patient.

†Metastatic squamous cell carcinoma of the lung led to death on day 667 of the study.

Table 4. Best response to treatment according to International Workshop on Chronic Lymphocytic Leukemia (iwCLL) 2008 criteria

Response, n (%)	Entire efficacy population	By cytogenetic abnormalities*					By *IGHV* status	
		del(17p)/ *TP53* mut	del(11q)	Trisomy 12	None	del(13q)	Mut	Unmut
R/R population, N†	43	16	9	2	4	11	4	26
ORR	41 (95)	15 (94)	8 (89)	2 (100)	4 (100)	11 (100)	4 (100)	24 (92)
CR/CRi	16 (37)	4 (25)	4 (44)	2 (100)	3 (75)	2 (18)	4 (100)	9 (35)
PR	25 (58)	11 (69)	4 (44)	0	1 (25)	9 (82)	0	15 (58)
SD	2 (5)	1 (6)	1 (11)	0	0	0	0	2 (8)
1L population, N†	32	5	6	6	1	11	11	16
ORR	32 (100)	5 (100)	6 (100)	6 (100)	1 (100)	11 (100)	11 (100)	16 (100)
CR/CRi	25 (78)	3 (60)	5 (83)	5 (83)	1 (100)	9 (82)	10 (91)	12 (75)
PR	7 (22)	2 (40)	1 (17)	1 (17)	0	2 (18)	1 (9)	4 (25)

*Responses by cytogenetic abnormalities according to hierarchical model. †N for responses according to cytogenetic abnormalities and *IGHV* status may include only patients with samples available for cytogenetic and *IGHV* status assessment, respectively. 1L indicates first-line; CR, complete response; CRi, CR with incomplete marrow recovery; Mut, mutated; ORR, overall response rate; PR, partial response; R/R, relapsed/refractory; SD, stable disease; and Unmut, unmutated.

Figure legends

Figure 1. Dosing schedule

Schedule A: venetoclax followed by obinutuzumab; Schedule B: obinutuzumab followed by venetoclax. For both the R/R and 1L populations, Schedule A was examined prior to Schedule B. Data from Schedule A provided safety guidance for subsequent dose finding for patients in Schedule B after a data review by an internal monitoring safety team and a scientific overview committee. Venetoclax ramp-up: 3 weeks for the 100 mg cohort, 4 weeks for the 200 mg cohort, and 5 weeks for the 400 mg cohort; each cohort dose was continued for a total of 12 months with potential for extension if BM MRD+ or PR (1L) or until disease progression (R/R); venetoclax + obinutuzumab (6 cycles), then venetoclax monotherapy. Cohort 4 (600 mg) was planned but not explored. Venetoclax ramp-up and maximum cohort dose are indicated by the blue arrows. Obinutuzumab dosing schedule: C1D1: 100 mg; C1D2: 900 mg; C1D8 and 15: 1000 mg; C2-6D1: 1000 mg. 1L indicates first-line; BM MRD+, bone marrow minimal residual disease positive; C, cycle; D, day; G, GA101/obinutuzumab; PR, partial response; RD1, ramp-up day 1; R/R relapsed/refractory; and W, week.

Figure 2. Minimal residual disease rates in peripheral blood and bone marrow

(A) MRD rates in PB according to time after last dose of obinutuzumab in the R/R population. (B) MRD rates in BM by best response achieved in the R/R population. (C) MRD rates in PB according to time after the last dose of obinutuzumab in the 1L population. (D) MRD rates in PB after completion of all treatment (last dose of venetoclax) in the 1L population. (E) MRD rates in BM by best response achieved in the

1L population. 'Discontinued' specifies the number of patients who discontinued the study before the landmark timepoint due to PD, death, or AE (if applicable). 'Missing' specifies the number of patients who reached the landmark timepoint but did not have samples available for MRD assessment. *Of 43 R/R patients included in the efficacy analysis, 1 was excluded from the MRD analysis because of an undetectable MRD result at screening assumed to be due to the use of anti-CD20 <2 months before starting the trial. †Two patients discontinued the study before achieving this timepoint due to other reasons than PD, death, or AE, and were excluded from the MRD analysis at this landmark timepoint. ‡Undetermined: $<10^{-4}$, but <200 000 leukocytes analyzed. §Median 4.4 months (range, 2.8-8.5) from last dose of venetoclax. 1L indicates first-line; BM, bone marrow; CR, complete response; CRi, complete response with incomplete marrow recovery; G, GA101/obinutuzumab; mo., months; PB, peripheral blood; PR, partial response; R/R, relapsed/refractory, and Tx, treatment.

Figure 3. MRD kinetics in individual patients (MRD efficacy-evaluable population)

Undetectable MRD was defined as <1 CLL cell per 10^4 mononuclear cells in samples with a minimum of 200 000 leukocytes ($<10^{-4}$). Low-level MRD was defined as between 1 CLL cell per 10^4 and 1 cell per 10^2 mononuclear cells ($\geq 10^{-4}$-$<10^{-2}$). High-level MRD was defined as ≥1 CLL cell per 10^2 mononuclear cells ($\geq 10^{-2}$). 1L indicates first-line; BM, bone marrow; del, deletion; MRD, minimal residual disease; mut, mutated; PB, peripheral blood; PD, disease progression; R/R, relapsed/refractory; Tx, treatment; and ven, venetoclax.

Figures

Figure 1

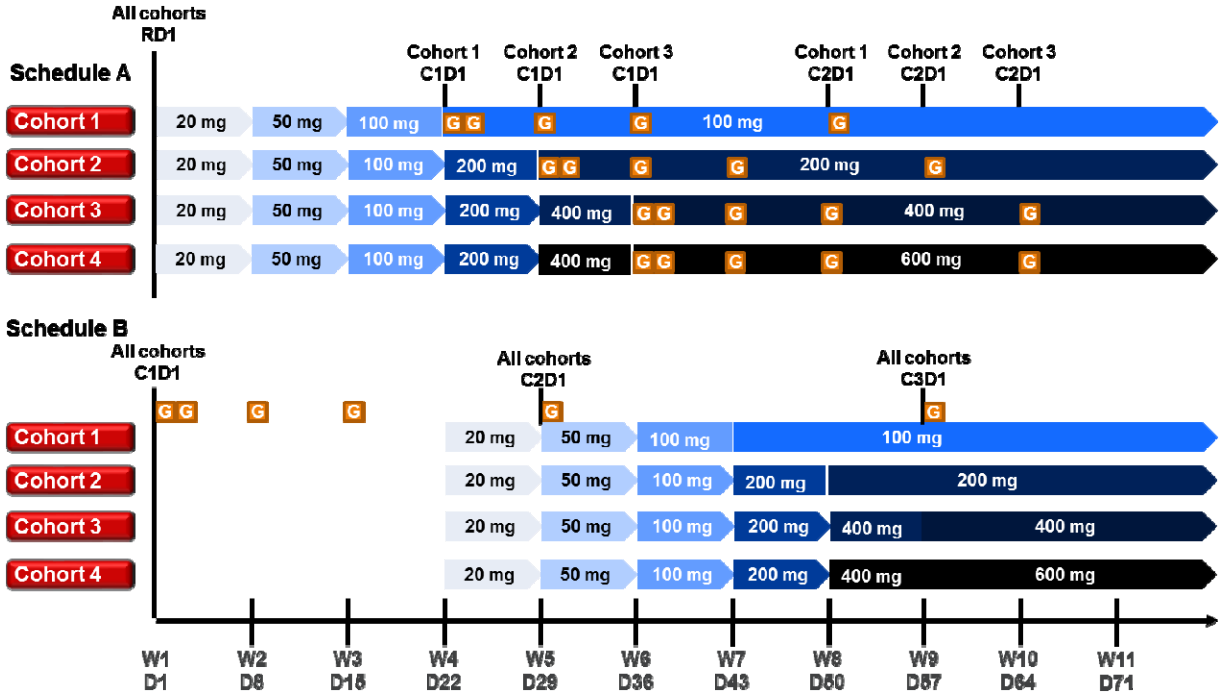
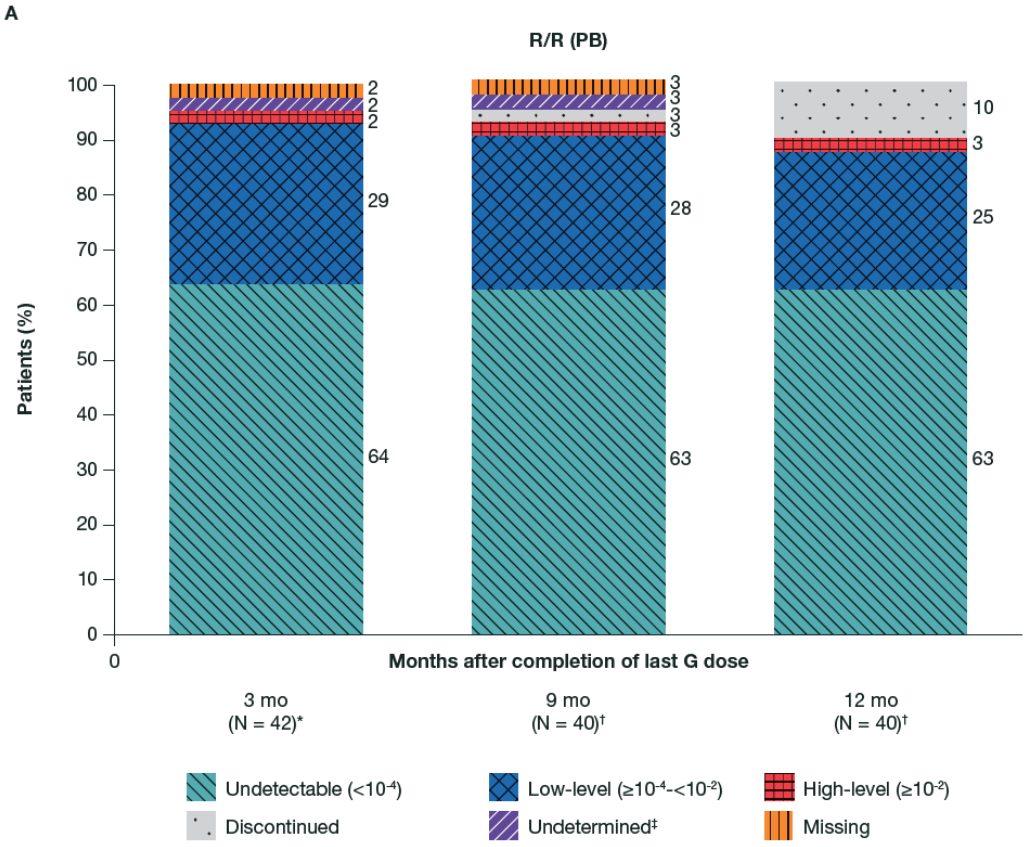
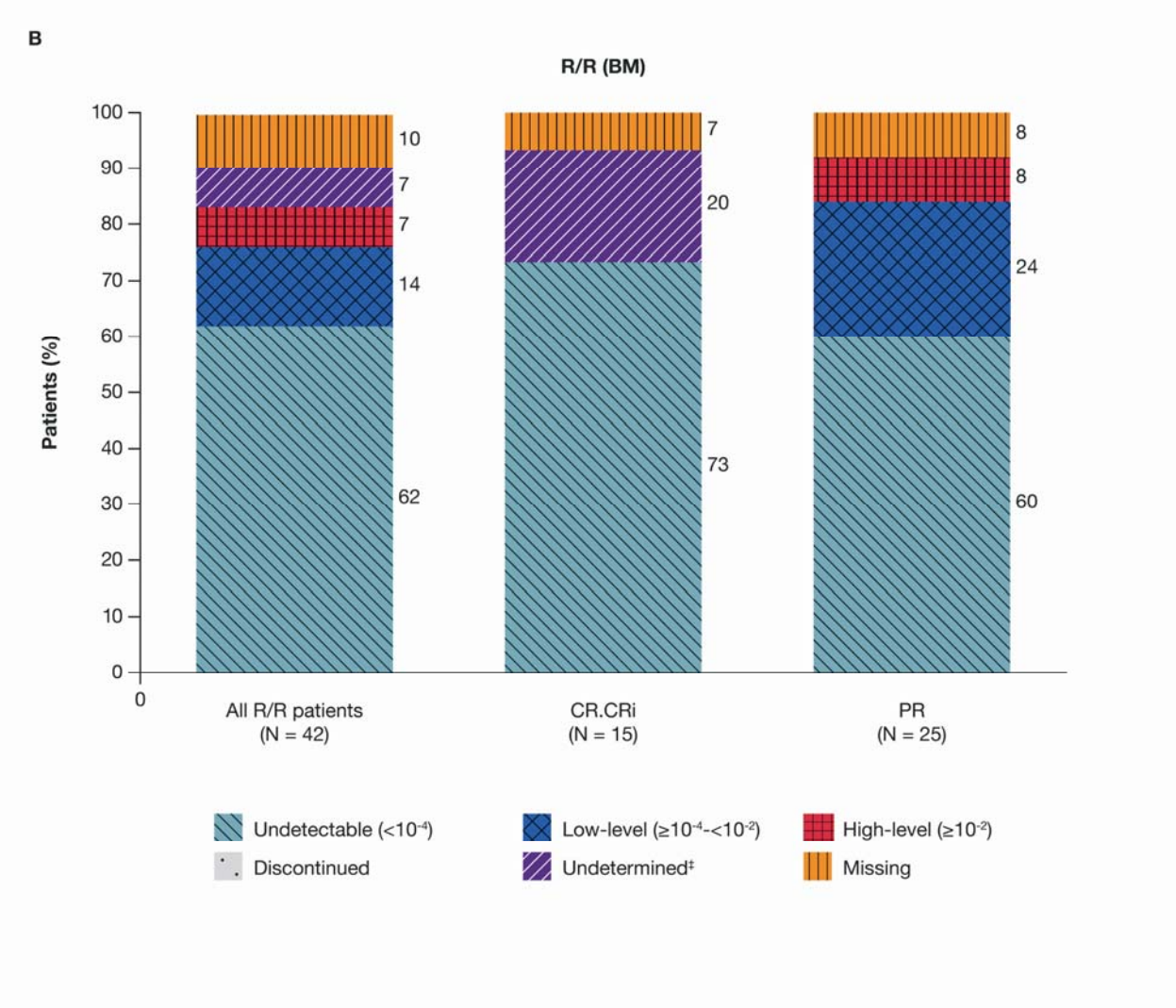
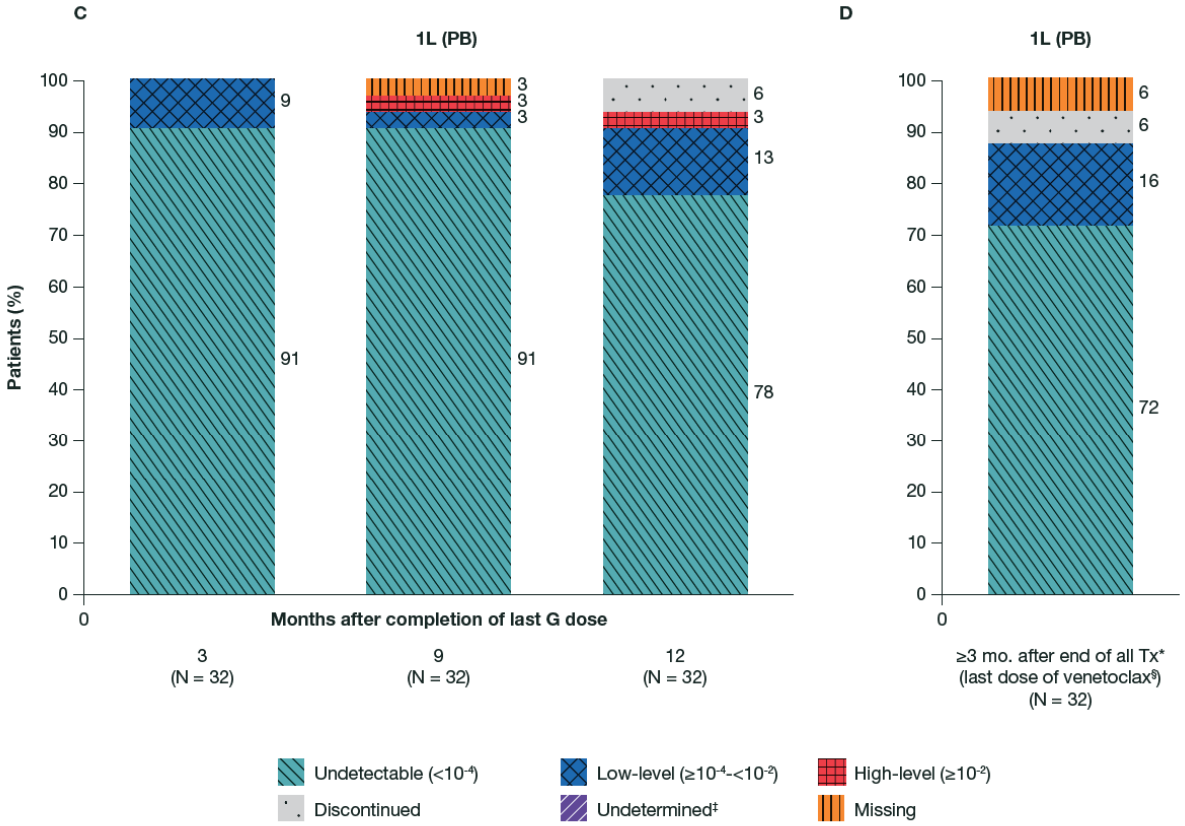


Figure 2







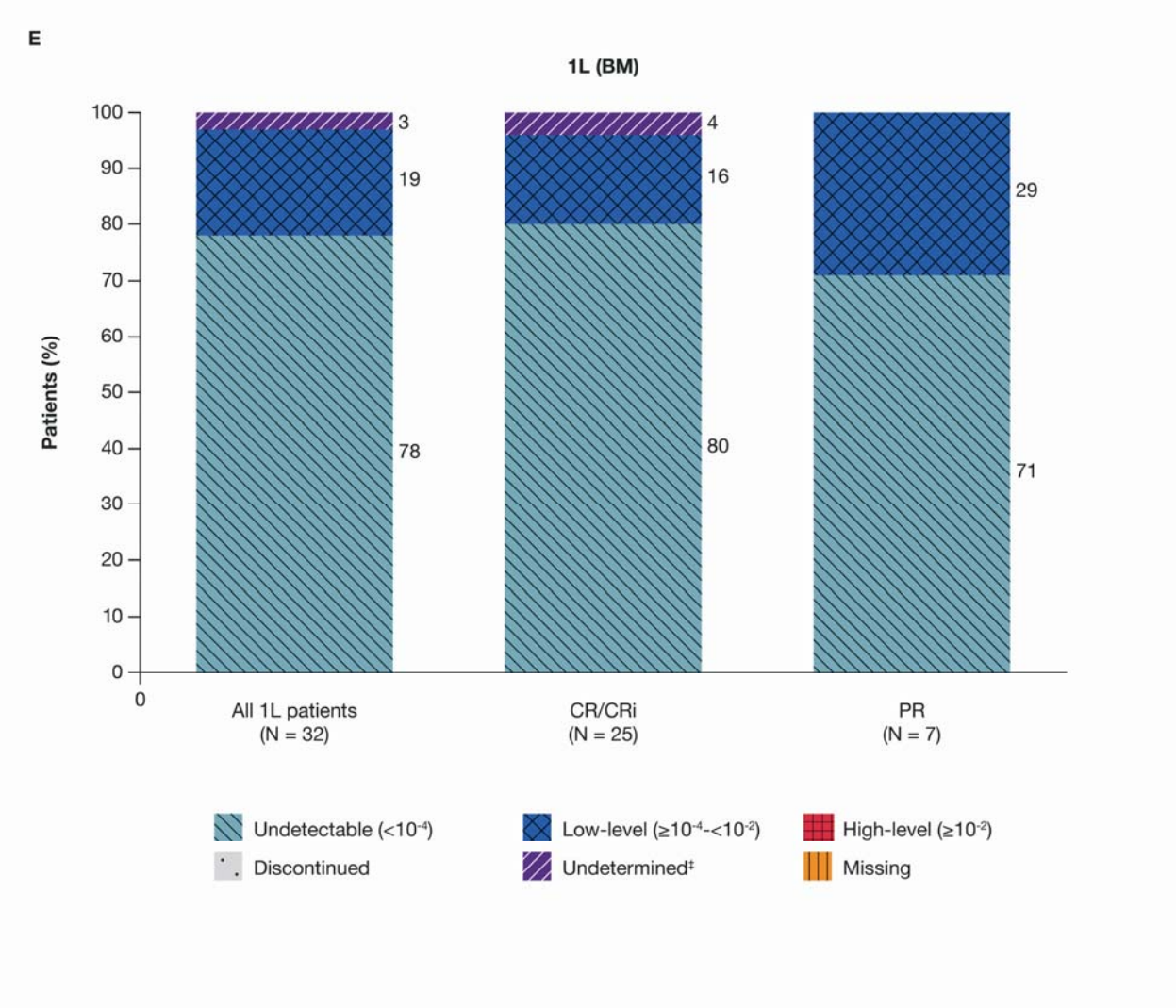


Figure 3

Prepublished online March 12, 2019;
doi:10.1182/blood-2019-01-896290

Phase 1b study of venetoclax-obinutuzumab in previously untreated and relapsed/refractory chronic lymphocytic leukemia

Ian W. Flinn, John G. Gribben, Martin J.S. Dyer, William Wierda, Michael B. Maris, Richard R. Furman, Peter Hillmen, Kerry A. Rogers, Swaminathan Padmanabhan Iyer, Anne Quillet-Mary, Loic Ysebaert, Harriet S. Walter, Maria Verdugo, Christian Klein, Huang Huang, Yanwen Jiang, Gerard Lozanski, Daniela Soriano Pignataro, Kathryn Humphrey, Mehrdad Mobasher and Thomas J. Kipps

Blood (print ISSN 0006-4971, online ISSN 1528-0020), is published weekly by the American Society of Hematology, 2021 L St, NW, Suite 900, Washington DC 20036.